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Review Article

Role of extracellular vesicles associated with microRNAs and their interplay with cuproptosis in osteoporosis

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ABSTRACT

Osteoporosis (OP)-associated fractures can result in severe morbidity and disability, reduced quality of life, and death. Previous studies have suggested that small noncoding RNAs, for example, small regulatory microRNAs (miRNAs), play a key role in OP by inhibiting target gene expression. Cuproptosis, a recently proposed copper-induced cell death pathway, is linked with OP. Here, we describe the contribution of exosomal miRNAs and cuproptosis to OP. First, we highlight the characteristics of exosomes and roles of exosome-related miRNAs. Next, we discuss the relationship between cuproptosis and OP. Subsequently, we analyze the crosstalk of exosomal miRNAs with cuproptosis in the development of OP. This review aims to investigate a new clinical treatment method for OP.

1. Introduction

Osteoporosis (OP), a bone-weakening disorder, leads to low bone density that increases fracture risk. OP is related to the aging process as the incidence of musculoskeletal tissue degeneration increases during aging. In recent years, OP has emerged as a critical health concern in the general population, with a progressive increase in its incidence in the elderly population. Moreover, treatment costs for OP have also rapidly increased worldwide [1,2]. OP-related fractures can result in critical disability, reduced quality of life, and death in severe cases. The mortality rate of patients with a hip fracture is 20–30% within 1 year [3]. Although recent studies have successfully investigated the biology of OP in great details, the mechanisms underlying OP remain unclear [4,5].

Cuproptosis, a recently identified cell death regulatory pathway, is induced by an excessive amount of Cu^{2+}. This cell death pathway differs from other such pathways, including ferroptosis, apoptosis, and necrosis. In this pathway, protein toxicity stress and the subsequent cell death are induced through (1) targeting and binding of intracellular Cu to lipid acylated components in the tricarboxylic acid (TCA) cycle, (2) aggregation of lipid acylated mitochondrial proteins bound to Cu, and (3) reduction of Fe–S (iron sulfur) clusters [6]. According to recent research, excessive cuproptosis is linked with various diseases, for example, tumors, cardiovascular diseases, rheumatoid arthritis, Wilson's disease, obesity, Menkes' disease, and neurodegenerative diseases [7]. Moreover, a recent study indicated that cuproptosis is associated with OP occurrence and development [8].

Exosomal microRNAs (miRNAs), as another hot research topic, have challenged the conventional views of intercellular communications. Compared to traditional cell-mediated transfer of bioactive substances or direct cell-to-cell communication, a third mechanism for intercellular communication has emerged in the last two decades [9].

Therefore, in the present review, we discuss the mechanisms of extracellular vesicles (EVs) and miRNAs and their physiological interaction with cuproptosis in the occurrence of OP as well as their potential clinical applications.

2. Sorting of miRNAs into EVs and releasing to the cellular environment

Overexpression or knockdown of a single miRNA can markedly alter cell phenotype; thus, this approach has strong therapeutic potential for diseases [10,11]. The interaction between mRNA and miRNA indicates that a single miRNA can typically bind up to more than 100 different mRNA species, and the 3'-UTR region of most mRNAs contains multiple miRNA binding sites. In other words, an miRNA cluster can target a single gene; conversely, one miRNA can regulate several genes.

miRNAs not only play a vital role intracellularly, but they also perform different functions extracellularly and circulate in the blood

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stream. Circulating miRNAs interact with RNA-binding proteins (RBPs), for example, nucleophosmin (NPM) or proteins of the Argonaute (Ago) family [12]; these miRNAs are encapsulated within EVs or within high-density lipoprotein (HDL)-formed vesicles [13]. However, there is no clear evidence to suggest that microvesicle-free, NPM- or AGO-related miRNAs are actively released from cells; it also remains to be established whether they are absorbed by recipient cells [14].

Vesicular encapsulation or miRNA-protein association contributes to the enhanced stability of miRNAs in biological fluids [15]. Most miRNAs derived from plasma can bind to proteins [12]; however, EVs provide unappreciated carrier effects that assist transfers of their miRNAs to targeted cells (Fig. 1).

