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Review

Lipid metabolic reprogramming and associated ferroptosis in osteosarcoma: From molecular mechanisms to potential targets

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ABSTRACT

Osteosarcoma is a common bone tumor in adolescents, which is characterized by lipid metabolism disorders and plays a key role in tumorigenesis and disease progression. Ferroptosis is an iron-dependent form of programmed cell death associated with lipid peroxidation. This review provides an in-depth analysis of the complex relationship between lipid metabolic reprogramming and associated ferroptosis in OS from the perspective of metabolic enzymes and metabolites. We discussed the molecular basis of lipid uptake, synthesis, storage, lipolysis, and the tumor microenvironment, as well as their significance in OS development. Key enzymes such as adenosine triphosphate-citrate lyase (ACLY), acetyl-CoA synthetase 2 (ACSS2), fatty acid synthase (FASN) and stearoyl-CoA desaturase-1 (SCD1) are overexpressed in OS and associated with poor prognosis.

Based on specific changes in metabolic processes, this review highlights potential therapeutic targets in the lipid metabolism and ferroptosis pathways, and in particular the HMG-CoA reductase inhibitor simvastatin has shown potential in inducing apoptosis and inhibiting OS metastasis. Targeting these pathways provides new strategies for the treatment of OS. However, challenges such as the complexity of drug development and metabolic interactions must be overcome. A comprehensive understanding of the interplay between dysregulation of lipid metabolism and ferroptosis is essential for the development of innovative and effective therapies for OS, with the ultimate goal of improving patient outcomes.

1. Introduction

Osteosarcoma(OS) is the most common type of bone tumor in children and adolescents, incidence of a disease which is about 4.4 cases per million children each year. In the past 40 to 50 years, with the emergence of various combination chemotherapy drugs, OS rates remained relatively stable, accompanied by a decline in mortality rates [1].This suggests that, in addition to surgery, new drug therapy in improving the condition of the patients with OS played a good role.

In recent years, metabolic alterations in cancer have opened a new perspective of oncogenic transformation. In the 1920 s, Otto Warburg first proposed that cancer cells prefer glycolysis over oxidative phosphorylation (OXPHOS) to meet their energy needs, even when sufficient oxygen is available. This phenomenon later became known as the "Warburg effect" [2]. Subsequent detailed investigations into tumor metabolism revealed that aerobic glycolysis alone does not fully capture the complexity of metabolic dysregulation in tumors. The cancer cells rely on aerobic glycolysis, a low-efficiency metabolic pathway, even in the presence of sufficient oxygen. However, the reduced efficiency of glycolysis can be compensated by increasing glucose uptake, which in turn meets the energy demand of cancer cells [3]. At the same time, large amounts of Acetyl-CoA and citrate, two key precursors for lipid metabolism, are produced during this process, linking glucose metabolism to lipid metabolism in tumors. (Fig. 1) Additionally, in the Warburg effect, the activation of glycolytic bypass pathways, such as the pentose phosphate pathway, generates substantial amounts of NADPH. NADPH serves as a reducing agent, facilitating the synthesis of fatty acids(FAs) and cholesterol. Numerous studies have confirmed that lipid metabolism, particularly its reprogramming, plays a crucial role in promoting tumorigenic behaviors. As a result, the reprogramming of lipid metabolism has gradually gained increasing attention in the field of cancer research [2,4,5].

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On the other hand, it is noteworthy that ferroptosis characterized by iron-dependent lipid peroxidation, and that tumor cells undergoing reprogramming of lipid metabolism tend to exhibit a unique vulnerability to ferroptosis [6]. Interestingly, a significant proportion of cancer cells remain sensitive to ferroptosis despite escaping other forms of programmed cell death, such as apoptosis or autophagy. This highlights the promising therapeutic potential of ferroptosis induction in the treatment of tumours [7,8].

