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Review Article

Potential Role of Natural Compounds Modulating Bone Formation by Mitochondrial Oxidative Phosphorylation

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Abstract

Mitochondria are the main cell organelles responsible for adenosine triphosphate production through cellular respiration. They also have roles in regulating other cellular processes, including reactive oxygen species, apoptosis, and others. The function and number of mitochondria are important for the maintenance of bone homeostasis. In recent years, the regulation of bone homeostasis by mitochondria has attracted particular interest. In addition, some natural compounds have been demonstrated to modulate mitochondria functions, such as resveratrol, quercetin, and curcumin, *etc.* Here, we review the recent discoveries concerning mitochondrial oxidative phosphorylation and bone formation, as well as the effects of some natural compounds (resveratrol, quercetin, and curcumin) on oxidative phosphorylation, and discuss their therapeutic implications in treating bone disorders.

Introduction

Mitochondria are the main cell organelles that convert nutrients into adenosine triphosphate (ATP) by cellular respiration.[1] Previous studies have demonstrated that cellular ATP level is involved in cell growth, apoptosis, necrosis, *etc.*[2–4] There are four stages of cellular respiration, including glycolysis, pyruvate oxidation, citric acid cycle, and oxidative phosphorylation. Oxidative phosphorylation is the most efficient stage for ATP synthesis. The defects of the mitochondrial respiratory chain have been proven to be involved in many diseases, such as tumors, cardiomyopathy, Fanconi's syndrome, seizures, ophthalmoplegia, *etc.*[5–11]

Bone is a tissue that mechanically supports the body, protects vital organs, and impacts endocrine regulation. Currently, four types of cells have been identified in bone, osteoblasts, osteocytes, bone lining cells, and osteoclasts.[12] Osteoblasts and osteocytes are derived from stem cells known as mesenchymal stem cells (MSCs).[13–15] The function and number of mitochondria are important factors in the maintenance of bone cells, including osteoblasts and osteoclasts,[16–18] as both bone formation and resorption depend strongly on energy expenditure.[19] An imbalance between bone formation mediated by osteoblasts and bone resorption mediated by osteoclasts has been shown to directly contribute to the onset of many bone diseases such as osteoporosis, osteolysis, arthritis, *etc.*[20,21] Mutations of mitochondrial DNA (mtDNA) that accumulate with age may play a significant role in bone homeostasis.[22] Accumulating mutations of mtDNA ultimately lead to mitochondrial and cellular dysfunction.[23] A recent case-control study showed that m.3243A>G, a mitochondrial point mutation, was associated with decreased bone mineral density and bone strength.[24] In aged mice, osteoclasts had reduced levels of ATP and mtDNA with increased bone-resorbing activity.[25] Osteoclast-specific deletion of mitochondrial transcription factor A, which regulates mtDNA copy number, leads to ATP depletion and increased bone resorption.[25] Mitochondrial dysfunction induced by mtDNA polymerase gamma deletion has been reported to impair osteogenesis, increase osteoclast activity, and accelerate age-related bone loss.[26] Superoxide dismutase 2 deletion in osteocytes increases reactive oxygen species (ROS) production and bone loss in an age-dependent manner.[27]

In this review, we discuss recent discoveries concerning mitochondrial oxidative phosphorylation and bone formation, as well as the effects of some natural compounds (including resveratrol, quercetin, and curcumin) on oxidative phosphorylation, and whether optimizing mitochondria function could improve bone

Keywords: Mitochondria; Oxidative phosphorylation; Bone; Natural compounds.

Abbreviations: ATP, adenosine triphosphate; BMP, bone morphogenetic protein; LRP, low-density lipoprotein receptor-related protein; MSC, mesenchymal stem cell; mtDNA, mitochondrial DNA; NAD^+, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; Nrf2, nuclear factor erythroid 2-related factor 2; PGC, peroxisome proliferator-activated receptor-gamma coactivator; RUNX2, runt-related transcription factor 2; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; Wnt, Wingless-type MMTV integration site family.

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quality or even reverse bone disorders.

Oxidative phosphorylation and bone formation

Oxidative phosphorylation is defined as the process by which electrons from reduced nicotinamide adenine dinucleotide and reduced flavine adenine dinucleotide are transferred to O_2 molecules through a series of electron carrier/protein complexes to generate ATP. It provides most of the ATP for the cell's energy needs. Defects in this process are a frequent cause of mitochondrial energy metabolism disturbance, which occurs with a prevalence of at least 1 in 7600.[28] Up to now, accumulating evidence has indicated that oxidative phosphorylation is involved in the regulation of cell fate decisions.[29–31] *In vitro* studies have indicated that oxidative phosphorylation plays a crucial role in osteogenesis. Upon osteogenic induction, energy metabolism can shift from glycolysis to mitochondrial oxidative phosphorylation with the increase of respiratory enzymes, copy number of mitochondrial DNA, oxygen consumption rate, and intracellular ATP content.[32] Other studies have also demonstrated that oxidative phosphorylation is increased during the osteogenesis of MSCs, while glycolysis is preferred in undifferentiated stem cells.[33,34] The increased β-catenin acetylation and activity might be one of the important underlying mechanisms that account for the effect of oxidative phosphorylation on the osteogenesis of MSCs.[35] Bone morphogenetic protein 2) has a critical role in regulating bone formation, a recent study reported that bone morphogenetic protein 2 triggered rapid metabolic adaptation in MSCs, which is characterized by the successive activation of glycolysis and oxidative phosphorylation.[36]