3. miRNAs related to the processes of bone modeling

3.1. miRNAs involved in reducing bone formation

Runt-related transcription factor 2 (RUNX2) and the SP7 transcription factor (OSTERIX) of osteoblasts are required to enable mesenchymal stem cell (MSC) differentiation into osteoblasts as well as for functional osteoblast formation. Osteoblast differentiation and maturation involve various signaling pathways such as PI3K/Akt, WNT, and BMP. Although many miRNAs quickly activate the osteogenic differentiation signaling pathway of BMSCs and efficiently induce their osteogenesis, recent research has confirmed that miRNAs also inhibit the osteogenic differentiation of BMSCs by targeting genes. For example, miR-185 downregulates the Wnt/β-catenin axis by targeting the *PTH* gene to inhibit osteoblast proliferation and growth during fracture healing [16]. miR-370 reduces the expression of BMP-2 and the oncogene homolog 1 (Ets1) protein of erythroblastic disease virus E26. The Ets1 protein is a key transcription factor that drives tissue destructive fibroblast polarization and shows a high expression in the proliferation phase of BMP2-stimulated MC3T3-E1 cells [17]. miR-34a inhibits glucose metabolism, osteogenic differentiation, and *in vivo* bone formation in human MSCs by activating the ligand (Jagged1) intracellular domain of Notch1 [18]. The transcription factor osterix contains zinc fingers, and it shows specific expression in developing bones. Its lack of specificity leads to the loss of bone formation ability in mice. miR-96 shows a high expression in the serum of osteoporotic elderly patients and in BMSCs from elderly and mouse sources. miR-96 directly targets the coding region (CDS region) of osterix to reduce the osteogenic differentiation of BMSCs [19].

3.2. miRNAs involved in enhancing bone resorption

miRNAs are critically involved in osteoclastogenesis regulation. miRNAs have been reported to exert the following effects in osteogenic differentiation. miR-182 is an important component that positively regulates osteoclast differentiation in pathological conditions such as OP or bone degeneration or in physiological bone metabolism. For example, miR-182 regulates the IFN-β signaling pathway through the targeting of protein kinase double-stranded RNA-dependent (PKR), thereby