Given the important role of lipid metabolic reprogramming and ferroptosis in the occurrence and development of OS, in-depth exploration of these mechanisms may reveal potential therapeutic targets and provide theoretical basis for the development of targeted therapeutic strategies focusing on lipid metabolism and ferroptosis. Therefore, this review aims to: (1) elucidate the overall pattern and mechanism of lipid metabolic reprogramming and associated ferroptosis in OS;(2) summarize the potential therapeutic targets of OS based on lipid metabolism. It is expected to provide new ideas and ways for the clinical treatment of OS.

2. Lipid metabolism reprogramming

Hanahan and Weinberg proposed that metabolic reprogramming, also known as metabolic remodeling, is a hallmark of malignant tumor development. Crucial to providing precursors for the synthesis of essential molecules, such as nucleotides and amino acids, are alterations in metabolic pathways, including glycolysis, lipid metabolism, glutaminolysis and enhanced mitochondrial biogenesis. These molecules serve as alternative energy sources that enable tumor cells to survive, proliferate, metastasize, and develop resistance to therapy, even under adverse conditions [2].

To adapt to the hypoxic and nutrient-deprived microenvironment, tumor cells undergo lipid metabolic reprogramming in addition to increasing glucose uptake and aerobic glycolysis, enhancing their biological behaviors. This metabolic adaptation allows tumor cells to thrive in a microenvironment characterized by hypoxia, acidity, and nutrient scarcity. These adaptive changes help maintain the homeostasis of the extracellular tumor microenvironment (TME), driving rapid tumor growth and even conferring new capabilities to the cells [5,9]. At the same time, the recruitment, activation, and function of immune cells and stromal cells are altered by lipid metabolic reprogramming. Tumor cells can actively modify the TME by secreting signaling molecules and metabolites, including bioactive lipids such as sphingosine-1-phosphate(S-1-P), prostaglandin E2(PGE2), and lipoprotein(a), which influence the function of cancer-associated fibroblasts (CAFs) and immune cells within the TME [10].

Given the critical role of lipids in cancer progression, targeting lipid metabolism pathways offers new therapeutic opportunities for cancer treatment. In OS, the research and reviews on the equally important lipid metabolism remain scarce. Therefore, summarizing the current research status and identifying potential therapeutic targets may provide valuable insights for further studies and clinical applications targeting lipid metabolism in cancer 1 [1].

3. Lipid metabolism reprogramming in osteosarcoma

The primary lipid molecules in the human diet are triglycerides (TAGs) and cholesterol. Once absorbed, TAGs are hydrolyzed into glycerol and fatty acids (FAs). Glycerol is then converted into glycerol-3-phosphate (G-3-P) and enters glycolysis. Fatty acids are either incorporated into phospholipids for storage as plasma membrane components or converted into acyl-CoA for β-oxidation to generate energy. In OS, several steps in lipid metabolism show a general increase, including lipid