Nicotinamide adenine dinucleotide (NAD^+) is an obligatory substrate for the reaction of glycolysis and oxidative phosphorylation. Its intracellular level and NAD^+/nicotinamide adenine dinucleotide ratio are essential for mitochondrial function, which links cellular metabolism to changes in transcriptional events and signaling pathways.[37] Nicotinamide mononucleotide (NMN), a key natural NAD^+ intermediate, has been found to promote osteogenesis and reduce adipogenesis of MSCs, as well as stimulate osteogenesis of endogenous MSCs, and protect bone from aging and irradiation-induced damage in mice.[38] A recent study by Boer Li *et al.* reported that osteogenesis-committed MSCs have increased oxidative phosphorylation activity and elevated NAD+ levels. Suppression of NAD^+ impairs mitochondrial fusion, leading to mitochondria dysfunction and reduced activity of oxidative phosphorylation, which subsequently blocks osteogenesis and bone fracture healing.[39]

As we know, aging is associated with mitochondria dysfunction, as well as decreased bone mass and accumulated marrow fat. It is reported that, during aging, the content of NAD^+ and ATP has a progressive, age-dependent decline.[40] Up to now, mitochondrial metabolic failure has been considered an important hallmark of aging.[41,42] Mills *et al.* conducted a 12-month administration of NMN, demonstrating that NMN effectively mitigates age-associated physiological decline in mice, including increasing energy metabolism, bone density, *etc.*[43] NMN supplementation could also attenuate senescent cell induction in growth plates, partially prevent osteoporosis, and accelerate bone healing in osteoporotic mice.[44] In addition, upregulation of oxidative phosphorylation activity and ATP production by mitochondria transfer could enhance the osteogenesis of MSCs and accelerate bone defect healing after transplantation of mitochondria-recipient MSCs *in situ*.[45] On the other hand, a recent study by Suh *et al.* found that changes in mitochondrial morphology had a more significant impact on osteogenic activity than moderate alterations in mitochondrial ATP production, as enhancing mitochondrial fission by overexpression of Fis1 accelerates osteogenesis but results in mild but significant decreases of ATP production.[46] Hence, it would be safe to assume that improvement of mitochondrial metabolism would enhance the osteogenesis of MSCs and bone formation, as well as hinder the progression of osteoporosis, especially senile osteoporosis.

Reactive oxygen species (ROS)

ROS are mainly formed as byproducts of oxidative phosphorylation in aerobic organisms. The ROS that have been found in living organisms include superoxide anions, hydroxyl radicals, nitric oxide, *etc.* The evidence so far has suggested that ROS serve as a double-edged sword for the cells. On one hand, ROS at low levels function as signaling molecules that are necessary to maintain cell viability, differentiation, self-renewal ability, migration, *etc.*[47] Studies of *Candida elegans* and yeast have shown that ROS were required for the increase of lifespan.[48,49] On the other hand, an excess of ROS is harmful as it can induce oxidative stress and cell death.[50] The levels of ROS are increased in dysfunctional mitochondria and senescent cells, implicating ROS are involved in various cellular damages.[51] The osteogenic differentiation of bone osteoblastic cells (MC3T3-E1), marrow stromal cells (M2-10B4), and MSCs were greatly suppressed by ROS, and adipogenesis was increased.[32,52–54] Many studies have shown that ROS may be involved in the pathogenesis of osteoporosis.[55,56]

Hopefully, the destructive effects of ROS can be inhibited by antioxidant agents, such as vitamin K, glutathione, and its precursor N-acetyl cysteine and other natural compounds. The cells have intrinsic mechanisms that coordinate changes in oxidative phosphorylation and antioxidant enzymes without generating excess ROS. For example, during the osteogenesis of MSCs, although ROS are produced by increased oxidative phosphorylation, they are quickly removed by the upregulation of antioxidant enzymes, such as manganese-dependent superoxide dismutase and catalase.[32] N-acetyl cysteine has beneficial effects that prevent osteoporosis by reducing stimuli of the loss of bone mass, osteoblast apoptosis, oxidative stress, and osteoclastogenesis after gonadectomy.[57,58] The effects of some natural compounds like quercetin, resveratrol, and curcumin on oxidative phosphorylation or mitochondria are discussed below.

Quercetin

Quercetin is an abundant polyphenolic flavonoid and has beneficial effects in many diseases. The main molecular mechanism responsible for its protective effects is the capacity to quench ROS-induced oxidative damage. However, studies about the effect of quercetin on mitochondrial function appear contradictory. It was previously shown to inhibit mitochondrial ATP synthase, inhibit oxidative phosphorylation, and decrease mitochondrial membrane potential.[59–61] However, recent studies have shown that quercetin treatment improved mitochondrial quality and reduced oxidative stress.[62] Qiu *et al.* found that quercetin not only enhanced mitochondrial membrane potential, oxygen consumption, and ATP in mitochondria, but also increased the mitochondrial copy number in rat chondrocytes.[63] Direct evidence from Fukaya *et al.* demonstrates that quercetin significantly increased oxygen consumption and ATP production in hepatocytes.[64] In addition, quercetin protects against bone loss by stimulating bone formation and inhibiting bone resorption.[65–67] The underlying mechanisms include

Wingless-type MMTV integration site family, bone morphogenetic protein, extracellular regulated protein kinases, nuclear factor erythroid 2-related factor 2 (Nrf2), and smad-dependent signaling pathways, *etc.* Nrf2 was maintained in an inactive state in the cytosol by binding to kelch-like ECH-associated protein-1, which was inhibited by quercetin, leading to nuclear translocation of Nrf2 and increased expression of antioxidative genes.[68] Pang *et al.* reported that quercetin promoted bone MSCs proliferation and osteogenic differentiation by stimulating the bone morphogenetic protein signaling pathway.[69] However, the effect of quercetin on oxidative phosphorylation has not been confirmed in bone-forming cells, including osteoblasts or MSCs. It would be interesting to find out whether quercetin protects bone by increasing oxidative phosphorylation or improving mitochondrial function or not.

