Metabolism and Bone Diseases

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Bone, a highly mineralized organ that serves as a skeleton of the body, is continuously depositing and resorbing bone matrix to maintain homeostasis. This highly coordinated event is regulated throughout life by bone cells such as osteoblasts, osteoclasts, and osteocytes, and requires synchronized activities from different metabolic pathways. The dysregulation of these metabolic pathways leads to bone disorders.

Keywords: Bone Development ; Metabolism ; Osteoblasts ; Bone Diseases ; Osteoclasts ; Bone homeostasis ; Bone metabolism

1. Introduction

Bone (re)modeling is responsible for the growth and repair/regeneration of the bony structures by maintaining a balance between bone matrix deposition and resorption during development and homeostasis [1]. Osteoblasts and osteoclasts are the cells responsible for bone deposition/mineralization and resorption, respectively. The functions of bones include acting as a locomotorium coordinated with muscles, tendons, and joints, the support of posture, the protection of the brain and other organs, the storage of minerals, and hematopoiesis in the bone marrow. Because various metabolic networks act in bone tissues, the metabolic status of bone cells affects bone formation and homeostasis via multiple biological reactions. The metabolism comprises complex physical and biochemical processes that allow organisms to generate, maintain, and regenerate their structures as well as respond to environmental cues [2][3]. In recent years, it has been reported that an imbalance of cellular and systemic metabolism is associated with various bone diseases and developmental defects. For example, type I and type II diabetes mellitus, obesity, and dyslipidemia are associated with increased risk of osteoporosis and a delay in bone healing [4][5][6].

2. Cholesterol Metabolism

Cholesterol is crucial as a source of numerous biomolecules, including bile acids, steroid hormones, and oxysterols, and is a vital component of cellular membranes; therefore, dysregulation of cholesterol synthesis leads to cellular dysfunction and results in disease. Its synthesis is regulated by more than 30 biochemical reactions, which are catalyzed by 15 different enzymes [7]. Either upregulation or downregulation of intracellular cholesterol synthesis compromises osteogenesis and chondrogenesis. In addition, there is a positive feedback loop for the expression of genes regulating the sterol metabolic pathway (e.g., *Cyp11a1*, *Cyp39a1*, *Cyp51*, *Lss*, *Dhcr7*), which is turn is regulated by *Runx2*, a key transcription factor associated with osteoblast differentiation. Thus, cholesterol synthesis is directly linked to osteogenic differentiation.

3. Fatty Acid Metabolism

Fatty acid metabolism involves an enzymatic cascade that degrades fatty acids into bioactive substrates and synthesizes straight-chain fatty acids to be stored as triglycerides in adipose tissues. The catabolic pathway starts with the release of free fatty acids from glycerol, consumed in the diet or derived from triglycerides in adipose tissue through lipolysis, followed by transport to peripheral cells and the entire body, according to its needs. Mice with a deficiency of palmitoyl-protein thioesterase 1 (*Ppt1*; *Ppt1*$^{-/-}$ mice), acyl-CoA synthetase bubblegum family member 2 (*Acsbg2*; *Acsbg2*$^{-/-}$ mice), carnitine palmitoyltransferase 2 (*Cpt2*; *Cpt*$^{+/-}$ mice), *Cd36*, and *Gpr40* display various defects in bone formation and/or homeostasis [8][9][10].

4. Glycolysis and Gluconeogenesis

Glycogen, a long, branched polymer of glucose residues, is a readily mobilized storage form of glucose that is mainly present in the liver and skeletal muscles; when the body needs energy, glycogen is broken down into glucose. Excessive glucose addition inhibits cell proliferation and osteogenic differentiation in a dose-dependent manner in human bone marrow mesenchymal stem cells and osteoblast cell lines. Glucose is uptaken through glucose transporters SLC2A1-4 (solute carrier family 2, member 1-4; a.k.a. GLUT1-4). Among them, SLC2A1 is expressed in osteoclasts, osteoblasts, and hypertrophic chondrocytes. The deletion of *Slc2a1* in these cells causes osteoclastogenesis deficiency [11], bone mineralization defects [12][13], and growth plate disorganization [14]. Thus, glucose uptake and the consequent aerobic glycolysis play crucial roles in bone formation and remodeling. Gluconeogenesis is the opposite pathway of glycolysis, where glucose-6-phosphatase (G6PC) catalyzes D-glucose-6- phosphate to D-glucose. Mice with deficient for *G6pc* exhibit cartilage dysplasia and delaying ossification [15] through suppression of the growth hormone-mediated insulin-like growth factor 1 pathway [16][17].