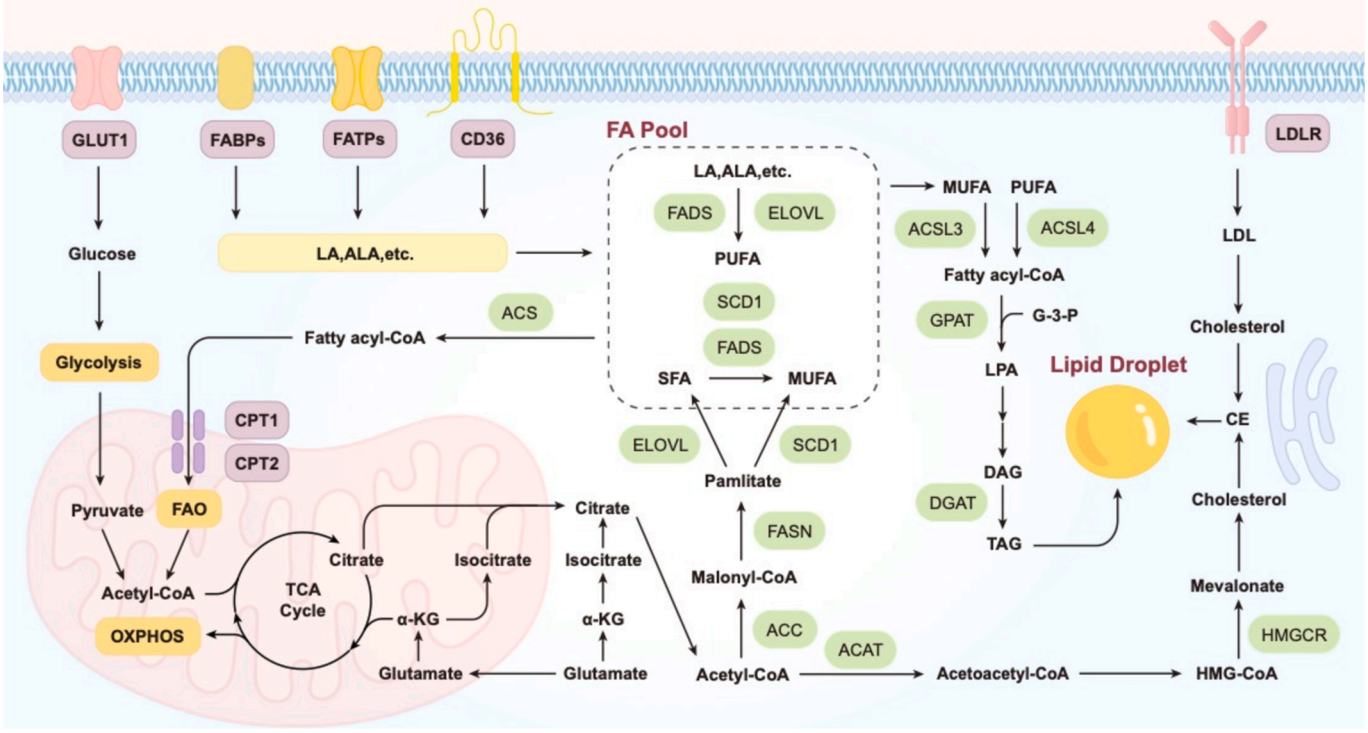

Fig. 1. Major lipid metabolism pathways. This figure summarizes the processes of lipid uptake, synthesis, storage, and degradation. In osteosarcoma cells, lipid acquisition occurs through both endogenous and exogenous mechanisms. On one hand, fatty acids and LDL are taken up exogenously through transporter molecules or by passive diffusion. On the other hand, acetyl-CoA within the cytoplasm serves as a precursor for endogenous lipid synthesis. Citrate, generated from glucose and glutamine metabolism, is converted to acetyl-CoA by ACLY, while acetate is converted via ACSS. Acetyl-CoA then serves as a key substrate for the synthesis of both fatty acids and cholesterol. Excess lipids in osteosarcoma cells are stored in lipid droplets in the form of cholesterol esters (CE) and triglycerides (TAG). Finally, fatty acids are converted to fatty acyl-CoA by acyl-CoA synthetase, which then enters the lipid degradation pathway, specifically fatty acid oxidation (FAO), to generate energy.

uptake, synthesis, and fatty acid oxidation (FAO). In the following sections, we will analyze the interactions between molecules in these pathways to reveal how OS exploits metabolic reprogramming to cope with energy and environmental stress [11].

3.1. Lipid uptake

The increase in intracellular lipid content can be achieved through both endogenous and exogenous pathways. Endogenous lipids are primarily produced via de novo lipogenesis (DNL) using acetyl-CoA as a substrate. Exogenous lipids require the involvement of transport molecules. CD36, the fatty acid transporter proteins (FATPs), and fatty acid binding proteins (FABPs) facilitate the transport of free fatty acids into cells, thereby participating in lipid metabolism [4]. Additionally, low-density lipoprotein receptors (LDLR) mediate the endocytosis of LDL, which is then hydrolyzed into free cholesterol within cells, contributing to cell proliferation and the synthesis of signaling molecules [12]. Recent studies have highlighted the correlation between the overexpression of these transport molecules in OS and poor prognosis. For instance, the expression of CD36 is significantly elevated on the surface of OS cell membranes, leading to an increased accumulation of free fatty acids within OS cells. While there is no direct evidence linking CD36-mediated fatty acid uptake to the promotion of OS progression, experimental data indicate that antagonizing CD36 can substantially inhibit OS cell metastasis and angiogenesis. [9] These findings highlight the need for further research to explore the potential therapeutic implications of targeting CD36 in OS. Besides, the tRNA methyltransferase NSUN2 is also upregulated in OS, where it enhances the stability of FABP5 mRNA through m5C modification. The increased expression of FABP5 promotes fatty acid metabolism in OS cells, thereby advancing OS progression [13](Fig. 1).