Resveratrol

Resveratrol (3,4,5-trihydroxystilbene) is an edible polyphenolic phytoalexin with anti-oxidant and anti-aging activity.[70] Lagouge *et al.* found that resveratrol improved mitochondrial function by inducing genes for oxidative phosphorylation, mitochondrial biogenesis, and an increase in the activity of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α.[71] Under normal conditions, PGC-1α is inactivated by acetylation by acetyltransferase, general control of nucleotide synthesis 5.[72] Resveratrol activates the NAD^+-dependent histone deacetylase Sirt1. Sirt1 mediates the deacetylation of PGC-1α, leading to the stimulation of genes involved in oxidative phosphorylation.[73] The effect of resveratrol is also related to mitofilin, a mitochondrial inner membrane protein that is required for mitochondrial homeostasis and osteogenesis of MSCs.[74] However, resveratrol cannot normalize oxidative phosphorylation activity in cells with oxidative phosphorylation defects,[75] implying the effect of resveratrol on mitochondrial activity is dependent on the induction of genes for oxidative phosphorylation. Moon *et al.* reported that resveratrol treatment (at 5 μM) promoted osteogenic differentiation of periosteum-derived MSCs, and increased both mitochondrial mass and mtDNA copy number, supporting the application of resveratrol for treating osteoporotic fractures.[76] In an ovariectomized rat model of osteoporosis, Feng *et al.* demonstrated that resveratrol prevented bone loss by upregulating FoxO1 transcription activity.[77] Tresguerres *et al.* found that resveratrol (10 mg/kg/day) increased bone microstructure and bone mechanical properties in old male rats, indicating resveratrol hindered the progression of senile osteoporosis.[78] A meta-analysis of randomized controlled trials of resveratrol and bone-health biomarkers showed that resveratrol supplementation increased some key bone biomarkers, such as alkaline phosphatase and bone alkaline phosphatase.[79] It should be noted that the effect of resveratrol on mitochondria is tissue- or cell-specific. Resveratrol also inhibits oxidative phosphorylation and mitochondrial metabolic pathways in mitochondria isolated from rat brains,[80] and cancer cells.[81,82]

Curcumin

Curcumin is a natural phenolic biphenyl compound isolated from the plant *Curcuma longa*. The evidence so far has shown that curcumin is a protonophoric uncoupler, causing a decrease in ATP biosynthesis in mitochondria.[83] In *Escherichia coli*, the ATP synthase F1 sector is inhibited by curcumin and its analogs.[84] One study indicated that curcumin preserved mitochondrial function, with increased membrane potential and complex III, which is involved in oxidative phosphorylation. It ultimately ameliorated oxidative stress-induced apoptosis in osteoblasts.[85]

Evidence from published studies indicates the effects of curcumin on osteogenesis and bone formation are contradictory. For example, it has been demonstrated that curcumin inhibited the osteogenesis of human adipose derived-MSCs in a dose-dependent manner.[86] However, another study showed that curcumin promoted osteogenesis and bone repair activity of human periodontal ligament stem cells under oxidative stress.[87] To reveal its relationship with mitochondria, the controversial roles of curcumin in mitochondrial function deserve further study, especially in MSCs or osteoblasts.

Conclusions

Oxidative phosphorylation, which produces most of the ATP in cells, is closely correlated with mitochondrial function and many diseases. The role of oxidative phosphorylation in bone formation and the effect of natural compounds are shown in Figure 1. Herbal medicines have been traditionally used to combat diseases. They contain thousands of natural compounds, some of which may be the material base for their therapeutic functions. However, few natural compounds have been found to modulate mitochondrial function, and new ones need to be identified in the near future. Resveratrol has been found to induce the expression of genes for oxidative phosphorylation, and subsequent mitochondrial biogenesis, which would be useful for combating bone diseases by increasing bone formation. We should note that oxidative phosphorylation is not the only pathway by which natural compounds influence the function of mitochondria. Dietary lipids have been observed in some studies to regulate the transfer of mitochondria to macrophages, which determines whether mitochondria from adipocytes are released into the systemic circulation to aid the metabolic adaptation of distant organs.[88,89] Mitochondrial transport may also be regulated by natural compounds or herbal medicines to impact bone formation or other biological processes. This is an interesting issue to be addressed in future studies. So far, natural compounds have many effects on mitochondria, but some data are contradictory. The discrepancies may arise from different cell models and under different conditions. There is an urgent need to clarify the discrepancies in using natural compounds that are beneficial for mitochondria to improve bone quality.