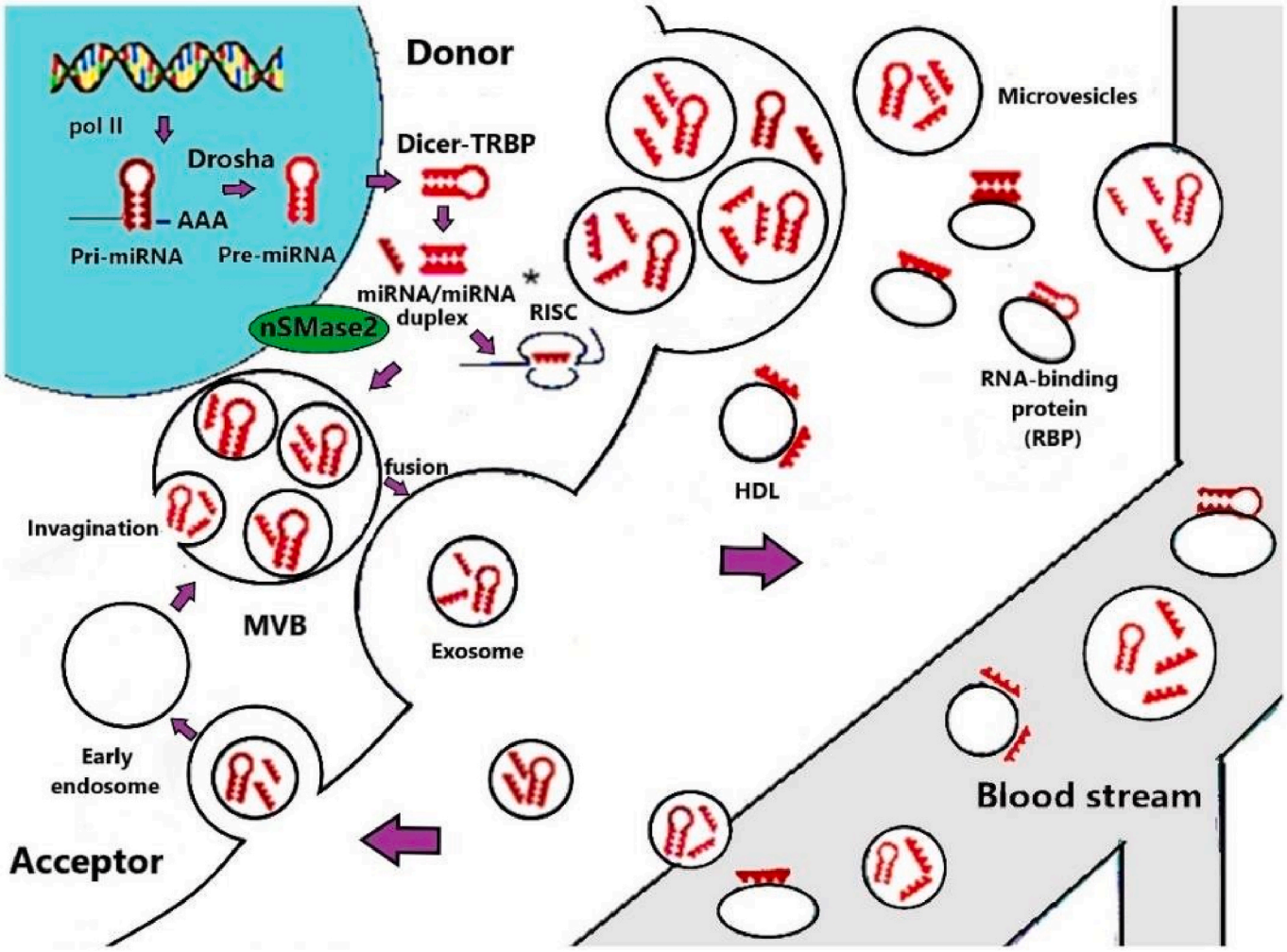

Fig. 1. Sorting of miRNAs into EVs and their release into the cellular environment.

regulating the pathological activation of osteoclasts [20]. miR-148a was found to enhance osteoclast differentiation and function; it negatively regulates RANKL-induced osteoclastogenesis by suppressing the nuclear factor of activated T cells cytoplasmic 1 (NFATc1) and other osteoclast-promoting factors [21]. miR-21, a pro-osteoclastic microRNA, can directly target and suppress the programmed cell death 4 (PDCD4) protein expression despite RANKL existence [22,23]. miR-29 comprises miR-29a, miR-29b, and miR-29c; it is a positive osteoclast differentiation regulator. miR-29 expression is increased *in vitro* during RANKL-induced osteoclast differentiation in both murine BMMs and RAW 264.7 mouse monocytes. Nuclear factor I/A (Nfia), a target of miR-29, inhibits monocyte differentiation into both macrophage and osteoclast cell lineages [24] (Fig. 1).

3.3. *miRNAs involved in both bone formation reduction and bone resorption enhancement*

miR-214 suppresses bone formation and regulates osteoblast activity as well as osteoclast differentiation [25]. Osteoblast-targeted miR-214 overexpression can inhibit collagen I and alkaline phosphatase expression and matrix mineralization in MC3T3E1 cells by targeting the *activating transcription factor 4 (ATF4)*, a gene encoding a transcription factor critical for osteoblast differentiation [26,27]. miR-214 also promotes osteoclastogenesis in bone marrow monocytes (BMMs) through the inhibition of the phosphatase and tensin homolog (PTEN), a crucial negative regulator of PI3K, and subsequently activates the PI3K/AKT signaling pathway [28] (Table 1).