5. Glycogenolysis and Glycogenesis

Glycogenolysis initiates with the breakdown of uptaken glycogen into glucose-1- phosphate (G1P) by amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase (AGL), and glycogen phosphorylase [18]. AGL has two enzymatic activities—glucosyltransferase and glucosidase—and breaks down (debranches) glycogen into G1P, together with glycogen phosphorylase [19]. In humans, mutations in *AGL* are associated with glycogen storage disease type III (GSD-III), an autosomal recessive metabolic disorder caused by the accumulation of glycogen in the liver and skeletal muscles, resulting in organ dysfunction. GSD-III is further characterized into two subtypes: 1) GSD-IIIa, which affects only the liver; and 2) GSD-IIIb, which involves both the liver and skeletal muscles. Unlike patients with GSD-IIIa, patients with GSD-IIIb exhibit low bone mineral density [20][21]. In addition, *Agl* knockout mice ($Agl^{-/-}$ mice) exhibit kyphosis [22].

6. TCA Cycle

The TCA cycle (a.k.a. the citric acid cycle or the Krebs cycle) is an essential metabolic cycle present in the mitochondria of all aerobic organisms. Through glycolysis, pyruvic acid and fatty acyl-CoA are converted into acetyl-CoA, with subsequent synthesis of guanosine triphosphate (GTP)/ATP, NADH, and amino acids. Studies in mice have shown that a deficiency of *Idh1* (isocitrate dehydrogenase 1, cytosolic) and *Sdhc* (succinate dehydrogenase complex subunit C) in the TCA cycle pathway induces defects in bone formation and/or homeostasis. In addition, exogenous supplementation of D-2-hydroxyglutarate inhibits osteoblast differentiation and bone formation [23].

7. Phospholipid Metabolism

Phospholipids are synthesized in the endoplasmic reticulum and include a hydrophobic fatty acid tail and a hydrophilic head that form the lipid bilayer in the eukaryotic plasma membrane. The metabolites of phospholipids serve as second messengers in signal transduction [e.g., phosphatidic acid (PA), phosphatidylinositol-(4,5)-bisphosphate (PIP2), diacylglycerol (DAG), and prostaglandins]. Phosphatidylserine receptors such as TIM4, BAI1, and STAB2 are expressed in mature osteoclasts; blocking these receptors or reducing extracellular phosphatidylserine inhibits fusion of pre-osteoclasts without affecting osteoclastogenesis [24][25]. In the phospholipid metabolic pathway, mice with a deficiency of either choline O-acetyltransferase (*Chat*), choline kinase beta (*Chkb*), phosphoethanolamine/phosphocholine phosphatase (*Phospho1*), phospholipase A2 group VI (*Pla2g6*), membrane-bound O-acyltransferase domain containing 7 (*Mboat7*), 1-acylglycerol-3-phosphate O-acyltransferase 3 (*Agpat3*), or 1-acylglycerol-3-phosphate O-acyltransferase 4 (*Agpat4*) exhibit defects in bone formation and/or homeostasis [26][27][28][29][30][31][32].

8. Summary

There are a variety of metabolic pathways that may affect bone development and homeostasis. While there is significant evidence showing a possible link between bone diseases and metabolic disorders, the specific players and molecular interactions in these metabolic networks remain to be determined.

References

1. Raggatt LJ, Partridge NC (2010) Cellular and molecular mechanisms of bone remodeling. J Biol Chem 285: 25103-25108.

2. Schilling CH, Letscher D, Palsson BO (2000) Theory for the systemic definition of metabolic pathways and their use in i nterpreting metabolic function from a pathway-oriented perspective. J Theor Biol 203: 229-248.

3. DeBerardinis RJ, Thompson CB (2012) Cellular metabolism and disease: what do metabolic outliers teach us? Cell 14 8: 1132-1144.

4. Alekos NS, Moorer MC, Riddle RC (2020) Dual Effects of Lipid Metabolism on Osteoblast Function. Front Endocrinol (L ausanne) 11: 578194.

5. Shah VN, Harrall KK, Shah CS, Gallo TL, Joshee P, et al. (2017) Bone mineral density at femoral neck and lumbar spin e in adults with type 1 diabetes: a meta-analysis and review of the literature. Osteoporos Int 28: 2601-2610.

6. Vestergaard P (2007) Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabete s--a meta-analysis. Osteoporos Int 18: 427-444.

7. Dietschy JM, Turley SD, Spady DK (1993) Role of liver in the maintenance of cholesterol and low density lipoprotein ho meostasis in different animal species, including humans. J Lipid Res 34: 1637-1659.

8. Gupta P, Soyombo AA, Atashband A, Wisniewski KE, Shelton JM, et al. (2001) Disruption of PPT1 or PPT2 causes neu ronal ceroid lipofuscinosis in knockout mice. Proc Natl Acad Sci U S A 98: 13566-13571.

9. Wauquier F, Philippe C, Leotoing L, Mercier S, Davicco MJ, et al. (2013) The free fatty acid receptor G protein-coupled receptor 40 (GPR40) protects from bone loss through inhibition of osteoclast differentiation. J Biol Chem 288: 6542-655 1.

10. Kevorkova O, Martineau C, Martin-Falstrault L, Sanchez-Dardon J, Brissette L, et al. (2013) Low-bone-mass phenotype of deficient mice for the cluster of differentiation 36 (CD36). PLoS One 8: e77701.

11. Li B, Lee WC, Song C, Ye L, Abel ED, et al. (2020) Both aerobic glycolysis and mitochondrial respiration are required fo r osteoclast differentiation. FASEB J.