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Conflict of interest

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Author contributions

Wrote the draft (MLD, QQZ), conceived the original idea, and

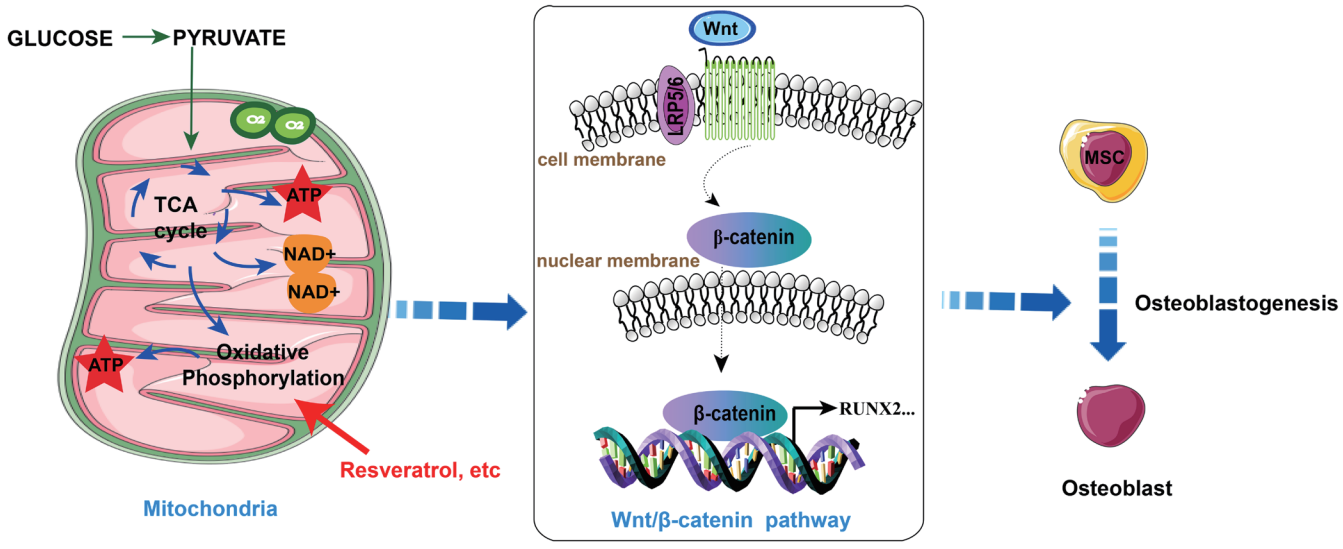

Fig. 1. Natural compounds regulate bone formation through oxidative phosphorylation. Osteoblasts derived from MSCs are cells required for bone formation. Oxidative phosphorylation produces a lot of ATP and other products including NAD+ and ROS. These factors play important roles in the regulation of osteogenesis through different mechanisms, such as Wnt/β-catenin signaling. Natural compounds including resveratrol and others modulate osteogenesis by regulating oxidative phosphorylation in mitochondria. ATP, adenosine triphosphate; LRP, low-density lipoprotein receptor-related protein; MSC, mesenchymal stem cell; NAD^+, nicotinamide adenine dinucleotide; ROS, reactive oxygen species; RUNX2, runt-related transcription factor 2; TCA, tricarboxylic acid cycle; Wnt, Wingless-type MMTV integration site family.

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References

[1] Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu Rev Genet 2005;39:359–407. doi:10.1146/annurev.genet.39.110304.095751, PMID:16285865.

[2] Feldenberg LR, Thevananther S, del Rio M, de Leon M, Devarajan P. Partial ATP depletion induces Fas- and caspase-mediated apoptosis in MDCK cells. Am J Physiol 1999;276(6):F837–F846. doi:10.1152/ajprenal.1999.276.6.F837, PMID:10362772.

[3] Yi CH, Pan H, Seebacher J, Jang IH, Hyberts SG, Heffron GJ, *et al*. Metabolic regulation of protein N-alpha-acetylation by Bcl-xL promotes cell survival. Cell 2011;146(4):607–620. doi:10.1016/j.cell.2011.06.050, PMID:21854985.

[4] Hiraoka H, Nakano T, Kuwana S, Fukuzawa M, Hirano Y, Ueda M, *et al*. Intracellular ATP levels influence cell fates in Dictyostelium discoideum differentiation. Genes Cells 2020;25(5):312–326. doi:10.1111/gtc.12763, PMID:32125743.

[5] Schapira AH. Primary and secondary defects of the mitochondrial respiratory chain. J Inherit Metab Dis 2002;25(3):207–214. doi:10.1023/a:1015629912477, PMID:12137229.

[6] Wang HW, Zhang Y, Tan PP, Jia LS, Chen Y, Zhou BH. Mitochondrial respiratory chain dysfunction mediated by ROS is a primary point of fluoride-induced damage in Hepa1-6 cells. Environ Pollut 2019;255(Pt 3):113359. doi:10.1016/j.envpol.2019.113359, PMID:31614248.

[7] Leonard JV, Schapira AH. Mitochondrial respiratory chain disorders I: mitochondrial DNA defects. Lancet 2000;355(9200):299–304. doi:10.1016/s0140-6736(99)05225-3, PMID:10675086.

[8] Meyers DE, Basha HI, Koenig MK. Mitochondrial cardiomyopathy: pathophysiology, diagnosis, and management. Tex Heart Inst J 2013;40(4):385–394. PMID:24082366.

[9] Ravera S, Vaccaro D, Cuccarolo P, Columbaro M, Capanni C, Bartolucci M, *et al*. Mitochondrial respiratory chain Complex I defects in Fanconi anemia complementation group A. Biochimie 2013;95(10):1828–1837. doi:10.1016/j.biochi.2013.06.006, PMID:23791750.

[10] Jarrett SG, Lewin AS, Boulton ME. The importance of mitochondria in age-related and inherited eye disorders. Ophthalmic Res 2010;44(3):179–190. doi:10.1159/000316480, PMID:20829642.

[11] Vlaikou AM, Nussbaumer M, Komini C, Lambrianidou A, Konidaris C, Trangas T, *et al*. Exploring the crosstalk of glycolysis and mitochondrial metabolism in psychiatric disorders and brain tumours. Eur J Neurosci 2021;53(9):3002–3018. doi:10.1111/ejn.15057, PMID:33226682.

[12] Downey PA, Siegel MI. Bone biology and the clinical implications for osteoporosis. Phys Ther 2006;86(1):77–91. doi:10.1093/ptj/86.1.77, PMID:16386064.