4. Cuproptosis and OP

The molecular characteristics of cuproptosis-related genes can provide important insights into the bone marrow microenvironment characteristics and the potential mechanism of OP. OP occurs not only because of alterations in the bone marrow microenvironment but also because of dysregulation of cellular homeostasis. Cells such as osteoblasts, BMSCs, osteocytes, osteoclasts, macrophages, chondrocytes, endothelial cells, and adipocytes possess metabolic mechanisms related to cuproptosis [31].

Osteoblasts participate in bone formation and are differentiated from BMSCs *in vivo*. Glutamine is critically involved in the energy metabolism of osteoblasts [32]. According to recent studies, the metabolism of glutamine regulates lineage allocation and cell proliferation in skeletal stem cells [33]. Glutamine shows an association with cuproptosis, and its decreased level markedly inhibits cuproptosis. Thus, it might influence the energy metabolism of osteoblasts. Glucose is the primary nutrient for osteoblasts. A study with advanced total-body PET/CT showed significant glucose uptake in skeleton, and this skeletal glucose uptake is influenced by dysregulated metabolism and age [34]. Huang et al. also demonstrated that aging decreases ERRalpha-directed mitochondrial glutaminase expression that suppresses glutamine anaplerosis and osteogenic differentiation of MSCs [35].

Osteoclasts, derived from hematopoietic stem cells (HSCs), share precursors with macrophages and have unique function of bone matrix resorption. According to several studies, reactive oxygen species (ROS)-induced oxidative stress has a critical involvement in OP. Copper ions generate excessive ROS through the Fenton reaction, thereby inducing lipid peroxidation and DNA damage [36]. ROS can indirectly affect the survival, differentiation, and activation of osteoclasts by stimulating bone formation-associated cells to generate macrophage colony-stimulating factor (M-CSF), osteoprotegerin, and RANKL; these are critical regulatory factors that identify osteoclasts and osteoclast precursor cells for conducting bone resorption signals [37].

A unique characteristic of OP and the early stage of osteoarthritis (OA) is increased subchondral bone loss. As shown in previous studies, Runx1 signals chondrocytes to osteoblast lineage commitment and augments endochondral bone formation by enhancing the expression of genes involved in both chondrogenesis and osteogenesis, thus indicating that Runx1 could serve as a therapeutic target to improve endochondral bone formation and prevent OP-related fractures [38]. Additionally, Stegen et al. demonstrated that SOX9, a crucial chondrogenic transcription factor, induces the metabolism of glutamine. This metabolic adaptation is essential to facilitate gene expression, redox homeostasis, and protein biosynthesis in chondrocytes [39]. Glutaminase 1 (GLS1), an essential cuproptosis-associated gene, also affects chondrocytes by promoting redox homeostasis, glutamine metabolism, efferocytosis, and antioxidant functions [8].

OP is also an inflammatory disease. For example, rheumatoid arthritis (RA) or ankylosing spondylitis is characterized by systemic bone loss [31]. Recently, the regulation of immunity by nutrients has received increasing attention, and related studies have been conducted on the effects of high salt, high sugar, etc. Mechanistic target of rapamycin complex 1 (mTORC1), a key cell metabolism regulator, is an atypical serine/threonine protein kinase. It coordinates upstream signals with downstream effectors, including transcription and translation, for regulating basic cellular processes such as protein synthesis, energy utilization, cell growth and proliferation, and autophagy. Because the mTORC1-dependent pathway is the core pathway of cell growth and metabolism, it is associated with several human diseases, including cancer, type 2 diabetes, neurodegeneration, obesity, and aging [40]. Therefore, effector T cells function through an mTORC1-dependent pathway by utilizing glycolytic uptake of glucose and glutamine for energy; this might suppress cuproptosis [8]. M1 macrophages are glycolytic cells that attenuate cuproptosis by releasing several proinflammatory factors that participate in OP development and progression.

