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Chapter 3

Fatty Acids on Osteoclastogenesis

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Abstract

Excessive bone resorption is a hallmark on the onset and development of bone diseases, including osteoporosis, periodontitis, and rheumatoid arthritis. Osteoclasts are bone-resorbing multinucleated cells that differentiate from hematopoietic progenitors of the myeloid lineage. The regulation of this differentiation process is considered an effective therapeutic intervention to the treatment of pathological bone loss. Dietary fatty acids (FAs), transported in the form of postprandial triglyceride-rich lipoproteins, have been linked with inflammation and oxidative stress associated to the overactivation of circulating leukocytes. Monocyte differentiation by soluble cytokines is known to up-regulate osteoclast maturation via increased expression levels of receptor activator for nuclear factor-κB ligand relative to osteoprotegerin. This review summarizes the effects of dietary omega-3 long-chain polyunsaturated fatty acids, monounsaturated fatty acids, and saturated fatty acids on plasticity during osteoclast formation and function.

Keywords: bone marrow, bone metabolism, fatty acids, osteoclasts, osteoporosis

1. Introduction

The links among bone and nutrition focus on considerable public health and research interests. Over the past 20 years, the fact that there is an inverse relationship between bone mass and marrow adiposity, observed under physiological and pathological conditions, has led to increased recent interest in bone lipids [1, 2]. Under different pathologies, for example, osteoporosis, an increase of bone marrow fat that was associated with osteoclast (OC) overabundance and a low bone mass [3]. Cholesterol, phospholipids, and fatty acids (FAs) either free or in the form of triglycerides, have been demonstrated to act on bone metabolism and

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bone cell development and functions. Thus, they can be regarded as regulatory molecules important in bone health. A growing body of evidence, including the recognition that specific FA receptors are expressed in bone-related cells, suggests that FAs both circulating and inside bone marrow, could be an active determinant role as messengers on metabolic activity and remodeling rate of bone [4]. This review will provide a current overview on the effects of FAs on OC maturation and function.

2. Osteoclast biology

Bone is a specialized, hard tissue consisting of a soft part (the bone marrow), and the mineralized osseous tissue itself. To ensure bone integrity during childhood and adulthood, bone undergoes a continuous remodeling process that consists of multiple cycles of bone digestion and rebuilding steps [5]. Two cell types mainly determine this remodeling process, the bone-forming osteoblasts (OBs) and the bone-resorbing OCs. A dysregulation of the bone remodeling balance is linked with several skeletal disorders such as osteopetrosis and osteoporosis. Osteopetrosis is characterized by an increase in bone mass due to a lower OC number or activity, whereas osteoporosis is characterized by the loss of bone mass due to an elevated OC activity [6]. Moreover, bone contains interconnected and embedded OBs, called osteocytes, which might respond to the mechanical pressure applied onto bone [7].

During initial bone formation, OBs produce organic bone matrix and promote its mineralization. At the same time, OBs indirectly affect bone resorption by the expression of ligands, including the receptor activator of NF-κB ligand (RANKL), which is important for OC differentiation [5]. In contact with bone, OCs change their plasma membrane to form different domains, including the ruffled border that faces the bone surface. This specialized cell membrane is provided with many lysosomal integral membrane proteins, mainly the V-type H^+-ATPase, ensuring the acidification of the resorption environment that is required to dissolve the bone inorganic matrix. OCs also release lysosomal hydrolases such as cathepsin K to digest the organic bone matrix [8]. Furthermore, the ruffled border is composed by actin-rich podosomes that ensure the attachment of OCs onto the bone. Bone degradation products are endocytosed through the ruffled border, transcytosed, and secreted into the extracellular space [9]. For efficient resorption, OCs undergo several cycles of adhesion, resorption, and migration along bone surfaces.

Bone biology has greatly benefited from studies using animal models. For example, silencing Src tyrosine kinase, receptor–activator of NF-κB (RANK), tartrate-resistant acid phosphatase (TRAP), and cathepsin K in mice result in an osteopetrotic mouse model due to the lack of OC precursor differentiation or a lack of mature OC activity [10, 11]. However, these mutant animal models do not provide an integrated view on the function of a particular gene on OC differentiation and function and its modulation by certain cytokines, nutrients, and drugs, which could provide a better understanding of their effects on OC biology.