[13] Kim J, Adachi T. Cell-fate decision of mesenchymal stem cells toward osteocyte differentiation is committed by spheroid culture. Sci Rep 2021;11(1):13204. doi:10.1038/s41598-021-92607-z, PMID:34168224.

[14] Khotib J, Marhaeny HD, Miatmoko A, Budiatin AS, Ardianto C, Rahmadi M, *et al*. Differentiation of osteoblasts: the links between essential transcription factors. J Biomol Struct Dyn 2023;41(19):10257–10276. doi:10.1080/07391102.2022.2148749, PMID:36420663.

[15] Xu L, Liu Y, Sun Y, Wang B, Xiong Y, Lin W, *et al*. Tissue source determines the differentiation potentials of mesenchymal stem cells: a comparative study of human mesenchymal stem cells from bone marrow and adipose tissue. Stem Cell Res Ther 2017;8(1):275. doi:10.1186/s13287-017-0716-x, PMID:29208029.

[16] Wang S, Deng Z, Ma Y, Jin J, Qi F, Li S, *et al*. The role of autophagy and mitophagy in bone metabolic disorders. Int J Biol Sci 2020;16(14):2675–2691. doi:10.7150/ijbs.46627, PMID:32792864.

[17] Aoki S, Shimizu K, Ito K. Autophagy-dependent mitochondrial function regulates osteoclast differentiation and maturation. Biochem Biophys Res Commun 2020;527(4):874–880. doi:10.1016/j.bbrc.2020.04.155, PMID:32430180.

[18] Park-Min KH. Metabolic reprogramming in osteoclasts. Semin Immunopathol 2019;41(5):565–572. doi:10.1007/s00281-019-00757-0, PMID:31552471.

[19] Da W, Tao L, Zhu Y. The role of osteoclast energy metabolism in the occurrence and development of osteoporosis. Front Endocrinol (Lausanne) 2021;12:675385. doi:10.3389/fendo.2021.675385, PMID:34054735.

[20] Tanaka Y, Nakayamada S, Okada Y. Osteoblasts and osteoclasts in bone remodeling and inflammation. Curr Drug Targets Inflamm Allergy 2005;4(3):325–328. doi:10.2174/1568010054022015, PMID:16101541.