Bone marrow adipocytes discovered in human bone marrow over a century ago are a unique group of cells derived from bone marrow lipogenic lineage precursor cells and bone marrow mesenchymal progenitor cells. Although these cells have long been considered space fillers for the bone marrow cavity, recent research has shown that these cells affect other cell populations in the bone marrow, influence systemic metabolism, and inhibit local bone composition by secreting a specific set of adipokines [41,42]. Previous research supports a relationship between bone loss and accumulation of promote adipogenesis [43,44]. Because of an imbalance in the population of adipocytes/osteoblasts, aging diminishes bone formation by promoting adipogenesis. Potentially, the loss of bone mass can lead to OP [45,46]. In the bone environment of oxidative stress, aging adipocytes can diffuse the aging phenomenon to surrounding bone cells and bones by secreting senescence-associated secretory phenotype (SASP) factors, resulting in aging cell accumulation in the local environment [47]. A previous study

Table 1
miRNAs with critical roles in bone modeling.

miRNA	Target gene/target protein	Ref.
miRNAs reducing bone formation:		
miR-185	*PTH*	[17]
miR-370	BMP-2	[29]
miR-34a	JAG1	[18]
miR-96	Osterix	[19]
miRNAs enhancing bone resorption:		
miR-182	PKR	[20]
miR-148a	NFATc1	[30]
miR-21	PDCD4 PI3K	
miR-29	RANKL Nfia	[21] [22, 23]
miRNAs both reducing bone formation and enhancing bone resorption:		[24]
miR-214	*ATF4*	[26, 27]
	PI3K	[28]

revealed that senescence is initiated by p53 and p21 (the downstream target of p53) through a telomere-dependent pathway [48]. p53, a crucial metabolic regulator, is associated with two critical components of the cuproptotic pathway: the copper chelator glutathione and biogenesis of iron-sulfur clusters. This suggests that p53 has a critical role in cuproptosis [49].

Several lines of evidence indicate that endothelial cells (ECs) play crucial roles in bone regeneration [50]. ECs stimulate osteoblast maturation and activation; however, they suppress the osteogenic differentiation of bone progenitor cells. Copper-catalyzed free radical reaction leads to the synthesis of the most active hydroxyl radical, which increases ROS concentration in cells, leading to the oxidation of low-density lipoprotein (LDL), damaging the endothelium, and resulting in the formation of early atherosclerosis [36]. Atherosclerosis can lead to plaque formation or lumen stenosis, destroy the aortic wall, and eventually form an aneurysm. Cu transport within the cytoplasm is closely coordinated by a finely tuned network of high-affinity Cu molecular chaperones. Companion antioxidant 1 (ATOX1) mediates copper transfer to ATP7A and ATP7B in the trans-Golgi network and promotes the production of copper enzymes such as lysine oxidase, tyrosinase, and plasma ceruloplasmin. ATP7A is expressed in various cells, and its mutations can lead to genetic disorders in copper metabolism. A decrease in the expression of the *ATP7A* gene increases miR-125b expression and augments proinflammatory signal transduction, thereby accelerating the formation of aortic aneurysms. This process is positively correlated with copper [51]. Ceruloplasmin, also known as copper oxidase, is a copper-containing glycoprotein synthesized by the liver and shows genetic polymorphism. Each protein can bind 6 copper atoms; this facilitates the metabolism of copper and iron in the body and affects the function of vascular endothelial cells through oxidation and nitric oxide reduction. The cytokine ceruloplasmin is involved in lipid peroxidation and atherosclerosis formation, and it is closely associated with the stability of the coronary artery plate [52]. Therefore, the inhibition of cuproptosis in cells could prevent or treat aneurysms and OP.

5. Interplay between exosomal miRNAs and cuproptosis in OP

5.1. Exosomal miRNAs regulate the participation of genes in the cuproptosis response

Cuproptosis is associated with three negative regulatory factors, including glutaminase (GLS), cyclin-dependent kinase inhibitor 2A (CDKN2A), and metal regulatory transcription factor 1 (MTF1). It is also associated with 7 positive regulatory factors, including ferredoxin 1 (FDX1) and 6 acylated proteins, including either the lipoic acid pathway elements (three essential components: lipoacyltransferase 1 (LIPT1), lipoic acid synthase (LiAS), and dihydroacylamide dehydrogenase (DLD)) or acylated protein targets (dihydroacylamide S-acetyltransferase (DLAT), pyruvate dehydrogenase E1 subunit α 1 (PDHA1), and the E1 subunit of pyruvate dehydrogenase β (PDHB) [6].