3. Osteoclastogenesis in the bone marrow

The bone-resorbing OCs are originated from the differentiation of hematopoietic mononucleated precursors and their subsequent fusion to form multinucleated mature OCs (**Figure 1**). Physiologically, osteoclastogenesis requires two essential hematopoietic factors in the bone marrow: macrophage colony-stimulating factor (M-CSF/CSF-1) and RANKL. M-CSF/CSF-1 is a survival and proliferation factor that induces RANK expression in OC precursor cells [12]. The role of M-CSF/CSF-1 in osteoclastogenesis is highlighted by the osteopetrotic phenotype M-CSF$^{-/-}$ mouse model, in which mutant animals had a deficiency in OCs and circulating monocytes [13]. The second key factor in osteoclastogenesis, RANKL, is a membrane-residing protein found on OBs and their precursors, and is recognized by its cognate receptor RANK expressed in the bone marrow macrophage/OC lineage, promoting their differentiation into OCs [14]. In mice, genetic experiments have shown the importance of RANK/RANKL axis for osteoclastogenesis, as targeted inhibition of RANK or RANKL gene results in a complete absence of OC maturation and osteopetrosis [15]. In humans *in vitro* studies, these two factors are able to generate OCs from circulating monocytes, dendritic cells, and bone marrow–derived macrophages [16]. In addition to RANKL, osteoprotegerin (OPG) is secreted by OBs, which acts as a soluble RANKL decoy receptor; therefore, OPG negatively regulates RANKL activity (**Figure 2**) [17]. From these observations, the RANKL/OPG ratio indicates the rate of osteoclastic bone resorption [18].

The binding of RANK receptor to RANKL triggers signaling cascades that terminally differentiate the hematopoietic precursor cells into OCs. The initial step in RANKL signaling is the binding of RANK receptor to the cytoplasmatic tumor necrosis factor receptor-associated factors (TRAF), mainly to TRAF6 [19]. The Src tyrosine kinase binds to TRAF6, regulating the aspects of OC function such as cytoskeletal reorganization. In addition, RANKL signaling leads to the OC specific gene expression such as β_3 integrins, TRAP, cathepsin K, and calcitonin receptor. It also leads to the morphological conversion of mononucleated cells into large multinucleated cells that are able to efficiently resorb large bone surface areas.

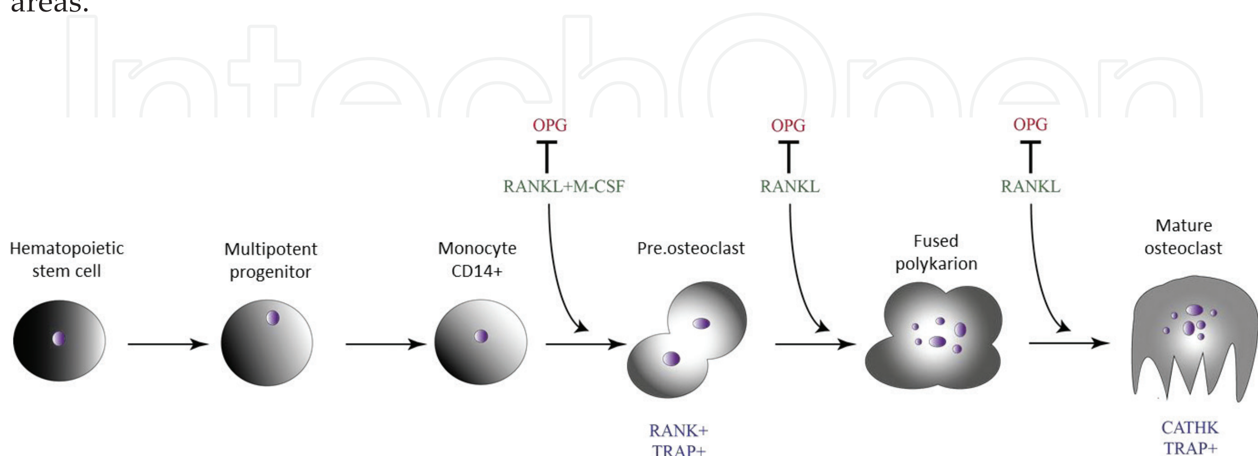

Figure 1. Diagram illustrating the differentiation of hematopoietic mononucleated precursors and their subsequent fusion to form multinucleated mature osteoclasts.