Members of the LDLR family, including LRP5, LRP6, and LRP8, are notably upregulated in OS. LRP5, which is highly expressed in various tissues, plays a role in cholesterol metabolism and cancer progression. Recent research has indicated that LRP5 is involved in chondrocyte subtype osteosarcoma, with LRP5-positive patients showing a trend towards reduced event-free survival [14]. Furthermore, LRP5 has been identified as a biomarker for high-grade OS progression. Mechanistically, LRP5 not only aids in the uptake of exogenous cholesterol by OS cells but also acts as a co-receptor in the canonical Wnt signaling pathway, promoting tumor progression through Wnt/β-catenin signaling [15]. However, in a mouse model of OS with dominant-negative LRP5 expression, Wnt signaling on the cell surface was impaired, yet this did not eliminate the formation of OS. Interestingly, further investigations revealed unexpectedly preserved Wnt signaling within the nuclei of OS cells, resulting in stabilized β-catenin that enhances the expression of Wnt target genes [16]. Therefore, it is proposed that OS formation may represent an adaptive reprogramming process aimed at overcoming obstacles encountered in complex signaling pathways.

3.2. Lipid synthesis

Compared to normal cells that primarily rely on the intake of exogenous fatty acids, cancer cells have a greater capacity for de novo lipid synthesis [17]. This alteration facilitates the synthesis of lipid membranes and signaling molecules in cancer cells. Lipid synthesis encompasses both the fatty acid synthesis pathway and the mevalonate pathway (Fig. 2).

3.2.1. Fatty acid synthesis pathway and aberrant expression of related enzymes

Fatty acids are crucial components of all biological membrane lipids and serve as important substrates for energy metabolism [19].Compared to exogenous (dietary) sources of fatty acids, the endogenous synthesis of fatty acids is a characteristic of OS cells (Fig. 1).