[21] Kim JM, Lin C, Stavre Z, Greenblatt MB, Shim JH. Osteoblast-osteoclast communication and bone homeostasis. Cells 2020;9(9):2073. doi:10.3390/cells9092073, PMID:32927921.
[22] Larsson NG. Somatic mitochondrial DNA mutations in mammalian aging. Annu Rev Biochem 2010;79:683–706. doi:10.1146/annurev-biochem-060408-093701, PMID:20350166.
[23] Hayashi J, Ohta S, Kikuchi A, Takemitsu M, Goto Y, Nonaka I. Introduction of disease-related mitochondrial DNA deletions into HeLa cells lacking mitochondrial DNA results in mitochondrial dysfunction. Proc Natl Acad Sci U S A 1991;88(23):10614–10618. doi:10.1073/pnas.88.23.10614, PMID:1720544.
[24] Langdahl JH, Frederiksen AL, Hansen SJ, Andersen PH, Yderstraede KB, Dunø M, *et al*. Mitochondrial point mutation m.3243A>G associates with lower bone mineral density, thinner cortices, and reduced bone strength: a case-control study. J Bone Miner Res 2017;32(10):2041–2048. doi:10.1002/jbmr.3193, PMID:28603900.
[25] Miyazaki T, Iwasawa M, Nakashima T, Mori S, Shigemoto K, Nakamura H, *et al*. Intracellular and extracellular ATP coordinately regulate the inverse correlation between osteoclast survival and bone resorption. J Biol Chem 2012;287(45):37808–37823. doi:10.1074/jbc.M112.385369, PMID:22988253.
[26] Dobson PF, Dennis EP, Hipps D, Reeve A, Laude A, Bradshaw C, *et al*. Mitochondrial dysfunction impairs osteogenesis, increases osteoclast activity, and accelerates age related bone loss. Sci Rep 2020;10(1):11643. doi:10.1038/s41598-020-68566-2, PMID:32669663.
[27] Kobayashi K, Nojiri H, Saita Y, Morikawa D, Ozawa Y, Watanabe K, *et al*. Mitochondrial superoxide in osteocytes perturbs canalicular networks in the setting of age-related osteoporosis. Sci Rep 2015;5:9148. doi:10.1038/srep09148, PMID:25779629.
[28] Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain 2003;126(Pt 8):1905–1912. doi:10.1093/brain/awg170, PMID:12805096.
[29] Shin B, Benavides GA, Geng J, Koralov SB, Hu H, Darley-Usmar VM, *et al*. Mitochondrial oxidative phosphorylation regulates the fate decision between pathogenic Th17 and regulatory T cells. Cell Rep 2020;30(6):1898–1909.e4. doi:10.1016/j.celrep.2020.01.022, PMID:32049019.
[30] Wanet A, Arnould T, Najimi M, Renard P. Connecting mitochondria, metabolism, and stem cell fate. Stem Cells Dev 2015;24(17):1957–1971. doi:10.1089/scd.2015.0117, PMID:26134242.
[31] Tatapudy S, Aloisio F, Barber D, Nystul T. Cell fate decisions: emerging roles for metabolic signals and cell morphology. EMBO Rep 2017;18(12):2105–2118. doi:10.15252/embr.201744816, PMID:29158350.
[32] Chen CT, Shih YR, Kuo TK, Lee OK, Wei YH. Coordinated changes of mitochondrial biogenesis and antioxidant enzymes during osteogenic differentiation of human mesenchymal stem cells. Stem Cells 2008;26(4):960–968. doi:10.1634/stemcells.2007-0509, PMID:18218821.
[33] Shum LC, White NS, Mills BN, Bentley KL, Eliseev RA. Energy metabolism in mesenchymal stem cells during osteogenic differentiation. Stem Cells Dev 2016;25(2):114–122. doi:10.1089/scd.2015.0193, PMID:26487485.
[34] Forni MF, Peloggia J, Trudeau K, Shirihai O, Kowaltowski AJ. Murine mesenchymal stem cell commitment to differentiation is regulated by mitochondrial dynamics. Stem Cells 2016;34(3):743–755. doi:10.1002/stem.2248, PMID:26638184.
[35] Shares BH, Busch M, White N, Shum L, Eliseev RA. Active mitochondria support osteogenic differentiation by stimulating β-catenin acetylation. J Biol Chem 2018;293(41):16019–16027. doi:10.1074/jbc.RA118.004102, PMID:30150300.
[36] Lin S, Yin S, Shi J, Yang G, Wen X, Zhang W, *et al*. Orchestration of energy metabolism and osteogenesis by Mg(2+) facilitates low-dose BMP-2-driven regeneration. Bioact Mater 2022;18:116–127. doi:10.1016/j.bioactmat.2022.03.024, PMID:35387176.
[37] Cantó C, Menzies KJ, Auwerx J. NAD(+) Metabolism and the control of energy homeostasis: a balancing act between mitochondria and the nucleus. Cell Metab 2015;22(1):31–53. doi:10.1016/j.cmet.2015.05.023, PMID:26118927.
[38] Song J, Li J, Yang F, Ning G, Zhen L, Wu L, *et al*. Nicotinamide mononucleotide promotes osteogenesis and reduces adipogenesis by regulating mesenchymal stromal cells via the SIRT1 pathway in aged bone marrow. Cell Death Dis 2019;10(5):336. doi:10.1038/s41419-019-1569-2, PMID:31000692.
[39] Li B, Shi Y, Liu M, Wu F, Hu X, Yu F, *et al*. Attenuates of NAD(+) impair BMSC osteogenesis and fracture repair through OXPHOS. Stem Cell Res Ther 2022;13(1):77. doi:10.1186/s13287-022-02748-9, PMID:35193674.
[40] Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, *et al*. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell 2013;155(7):1624–1638. doi:10.1016/j.cell.2013.11.037, PMID:24360282.
[41] Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, Guo M, *et al*. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 2011;470(7334):359–365. doi:10.1038/nature09787, PMID:21307849.
[42] Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature 2010;464(7288):520–528. doi:10.1038/nature08982, PMID:20336134.
[43] Mills KF, Yoshida S, Stein LR, Grozio A, Kubota S, Sasaki Y, *et al*. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. Cell Metab 2016;24(6):795–806. doi:10.1016/j.cmet.2016.09.013, PMID:28068222.
[44] Lu Z, Jiang L, Lesani P, Zhang W, Li N, Luo D, *et al*. Nicotinamide mononucleotide alleviates osteoblast senescence induction and promotes bone healing in osteoporotic mice. J Gerontol A Biol Sci Med Sci 2023;78(2):186–194. doi:10.1093/gerona/glac175, PMID:36037105.
[45] Guo Y, Chi X, Wang Y, Heng BC, Wei Y, Zhang X, *et al*. Mitochondria transfer enhances proliferation, migration, and osteogenic differentiation of bone marrow mesenchymal stem cell and promotes bone defect healing. Stem Cell Res Ther 2020;11(1):245. doi:10.1186/s13287-020-01704-9, PMID:32586355.
[46] Suh J, Kim NK, Shim W, Lee SH, Kim HJ, Moon E, *et al*. Mitochondrial fragmentation and donut formation enhance mitochondrial secretion to promote osteogenesis. Cell Metab 2023;35(2):345–360.e7. doi:10.1016/j.cmet.2023.01.003, PMID:36754021.
[47] Ludin A, Gur-Cohen S, Golan K, Kaufmann KB, Itkin T, Medaglia C, *et al*. Reactive oxygen species regulate hematopoietic stem cell self-renewal, migration and development, as well as their bone marrow microenvironment. Antioxid Redox Signal 2014;21(11):1605–1619. doi:10.1089/ars.2014.5941, PMID:24762207.
[48] Schulz TJ, Zarse K, Voigt A, Urban N, Birringer M, Ristow M. Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress. Cell Metab 2007;6(4):280–293. doi:10.1016/j.cmet.2007.08.011, PMID:17908557.
[49] Pan Y, Schroeder EA, Ocampo A, Barrientos A, Shadel GS. Regulation of yeast chronological life span by TORC1 via adaptive mitochondrial ROS signaling. Cell Metab 2011;13(6):668–678. doi:10.1016/j.cmet.2011.03.018, PMID:21641548.
[50] Picard M, Shirihai OS, Gentil BJ, Burelle Y. Mitochondrial morphology transitions and functions: implications for retrograde signaling? Am J Physiol Regul Integr Comp Physiol 2013;304(6):R393–R406. doi:10.1152/ajpregu.00584.2012, PMID:23364527.
[51] Jeong SG, Cho GW. Endogenous ROS levels are increased in replicative senescence in human bone marrow mesenchymal stromal cells. Biochem Biophys Res Commun 2015;460(4):971–976. doi:10.1016/j.bbrc.2015.03.136, PMID:25839657.
[52] Mody N, Parhami F, Sarafian TA, Demer LL. Oxidative stress modulates osteoblastic differentiation of vascular and bone cells. Free Radic Biol Med 2001;31(4):509–519. doi:10.1016/s0891-5849(01)00610-4, PMID:11498284.
[53] Kawakami M, Ishikawa H, Tanaka A, Mataga I. Induction and differentiation of adipose-derived stem cells from human buccal fat pads into salivary gland cells. Hum Cell 2016;29(3):101–110. doi:10.1007/s13577-016-0132-z, PMID:26842556.
[54] Higuchi M, Dusting GJ, Peshavariya H, Jiang F, Hsiao ST, Chan EC, *et al*. Differentiation of human adipose-derived stem cells into fat involves reactive oxygen species and Forkhead box O1 mediated upregulation of antioxidant enzymes. Stem Cells Dev 2013;22(6):878–888.