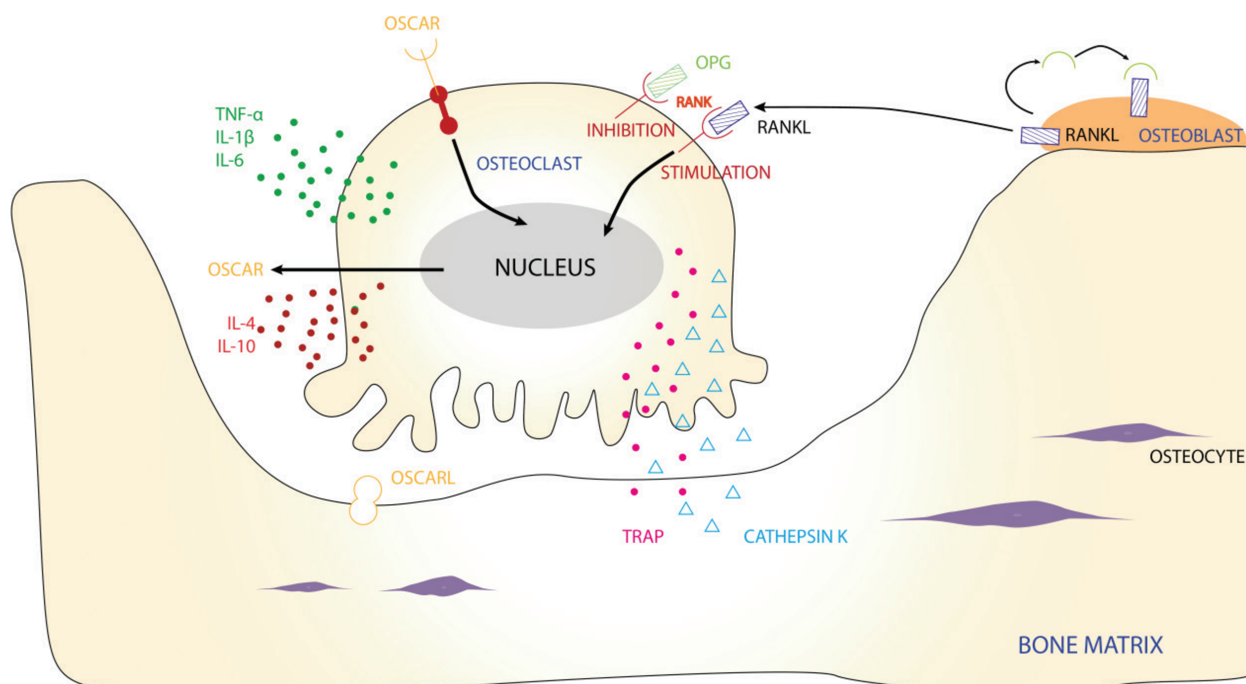

Figure 2. Key factors affecting osteoblast and osteoclast survival and functions.

4. Fatty acids in the bone marrow

FAs are carboxylic acids and often contain a long, unbranched aliphatic chain. FAs are categorized as saturated (SFAs), monounsaturated (MUFAs), and polyunsaturated (PUFAs) based on their structural and chemical properties. SFAs do not contain any double bonds or other functional groups along the chain, which is fully saturated with hydrogen atoms. The principal dietary SFAs are palmitic acid (16:0) and stearic acid (18:0), which are composed of 16 and 18 carbon atoms, respectively. MUFAs contain one pair of carbon atoms linked by a *cis* double bond. Oleic acid (18:1n−9), which contains 18 carbon atoms with a double bond at the 9th carbon from the methyl end of the FA molecule, is the major dietary MUFA and represents 55–83% of the total FAs in virgin olive oil [20]. Carbon chains containing 2 or more *cis* double bonds, with the first double bond located between either the 3rd and 4th or the 6th and 7th carbon atoms from the methyl end of the FA molecule, that belong to the n−3 or n−6, respectively, PUFA families. These families cannot be synthesized by the human body (double bonds can be introduced into all positions of the FA chain with the exception of the n−3 and n−6 positions); and therefore, must be obtained from the diet as α-linolenic acid (18:3n−3) and linoleic acid (18:2n−6) or their long-chain PUFA derivatives. Of these FAs, eicosapentaenoic acid (EPA, 20:5n−3), docosahexaenoic acid (DHA, 22:6n−3), dihomo-γ–linolenic acid (20:3n−6), and arachidonic acid (AA, 20:4n−6) are the most metabolically significant [21].