12. Wei J, Shimazu J, Makinistoglu MP, Maurizi A, Kajimura D, et al. (2015) Glucose Uptake and Runx2 Synergize to Orch estrate Osteoblast Differentiation and Bone Formation. Cell 161: 1576-1591.

13. Chen H, Ji X, Lee WC, Shi Y, Li B, et al. (2019) Increased glycolysis mediates Wnt7b-induced bone formation. FASEB J 33: 7810-7821.

14. Lee SY, Abel ED, Long F (2018) Glucose metabolism induced by Bmp signaling is essential for murine skeletal develop ment. Nat Commun 9: 4831.

15. Lei KJ, Chen H, Pan CJ, Ward JM, Mosinger B, Jr., et al. (1996) Glucose-6-phosphatase dependent substrate transport in the glycogen storage disease type-1a mouse. Nat Genet 13: 203-209.

16. Brooks ED, Little D, Arumugam R, Sun B, Curtis S, et al. (2013) Pathogenesis of growth failure and partial reversal with gene therapy in murine and canine Glycogen Storage Disease type Ia. Mol Genet Metab 109: 161-170.

17. Dixit M, Poudel SB, Yakar S (2020) Effects of GH/IGF axis on bone and cartilage. Mol Cell Endocrinol 519: 111052.

18. Adeva-Andany MM, Gonzalez-Lucan M, Donapetry-Garcia C, Fernandez-Fernandez C, Ameneiros-Rodriguez E (2016) Glycogen metabolism in humans. BBA Clin 5: 85-100.

19. Zhai L, Feng L, Xia L, Yin H, Xiang S (2016) Crystal structure of glycogen debranching enzyme and insights into its cat alysis and disease-causing mutations. Nat Commun 7: 11229.

20. Melis D, Rossi A, Pivonello R, Del Puente A, Pivonello C, et al. (2016) Reduced bone mineral density in glycogen stora ge disease type III: evidence for a possible connection between metabolic imbalance and bone homeostasis. Bone 86: 79-85.

21. Mundy HR, Williams JE, Lee PJ, Fewtrell MS (2008) Reduction in bone mineral density in glycogenosis type III may be due to a mixed muscle and bone deficit. J Inherit Metab Dis 31: 418-423.

22. Pagliarani S, Lucchiari S, Ulzi G, Violano R, Ripolone M, et al. (2014) Glycogen storage disease type III: A novel Agl kn ockout mouse model. Biochim Biophys Acta 1842: 2318-2328.

23. Suijker J, Baelde HJ, Roelofs H, Cleton-Jansen AM, Bovee JV (2015) The oncometabolite D-2-hydroxyglutarate induce d by mutant IDH1 or -2 blocks osteoblast differentiation in vitro and in vivo. Oncotarget 6: 14832-14842.

24. Kang JH, Ko HM, Han GD, Lee SY, Moon JS, et al. (2020) Dual role of phosphatidylserine and its receptors in osteocla stogenesis. Cell Death Dis 11: 497.

25. Verma SK, Leikina E, Melikov K, Gebert C, Kram V, et al. (2018) Cell-surface phosphatidylserine regulates osteoclast p recursor fusion. J Biol Chem 293: 254-270.

26. Misgeld T, Burgess RW, Lewis RM, Cunningham JM, Lichtman JW, et al. (2002) Roles of neurotransmitter in synapse f ormation: development of neuromuscular junctions lacking choline acetyltransferase. Neuron 36: 635-648.

27. Kular J, Tickner JC, Pavlos NJ, Viola HM, Abel T, et al. (2015) Choline kinase beta mutant mice exhibit reduced phosph ocholine, elevated osteoclast activity, and low bone mass. J Biol Chem 290: 1729-1742.
28. Yadav MC, Simao AM, Narisawa S, Huesa C, McKee MD, et al. (2011) Loss of skeletal mineralization by the simultane ous ablation of PHOSPHO1 and alkaline phosphatase function: a unified model of the mechanisms of initiation of skele tal calcification. J Bone Miner Res 26: 286-297.
29. Anderson KE, Kielkowska A, Durrant TN, Juvin V, Clark J, et al. (2013) Lysophosphatidylinositol-acyltransferase-1 (LPI AT1) is required to maintain physiological levels of PtdIns and PtdInsP(2) in the mouse. PLoS One 8: e58425.
30. Li Z, Wu G, Sher RB, Khavandgar Z, Hermansson M, et al. (2014) Choline kinase beta is required for normal endochon dral bone formation. Biochim Biophys Acta 1840: 2112-2122.
31. Houston B, Stewart AJ, Farquharson C (2004) PHOSPHO1-A novel phosphatase specifically expressed at sites of min eralisation in bone and cartilage. Bone 34: 629-637.
32. Wu X, Ma Y, Su N, Shen J, Zhang H, et al. (2019) Lysophosphatidic acid: Its role in bone cell biology and potential for u se in bone regeneration. Prostaglandins Other Lipid Mediat 143: 106335.