doi:10.1089/scd.2012.0306, PMID:23025577.
[55] Mohamad S, Shuid AN, Mokhtar SA, Abdullah S, Soelaiman IN. Tocotrienol supplementation improves late-phase fracture healing compared to alpha-tocopherol in a rat model of postmenopausal osteoporosis: a biomechanical evaluation. Evid Based Complement Alternat Med 2012;2012:372878. doi:10.1155/2012/372878, PMID:22829855.
[56] Li X, Li B, Shi Y, Wang C, Ye L. Targeting reactive oxygen species in stem cells for bone therapy. Drug Discov Today 2021;26(5):1226–1244. doi:10.1016/j.drudis.2021.03.002, PMID:33684524.
[57] Chen L, Wang G, Wang Q, Liu Q, Sun Q, Chen L. N-acetylcysteine prevents orchiectomy-induced osteoporosis by inhibiting oxidative stress and osteocyte senescence. Am J Transl Res 2019;11(7):4337–4347. PMID:31396339.
[58] Raffaele M, Barbagallo I, Licari M, Carota G, Sferrazzo G, Spampinato M, *et al*. N-Acetylcysteine (NAC) ameliorates lipid-related metabolic dysfunction in bone marrow stromal cells-derived adipocytes. Evid Based Complement Alternat Med 2018;2018:5310961. doi:10.1155/2018/5310961, PMID:30416532.
[59] Lang DR, Racker E. Effects of quercetin and F1 inhibitor on mitochondrial ATPase and energy-linked reactions in submitochondrial particles. Biochim Biophys Acta 1974;333(2):180–186. doi:10.1016/0005-2728(74)90002-4, PMID:19400030.
[60] Ortega R, García N. The flavonoid quercetin induces changes in mitochondrial permeability by inhibiting adenine nucleotide translocase. J Bioenerg Biomembr 2009;41(1):41–47. doi:10.1007/s10863-009-9198-6, PMID:19296209.
[61] Dorta DJ, Pigoso AA, Mingatto FE, Rodrigues T, Prado IM, Helena AF, *et al*. The interaction of flavonoids with mitochondria: effects on energetic processes. Chem Biol Interact 2005;152(2-3):67–78. doi:10.1016/j.cbi.2005.02.004, PMID:15840381.
[62] Wang WW, Han R, He HJ, Li J, Chen SY, Gu Y, *et al*. Administration of quercetin improves mitochondria quality control and protects the neurons in 6-OHDA-lesioned Parkinson's disease models. Aging (Albany NY) 2021;13(8):11738–11751. doi:10.18632/aging.202868, PMID:33878030.
[63] Qiu L, Luo Y, Chen X. Quercetin attenuates mitochondrial dysfunction and biogenesis via upregulated AMPK/SIRT1 signaling pathway in OA rats. Biomed Pharmacother 2018;103:1585–1591. doi:10.1016/j.biopha.2018.05.003, PMID:29864946.
[64] Fukaya M, Sato Y, Kondo S, Adachi SI, Yoshizawa F, Sato Y. Quercetin enhances fatty acid β-oxidation by inducing lipophagy in AML12 hepatocytes. Heliyon 2021;7(6):e07324. doi:10.1016/j.heliyon.2021.e07324, PMID:34195429.
[65] Wong SK, Chin KY, Ima-Nirwana S. Quercetin as an agent for protecting the bone: a review of the current evidence. Int J Mol Sci 2020;21(17):6448. doi:10.3390/ijms21176448, PMID:32899435.
[66] Yamaguchi M, Weitzmann MN. Quercetin, a potent suppressor of NF-κB and Smad activation in osteoblasts. Int J Mol Med 2011;28(4):521–525. doi:10.3892/ijmm.2011.749, PMID:21769418.
[67] Wong RW, Rabie AB. Effect of quercetin on bone formation. J Orthop Res 2008;26(8):1061–1066. doi:10.1002/jor.20638, PMID:18383168.
[68] Ji LL, Sheng YC, Zheng ZY, Shi L, Wang ZT. The involvement of p62-Keap1-Nrf2 antioxidative signaling pathway and JNK in the protection of natural flavonoid quercetin against hepatotoxicity. Free Radic Biol Med 2015;85:12–23. doi:10.1016/j.freeradbiomed.2015.03.035, PMID:25881548.
[69] Pang XG, Cong Y, Bao NR, Li YG, Zhao JN. Quercetin stimulates bone marrow mesenchymal stem cell differentiation through an estrogen receptor-mediated pathway. Biomed Res Int 2018;2018:4178021. doi:10.1155/2018/4178021, PMID:29736392.
[70] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 2006;5(6):493–506. doi:10.1038/nrd2060, PMID:16732220.
[71] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, *et al*. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127(6):1109–1122. doi:10.1016/j.cell.2006.11.013, PMID:17112576.
[72] Lerin C, Rodgers JT, Kalume DE, Kim SH, Pandey A, Puigserver P. GCN5 acetyltransferase complex controls glucose metabolism through transcriptional repression of PGC-1alpha. Cell Metab 2006;3(6):429–438. doi:10.1016/j.cmet.2006.04.013, PMID:16753578.
[73] Koo SH, Montminy M. In vino veritas: a tale of two sirt1s? Cell 2006;127(6):1091–1093. doi:10.1016/j.cell.2006.11.034, PMID:17174885.