The exosomal miRNA miR-21-5p, which is obtained from cisplatin-resistant SKOV3 ovarian cancer cells, enhances the glycolysis process and suppresses chemosensitivity of its progenitor SKOV3 cells through PDHA1 targeting [53]. PDHA1 is a cuproptosis-related gene (CRG), and it has an essential role in glucose metabolism, the TCA cycle, and mitochondrial oxidative phosphorylation [54]. PDHA1 inhibition might facilitate the proliferation of osteoblasts, while PDHA1 activation could affect macrophages and osteoblasts by inhibiting the release of inflammatory factors [8].

Exosomal miR-4536-5p from human keloid fibroblasts inhibited the expression of PDHB [55]. PDHB may influence osteoclast differentiation by interacting with NIMA-associated kinase ten [8]. Exosomal miR-663a derived from human umbilical cord mesenchymal stem cells (hucMSCs) repairs hypoxia-induced injury of endometrial epithelial cells by regulating CDKN2A [56]. CDKN2A is associated with OP through the P16 protein, which is mainly involved in cellular senescence [8].

MSC-Exo shuttling miR-182 can modify the polarization status of macrophages [57]. Two typical subtypes of macrophages are (1) M1 macrophages that are classically activated and (2) M2 macrophages that are alternatively activated. Several lines of evidence indicate that MSCs trigger macrophages to switch toward the anti-inflammatory M2 phenotype. Exosomal miR-182-5p derived from BMSCs minimizes inflammatory responses by targeting TLR4 [58]. The modulation of the TLR4/NF-κB and MAPK signaling pathway can prevent Cu cardiotoxicity by decreasing inflammatory response, oxidative injury, and apoptosis [59].

5.2. Cuproptosis regulates the expression of several exosomal miRNAs

Aging, inflammation, and oxidative stress upregulate miR-34a expression in exosomes derived from muscles, and this miRNA subsequently induces cellular senescence in bone stem cells. In C2C12 myoblasts, exosomal miR-34a overexpression inhibits the expression of Sirt1 mRNA and protein [60]. miR-34a is critically involved in regulating myocardial physiology as well as pathophysiological processes that induce senescence in cardiomyocytes and vascular smooth muscle cells and promote cardiac fibrosis [61]. Aging and an increased amount of exposure to inflammatory factors and ROS, both of which increase cuproptosis, are suggested to contribute to cancer, injury, and inflammation [62].

A common chemical reaction in cells is the Fenton reaction that generates ROS through metal catalysis. Cu + catalyzes the degradation of H_2O_2 to ·OH, OH-, and O_2, thereby producing excessive amounts of ROS [63]. H_2O_2 treatment increases miR-183-5p abundance in bone-derived exosomes in MSCs. Furthermore, the exosomal miRNA miR-183-5p is a significant active contributor in the impairment of MSC proliferation and induction of bone stem cell senescence [64].

6. Conclusions

The study of vesicular miRNAs and their interplay with cuproptosis provides a novel and intriguing approach to understand the molecular mechanisms underlying OP biology. Despite their nano size, EVs function as crucial communication facilitators between cells. EVs secrete various biological molecules, including miRNAs, proteins, and their complexes. Together with designing of modified miRNA molecules for application in gene therapies and in addition to the potential application of EVs, advanced techniques for rapid, reliable, sensitive, and efficient OP treatment should be evaluated in future studies [65,66].

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CRediT authorship contribution statement

Yong Sun: Writing – original draft. **Peng Chen:** Conceptualization. **Bin Zhao:** Writing – review & editing, Visualization, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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