Lipid Metabolism

Subjects: Cell Biology
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Bone is a dynamic tissue and is constantly being remodeled by bone cells. Metabolic reprogramming plays a critical role in the activation of these bone cells and skeletal metabolism, which fulfills the energy demand for bone remodeling. Among various metabolic pathways, the importance of lipid metabolism in bone cells has long been appreciated. More recent studies also establish the link between bone loss and lipid-altering conditions—such as atherosclerotic vascular disease, hyperlipidemia, and obesity—and uncover the detrimental effect of fat accumulation on skeletal homeostasis and increased risk of fracture. Targeting lipid metabolism with statin, a lipid-lowering drug, has been shown to improve bone density and quality in metabolic bone diseases. However, the molecular mechanisms of lipid-mediated regulation in osteoclasts are not completely understood. Thus, a better understanding of lipid metabolism in osteoclasts can be used to harness bone cell activity to treat pathological bone disorders.

Keywords: Lipid Metabolism ; bone ; osteoclast

1. Introduction

Lipids are composed of several species such as fatty acids, cholesterol, triglycerides (TGs), and phospholipids. The majority of lipids in bone are present within bone marrow, and a minority of lipids are in mineralized bone tissue [1]. Human bone marrow contains 28–84% of neutral lipids—including TGs, cholesterol, and free fatty acids—and less than 3% of phospholipids [2]. Lipid metabolic pathways process lipids and provide lipids to bone cells. They generate energy and are obtained by de novo lipid synthesis and the ingestion of dietary lipids. The dietary lipids are processed, and TGs and cholesterol are packaged into chylomicrons in intestinal epithelial cells. These complexes enter the lymphatic system and then into circulation; they subsequently acquire different apolipoproteins (Apo) including ApoB, ApoC-II, ApoC-III, and ApoE during the exogenous lipoprotein pathway. TGs and cholesterol are insoluble and are transported as a complex with other proteins. The TGs carried in chylomicrons are hydrolyzed in muscle and adipose tissue by lipoprotein lipase (LPL), which releases free fatty acids for cellular uptake and chylomicron remnants that are later taken up by the liver. Cholesterol is esterified into cholesteryl esters, packaged into lipid carrying lipoproteins, which are defined by their density. Packages of very-low-density lipoproteins (VLDLs) with TGs and cholesterol are synthesized in the liver and hydrolyzed in muscle and adipose tissue by LPL and VLDL remnants (intermediate lipoproteins, IDLs); free fatty acids are released for cellular uptake. VLDL remnants are further hydrolyzed by hepatic lipases to form low density lipoproteins (LDLs). LDLs bind to LDL receptors (LDLR) and are then taken up by tissues and cells. This endogenous lipoprotein pathway allows free cholesterol to be released into the numerous tissues and cells. Reverse cholesterol transport returns cholesterol to the liver and plays a key role in lipid homeostasis [3]. A cellular ABC transporter (ABCA1) mediates the first step of reverse cholesterol transport. Nascent high-density lipoproteins (HDLs) form mature HDL by acquiring cholesterol and phospholipids. Cholesterol efflux from cells to HDL is mediated by ABCA1, ATP binding cassette subfamily G (ABCG1), scavenger receptor B1 (SR-B1), or passive diffusion [4]. The HDL then transports the cholesterol to the liver via hepatic SR-B1 facilitated diffusion or by transferring the cholesterol to VLDL or LDL. Accumulation of cellular cholesterol leads to activation of several nuclear receptors, including liver X receptor α and β (LXRα and LXRβ), the retinoid X receptor (RXR), and the peroxisome proliferator-activated receptors (PPARα, PPARβ/δ, and PPARγ) [5]. These transcription factors also regulate the expression of cholesterol efflux transporters, including ABCA1 and ABCG1.

2. Regulation of Osteoclast Differentiation and Activity by Lipid Metabolism

Controlling cellular and systemic lipid levels is essential for physiological bone homeostasis. Recent studies provide evidence that metabolic reprogramming is an important player for osteoclast differentiation and function [6]. Metabolic alteration has been identified in many bone diseases, including osteoporosis, and the close correlation between dysregulated lipid metabolism and bone has been increasingly appreciated. Accordingly, metabolism can be an attractive

target of treatments for pathological bone resorption. Moreover, lipids can impact the phenotype of osteoclasts and osteoblasts in pathological conditions. While the role of lipids on osteoblasts and their bone formation activity are relatively well-studied, the molecular mechanisms of how lipid metabolism regulates osteoclast differentiation and activity are not yet fully elucidated. Thus, it is important to understand lipid metabolism in the context of osteoclastic bone resorption in dyslipidemic conditions. To understand the role of lipid metabolism in osteoclasts, several factors need to be considered. First, dyslipidemia can not only cause an increased lipid load in osteoclasts but also can indirectly affect osteoclasts by stimulating other cell types or by inducing inflammatory mediators. Thus, the role of crosstalk between osteoclasts and other cells in bone metabolism under dyslipidemic conditions needs to be further characterized. In addition to importing lipids from outside of cells, de novo lipid synthesis is active in osteoclasts. However, the differential effects, between exogenous lipids and endogenous lipids that are synthesized in osteoclasts, on osteoclast differentiation and function remain unclear. It is important to identify how the regulation of de novo lipid synthesis impacts osteoclast differentiation and function using in vivo mouse models, including mice that are deficient or overexpress key regulators of lipid metabolism, or fat-modifying-diet-fed mice (high-fat-diet-fed model, or low-fat/fat-free-diet-fed model). Thirdly, genetic variation in components of the transcriptional program of SREBPs such as LDLR, PCSK9, and HMGCR has been associated with lipid traits and a craniofacial phenotype [7][8]. It is important to identify whether the genetic variation in the genes related to lipid reprogramming also controls bone and the activity of osteoclasts. Lastly, lipid metabolism is closely linked to the different metabolic pathways, including glucose, glutamine, and acetate metabolism [6]. How the metabolic circuit between lipid metabolism and different metabolic pathways affects osteoclasts needs to be determined. Moreover, various metabolism-targeting drugs have been developed, and Enasidenib has been FDA-approved for treating any cancer [9]. However, the efficacy of these metabolic drugs on bone loss has not been fully evaluated yet. A better understanding of how lipid metabolism rewinds cellular energy to fulfill the energy demand for osteoclast differentiation and activity—especially in pathological conditions—will provide a new therapeutic insight into pathological bone loss.

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