[74] Lv YJ, Yang Y, Sui BD, Hu CH, Zhao P, Liao L, *et al*. Resveratrol counteracts bone loss via mitofilin-mediated osteogenic improvement of mesenchymal stem cells in senescence-accelerated mice. Theranostics 2018;8(9):2387–2406. doi:10.7150/thno.23620, PMID:29721087.
[75] De Paepe B, Vandemeulebroecke K, Smet J, Vanlander A, Seneca S, Lissens W, *et al*. Effect of resveratrol on cultured skin fibroblasts from patients with oxidative phosphorylation defects. Phytother Res 2014;28(2):312–316. doi:10.1002/ptr.4988, PMID:23620374.
[76] Moon DK, Kim BG, Lee AR, In Choe Y, Khan I, Moon KM, *et al*. Resveratrol can enhance osteogenic differentiation and mitochondrial biogenesis from human periosteum-derived mesenchymal stem cells. J Orthop Surg Res 2020;15(1):203. doi:10.1186/s13018-020-01684-9, PMID:32493422.
[77] Feng YL, Jiang XT, Ma FF, Han J, Tang XL. Resveratrol prevents osteoporosis by upregulating FoxO1 transcriptional activity. Int J Mol Med 2018;41(1):202–212. doi:10.3892/ijmm.2017.3208, PMID:29115382.
[78] Tian Y, Song W, Li D, Cai L, Zhao Y. Resveratrol as a natural regulator of autophagy for prevention and treatment of cancer. Onco Targets Ther 2019;12:8601–8609. doi:10.2147/OTT.S213043, PMID:31802896.
[79] Asis M, Hemmati N, Moradi S, Nagulapalli Venkata KC, Mohammadi E, Farzaei MH, *et al*. Effects of resveratrol supplementation on bone biomarkers: a systematic review and meta-analysis. Ann N Y Acad Sci 2019;1457(1):92–103. doi:10.1111/nyas.14226, PMID:31490554.
[80] Zheng J, Ramirez VD. Rapid inhibition of rat brain mitochondrial proton F0F1-ATPase activity by estrogens: comparison with Na+, K+ -ATPase of porcine cortex. Eur J Pharmacol 1999;368(1):95–102. doi:10.1016/s0014-2999(99)00012-6, PMID:10096774.
[81] Rodríguez-Enríquez S, Pacheco-Velázquez SC, Marín-Hernández Á, Gallardo-Pérez JC, Robledo-Cadena DX, Hernández-Reséndiz I, *et al*. Resveratrol inhibits cancer cell proliferation by impairing oxidative phosphorylation and inducing oxidative stress. Toxicol Appl Pharmacol 2019;370:65–77. doi:10.1016/j.taap.2019.03.008, PMID:30878505.
[82] Olivares-Marin IK, González-Hernández JC, Madrigal-Perez LA. Resveratrol cytotoxicity is energy-dependent. J Food Biochem 2019;43(9):e13008. doi:10.1111/jfbc.13008, PMID:31385323.
[83] Lim HW, Lim HY, Wong KP. Uncoupling of oxidative phosphorylation by curcumin: implication of its cellular mechanism of action. Biochem Biophys Res Commun 2009;389(1):187–192. doi:10.1016/j.bbrc.2009.08.121, PMID:19715674.
[84] Sekiya M, Chiba E, Satoh M, Yamakoshi H, Iwabuchi Y, Futai M, *et al*. Strong inhibitory effects of curcumin and its demethoxy analog on Escherichia coli ATP synthase F1 sector. Int J Biol Macromol 2014;70:241–245. doi:10.1016/j.ijbiomac.2014.06.055, PMID:25010476.
[85] Dai P, Mao Y, Sun X, Li X, Muhammad I, Gu W, *et al*. Attenuation of oxidative stress-induced osteoblast apoptosis by curcumin is associated with preservation of mitochondrial functions and increased Akt-GSK3β signaling. Cell Physiol Biochem 2017;41(2):661–677. doi:10.1159/000457945, PMID:28291961.
[86] Li H, Yue L, Xu H, Li N, Li J, Zhang Z, *et al*. Curcumin suppresses osteogenesis by inducing miR-126a-3p and subsequently suppressing the WNT/LRP6 pathway. Aging (Albany NY) 2019;11(17):6983–6998. doi:10.18632/aging.102232, PMID:31480018.
[87] Tan L, Cao Z, Chen H, Xie Y, Yu L, Fu C, *et al*. Curcumin reduces apoptosis and promotes osteogenesis of human periodontal ligament stem cells under oxidative stress in vitro and in vivo. Life Sci 2021;270:119125. doi:10.1016/j.lfs.2021.119125, PMID:33513394.
[88] Borcherding N, Jia W, Giwa R, Field RL, Moley JR, Kopecky BJ, *et al*. Dietary lipids inhibit mitochondria transfer to macrophages to divert adipocyte-derived mitochondria into the blood. Cell Metab 2022;34(10):1499–1513.e8. doi:10.1016/j.cmet.2022.08.010, PMID:36070756.
[89] Brestoff JR, Wilen CB, Moley JR, Li Y, Zou W, Malvin NP, *et al*. Intercellular mitochondria transfer to macrophages regulates white adipose tissue homeostasis and is impaired in obesity. Cell Metab 2021;33(2):270–282.e8. doi:10.1016/j.cmet.2020.11.008, PMID:33278339.