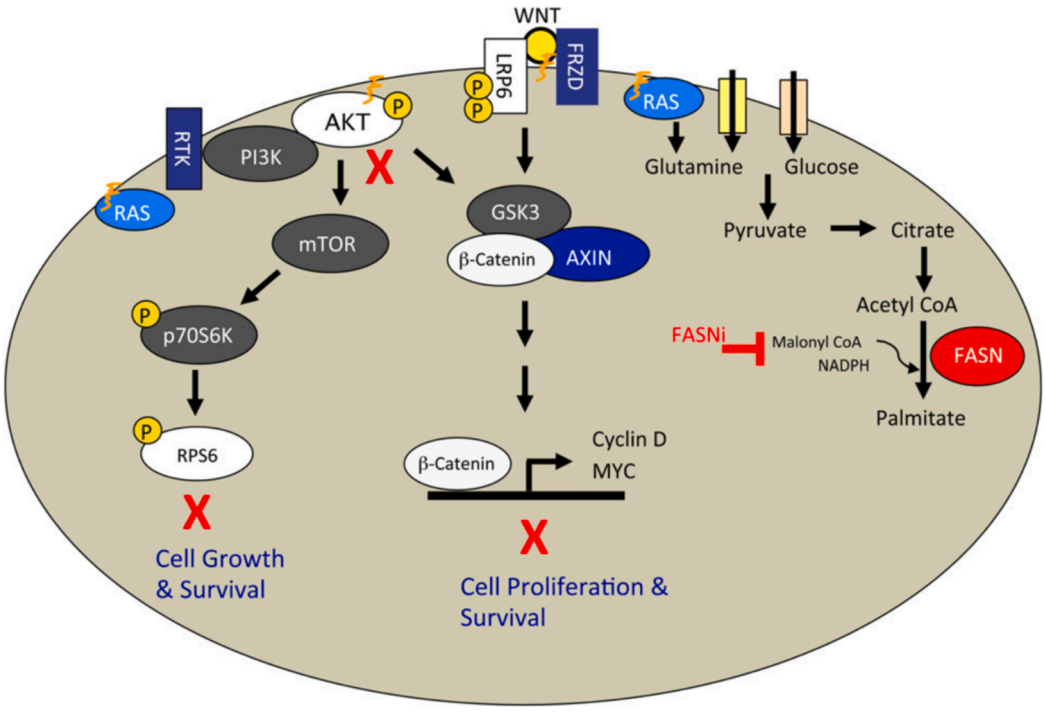

Fig. 2. FASN inhibition blocks metabolic and signal transduction pathways vital to cancer cell growth, proliferation, and survival. FASN inhibition results in inhibition of Akt and S6 phosphorylation in the AKT–mTOR signal transduction pathway. In the Wnt–β-catenin pathway, FASN inhibition results in the inhibition of Lrp6 and β-catenin phosphorylation as well as the expression of TCF promoter-driven genes such as c-Myc. FASN inhibition impairs the plasma membrane localization of palmitoylated and other lipid-raft-associated proteins such as N-Ras. Image from Ventura R et al. 2015 [18] (open-access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited).

(1) ACLY (ATP-citrate lyase):

ACLY is a key enzyme in the fatty acid synthesis pathway. Its substrate, citrate, is an intermediate in carbohydrate metabolism and is transported from the TCA cycle into the cytoplasm, where it participates in fatty acid metabolism. Additionally, citrate can be produced via glutamine metabolism in the mitochondria. These pathways ensure an ample supply of substrate for ACLY to catalyze the conversion of citrate into acetyl-CoA [20]. Overexpression of ACLY in OS has been reported, correlating with the increased fatty acid demand of tumor cells [21,22]. Mechanistic studies reveal that OS cells selectively recruit exosomes derived from bone marrow mesenchymal stem cells (BMSCs). The exosomal lncRNA XIST enhances ACLY protein expression by binding to miR-655, thereby mediating lipid accumulation. Furthermore, ACLY can interact with β-catenin and activate it, which subsequently drives OS cell proliferation, migration, and invasion [23].

(2) ACSS2 (Acyl-CoA synthetase short-chain family member 2):

ACSS2 produces acetyl-CoA by linking acetate and CoA. ACSS1 and ACSS3 are mitochondrial proteins, while ACSS2 is located in the cytoplasm and nucleus [24]. ACSS2, upregulated by SREBP transcription, is expressed in most human tumors, including OS [25]. A recent study indicates that cancer cells up-regulate ACSS2 levels to effectively cope with stresses such as low nutrient availability and hypoxia [26]. Interestingly, other research has shown that low ACSS2 expression promotes tumor progression and serves as an independent adverse prognostic factor for cancer [27,28]. This adverse effect can be mitigated by ACSS2 agonists. Although ACSS2 has been less studied in OS, Wu et al. found that ACSS2 expression is down-regulated in OS cells. Their study suggests that ACSS2 could be a potential biomarker for the early diagnosis and prognosis of OS [16].

(3) FASN (Fatty Acid Synthase):

FASN is a terminal enzyme in the de novo synthesis of fatty acids and produces palmitic acid by condensation of malonyl-CoA and acetyl-CoA. Although the mechanisms behind tumor-associated FASN overexpression are not fully understood, two major pathways have been identified. First, growth factors (GF) can regulate SREBP-1c expression and/or nuclear maturation by activating downstream PI3K-Akt and ERK signaling cascades via receptor tyrosine kinases (RTKs), such as EGFR (ERBB1) and HER2(ERBB2), ultimately promoting FASN expression. Second, overexpression of FASN can be achieved post-translational by interaction with USP2a, a deubiquitinating enzyme that stabilizes FASN by removing ubiquitin. These two pathways may simultaneously regulate FASN in tumor cells [29].