FA compositions of total lipids present in bone marrows change with the species studied. Thus, palmitic acid, stearic acid, and oleic acid are predominant in rats and cows [22], whereas palmitic acid, oleic acid, and linoleic acid are the main FAs in bone marrows of humans, dogs,

guinea pigs, and rabbits [23]. Bone FA profile usually reflects the FA composition of the diet. For example, when animals were fed diet supplemented with linoleic acid or α-linolenic acid, concentrations of these two FAs were higher in femoral cortical bone and marrow [24]. Recent animal and human intervention studies reported that dietary FAs affect bone health. In general, high intakes of long-chain omega-3 PUFAs rather than long-chain omega-6 PUFAs are beneficial for bone mass [25], whereas SFAs intake is harmful [26].

5. Direct action of exogenous fatty acids on bone cells

At the level of bone cell biology, *de novo* biosynthesized FAs or FAs taken up by cells are mostly incorporated into both phospholipids located in cell membranes and triglycerides in cytoplasmic lipid droplets. On the other hand, membrane FA composition has demonstrated to modulate intracellular signaling pathways and many cell functions such as membrane fluidity and permeability [20]. Thus, FAs may influence the bone formation/resorption balance by affecting the functionality of OBs and OCs.

In vitro studies have demonstrated that exogenous FAs supplemented to the OBs or OCs culture media can affect their survival and functions. Data indicate that SFAs, mainly palmitic and stearic acids, are pivotal for OBs by inducing both autophagy and apoptosis [27, 28]. PUFAs also alter OB proliferation and functions [29, 30], while oleic acid seems to be neutral in OBs [31].

Few studies, summarized in **Table 1**, have focused at exogenous FA effects on OCs and the data are partially contradictory, at least for SFAs. Indeed, SFAs, mostly myristic, palmitic, and stearic acids 16:0 were first reported to inhibit osteoclastogenesis [32], and recently, to enhance it by inhibiting apoptosis of mature OCs [33]. The actions of exogenous FAs on bone cells include their ability to modulate different signaling pathways that are involved in general cell growth, differentiation, inflammation, and apoptosis processes. FAs can also alter expression/activation of different nuclear transcription factors which play an important role in bone metabolism, such as nuclear factor κB (NF-κB, crucial for many bone cell processes and for OC activity), and peroxisome proliferator–activated receptor γ (PPARγ, role in bone-fat relationship) [35]. To start cell signaling, FAs play via protein sensors located either in cytosol (i.e., FA-binding proteins (FABPs) and PPARs) or at cell surface (i.e., specific receptors that belong to the family of G-protein–coupled receptors (GPCs)). These extracellular receptors are likely to play an important role in bone physiology since they are expressed at the surface of OBs and OCs [32]. As outlined in **Table 2**, there are currently six receptors known to be linked by FAs of different carbon chain length and degree of saturation. GPR120 has been reported to be expressed in OBs; however, these cells do not express GPR40, 41, or 43 [32]. In a review of the effects of exogenous FAs on osteoclast OC development at concentrations of 0.1–10 μg/ml, the most potent effects were observed in response to palmitic and stearic acids, implying that signaling through GPR120 mediates, at least in part, the direct osteoclastogenic actions of medium and long-chain SFAs [32].

On the other hand, limited evidence exists as to the actions of PUFAs on OC development. Two studies have reported inhibitory actions of linoleic acid on osteoclastogenesis in bone

FAs and concentration used [Reference]	Cell model	Effects on the studied markers	Main outcomes
4:0, 8:0, 12:0, 14:0, 16:0, 18:0, 18:1, 18:2n−6, 18:3n−3, 20:4n−6, 20:5n−3, and 22:6n−3 (0.3–115 μM) [32]	1,25-Dihydroxyvitamin D3-stimulated murine bone marrow–derived macrophages and RANKL-stimulated murine macrophage cell line RAW264.7	↓TRAP positive cells by SFAs and no clear-cut differences between n-3 and n-6 PUFAs	SFAs inhibit osteoclastogenesis, probably via receptors expressed at the surface of OCs
12:0 and 16:0 (20–100 μM) [33]	RANKL/M-CSF-stimulated murine bone marrow–derived macrophages	↓ Annexin V staining ↑ TRAP positive cells (SFAs) ↑ MIP-1α production (SFAs) ↑ NF-κB, TLR4, and MyD88 activation (SFAs) ↓TRAP positive cells (PUFAs)	SFAs enhance cell survival in mature OCs
18:2n−6 (1–100 μM) [34]	RANKL-stimulated murine macrophage cell line RAW264.7	↓TRAP positive cells ↓Bone resorption area	Linoleic acid inhibit OC differentiation, possibly by modulating the downstream molecules of RANKL signaling

Table 1. Effect of exogenous free fatty acids (FAs) on osteoclast functions and survival (Adapted from Ref. [4]).

Receptor	Ligand(s)	Sites of expression	Function
GPR40	C6–C22 FAs, saturated and unsaturated	Pancreatic islets Gut Brain Monocytes **Osteoclasts**	Glucose-stimulated insulin secretion
GPR41	C1–C6 FAs	Adipocytes Bone marrow Spleen Lymph node PBMCs **Osteoclasts**	Leptin production
GPR43	C1–C6 FAs	Adipocytes Colon PBMCs **Osteoclasts**	Adipogenesis lipolysis inhibition
GPR84	C9–C14 FAs	PBMCs Lung	Regulation of inflammatory response
GPR119	Lysophosphatidylcholine and oleoylethanolamide	L cells Pancreas	GLP-1 and insulin secretion
GPR120	C14–C18 Saturated and C16–C22 unsaturated	L cells **Osteoclasts** **Osteoblasts**	GLP-1 secretion

Boldface, the main bone cells (Osteoclasts and osteoblasts)

Table 2. Fatty acid (FA) receptors (Adapted from Ref. [36]).

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marrow cultures and RAW264.7 cells [32, 34]. A subsequent report found that DHA, but not EPA, substantially decreased OC development in RANKL-treated in bone marrow cultures and RAW264.7 cells [37, 38]. The mechanism(s) by which PUFAs modulate bone cell function are uncertain, but may include direct incorporation into cell membranes, with subsequent alteration of levels of intracellular prostanoids and eicosanoids [37].

6. Effect of postprandial triglyceride–rich lipoproteins on bone cells

The postprandial state, the period that comprises and follows a meal, plays an important, yet underappreciated role in the genesis of numerous pathological conditions. After fatty food consumption, dietary FAs are largely incorporated into nascent triglyceride-rich lipoproteins (TRLs), which are released from the small intestine into the blood. It has been previously shown that SFAs, MUFAs, and PUFAs have dissimilar postprandial effects on risk factors for chronic diseases [39], suggesting that short-term outcomes in response to dietary FA adjustment could be useful to finely tune fat consumption, even for preventing diet-related chronic diseases [40]. However, *in vivo* studies on markers of osteoclastogenesis during the postprandial state in humans or *in vitro* studies on interaction of human postprandial TRLs with monocyte-derived OCs were unknown. In fact, there are only a few labs studying the link between the postprandial state and osteoclastogenesis. One of them has demonstrated that serum obtained from healthy subjects following the consumption of a meal containing almonds may inhibit OC maturation and function in primary human OC precursor cells, providing direct evidence to support the association between regular almond consumption and a reduced risk of osteoporosis [41]. Inspired in these findings, our group demonstrated for the first time in 2016 that the RANKL/OPG ratio is postprandially modulated by the predominant FAs in dietary fats, being particularly increased after the ingestion of an SFA-enriched meal when compared to the ingestion of MUFA-enriched meals [42]. *In vitro*, we also observed an increase of OC marker gene expression and a decrease of OPG gene expression in human monocyte-derived OCs in response to postprandial TRL-SFAs, further supporting the notion that dietary saturated fats may promote osteoclastogenesis through pathways involving the metabolism of intestinal lipoproteins. Importantly, TRL-MUFAs and TRL-PUFAs did not alter these osteoclastogenic markers or OPG, suggesting that the substitution of dietary saturated fats by monounsaturated fats (in combination with omega-3 PUFAs) may be useful to prevent excessive osteoclastogenesis associated to postprandial events.

In spite of the increasing evidence of the pivotal role of FAs on bone physiology as biological modulators of osteoclastogenesis, nutritional interventions might be a reliable therapeutic target to induce positive effects on skeletal health. Further, careful preclinical and clinical studies are likely to shed additional light on this important area of bone biology.

Conflicts of interest

The authors state no conflict of interest.

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