However, a study found that in OS cells, the tumorigenic molecular mechanism by which the HER2/PI3K/AKT axis increases FASN levels resulted in a decrease in FASN expression as expected when HER2 was inhibited. Conversely, inhibiting FASN led to an unexpected significant reduction in HER2 protein activity [30]. Mechanistically, another study have shown that FASN can stabilize HER2 by regulating the membrane microdomains of receptor tyrosine kinases and promote AKT recruitment [31]. These findings confirm a positive feedback loop between HER2 and FASN in OS cells, ensuring excessive de novo fatty acid biosynthesis.

Additionally, in the Wnt/β-catenin pathway, which is essential for tumor cell growth, high FASN expression in tumors increases Wnt-1 palmitoylation and stabilizes β-catenin, thereby activating downstream transcription factors [18]. Beyond its role in lipid metabolism, FASN is also associated with OS metastasis. Several studies have demonstrated a correlation between FASN expression and Ki-67 protein levels in OS cells, further supporting its role in promoting OS metastasis [32]. FASN contributes to tumor cell proliferation and metastasis by activating the ERK1/2/Bcl-xL pathway or mediating interactions with miRNAs and hnRNPA1 [33]. Additionally, FASN has been shown to support OS metastasis through the PI3K/Akt pathway.

Several studies have shown that non-coding RNAs such as miR-195 [34] and miRNA-424 [35] target and regulate abnormal lipid metabolism in OS cells, significantly affecting OS migration and invasion. miRNAs are crucial in the formation of the RNA-induced silencing complex (RISC), where they bind to target mRNAs to induce their degradation or reduce their expression. This process can inhibit both the transcription and translation of FASN. Extensive biological studies have shown that miRNAs often target multiple genes, with a single miRNA capable of regulating various mRNAs. This suggests that the different targets of the same miRNA may explain stage-specific differences in lipid metabolism in OS.

At the transcriptional level, overexpression of lncRNA PVT1 in OS tissues acts as a molecular sponge, inhibiting miR-195 and increasing FASN expression, which promotes cell migration and invasion. Evidence also indicates that FASN enhances OS cell migration and invasion by mediating resistance to anoikis [36]. Recent studies have confirmed that FASN influences the composition and stability of lipid rafts on cell membranes, affecting proteins located in these rafts, such as N-Ras, or modulating protein palmitoylation, which ultimately regulates epithelial-mesenchymal transition [18].

In summary, the role of FASN in OS cell biology warrants further investigation, as it may bridge lipid metabolism and programmed cell death. Although existing research provides insights, studies on FASN in OS are still relatively limited, and more detailed research is needed to elucidate the underlying mechanisms.

(4) SCD1 (Stearoyl-CoA desaturase 1):

SCD1 is an endoplasmic reticulum membrane-bound protein that catalyzes the conversion of saturated fatty acids (SFAs), such as stearic acid or palmitic acid, into monounsaturated fatty acids (MUFAs), such as oleic acid or palmitoleic acid. It plays a crucial role in regulating body fat composition and metabolism [37]. The SFA/MUFA ratio has been proposed as a malignant prognostic marker, with increased expression of SCD1 and MUFA content observed in OS cells [38,39]. Despite the strong capability of OS cells to synthesize endogenous fatty acids, these cells exhibit a degree of dependence on exogenous unsaturated fatty acids due to the requirement of NADPH and oxygen for SCD1 activity, particularly under hypoxic conditions [40]. In the absence of exogenous lipids, SCD1 inhibition can induce ferroptosis and apoptosis. Additionally, inhibiting SCD1 reduces the levels of coenzyme Q10 (CoQ10), an endogenous antioxidant associated with ferroptosis. Evidence suggests that SCD1 inhibition effectively suppresses tumor cell proliferation by modulating endogenous fatty acid synthesis. [31] However, since tumors can acquire unsaturated lipids from their microenvironment, the impact of SCD1 inhibition on tumor growth may be limited.

Consequently, combining the inhibition of both endogenous and exogenous lipid uptake in OS cells is a potential strategy. However, challenges such as low specificity of targeting lipid uptake receptors in tumor regions and the complexity of the tumor microenvironment necessitate further research to elucidate the underlying mechanisms. Given the abnormalities in the tumor microenvironment, targeting these metabolic features may impede OS progression. Research has shown that SCD1 inhibitors significantly reduce OS growth and induce ferroptosis, suggesting that SCD1 could be a potential therapeutic target for OS [41]. Furthermore, Zhang et al. demonstrated that SCD1 expression is regulated by hypoxia-inducible factor 2α (HIF-2α) under hypoxic stress, highlighting its oncogenic properties. Interestingly, a positive feedback loop mediated by the PI3K/AKT pathway was identified between HIF-2α and SCD1. This feedback loop plays a synergistic role in regulating tumor cell growth, survival, and migration. Therefore, drugs targeting both SCD1 and HIF-2α may offer promising therapeutic options for cancer treatment [42].

3.2.2. Cholesterol synthesis pathway and Aberrant expression of related enzymes

Previous studies have found that the mevalonate pathway of cholesterol synthesis is highly activated in various tumors, as reflected by the highly expressed HMGCR [43–45]. Moreover, activated mevalonate(MVA) pathway is positively correlated with tumor cell proliferation and metastasis, including gastric cancer, breast cancer, prostate

cancer and OS [46,47].

HMGCR, a rate-limiting enzyme in cholesterol biosynthesis within the mevalonate pathway, is a glycoprotein located in the endoplasmic reticulum. It catalyzes the conversion of HMG-CoA to MVA, which is further metabolized to farnesyl pyrophosphate (FPP), a precursor of cholesterol and sterols. FPP is subsequently converted to geranylgeranyl pyrophosphate (GGPP), ultimately leading to cholesterol synthesis. This process is crucial for membrane biosynthesis and various other biological functions.(Fig. 1) Overexpression of HMGCR due to metabolic reprogramming may promote tumorigenesis by enhancing cholesterol biosynthesis, facilitating tumor initiation, migration, and angiogenesis. These processes can be mediated through epigenetic mechanisms or via Rho and Ras pathways [48]. For instance, activation of the MVA pathway enhances prenylation and activities of RhoA, leading to its translocation to the plasma membrane and activation of YAP1. YAP1, a transcriptional co-activator, promotes transcription of downstream target genes through nuclear translocation, thereby inducing epithelial-mesenchymal transition (EMT) and lung metastasis in OS cells [42]. Moreover, GGPP biosynthesis catalyzed by the MVA pathway stabilizes the membrane localization of K-Ras and inhibits angiogenesis in osteosarcoma through the Ras/ERK and Ras/Akt pathways [49]. Research on potential therapeutic targets in osteosarcoma based on cholesterol metabolism has yielded valuable insights, potentially paving the way for novel treatments and ultimately improving patient prognosis.

3.2.3. *Oncogenic regulation of lipid synthesis in osteosarcoma*

Sterol regulatory element binding protein (SREBP) family transcription factors play an important role in regulating lipid metabolism in OS, including cholesterol and fatty acid synthesis, and have been confirmed to be significantly up-regulated in OS. [3] Mammalian cells express three SREBP proteins, SREBP-1a, -1c, and -2, which are encoded by two genes, SREBF1 and SREBF2. SREBF1 encodes SREBP-1a to regulate fatty acid and cholesterol synthesis and cholesterol uptake, whereas SREBP-1c mainly controls fatty acid synthesis. SREBF2 encodes the SREBP-2 protein, which plays an important role in regulating cholesterol synthesis and uptake. (Fig. 3).

Currently, multiple signaling pathways control SREBP-1 activation to regulate adipogenesis involving downstream FASN, SCD1, etc., including EGFR, PI3K/Akt/mTOR, and AMPK pathways. Among them,

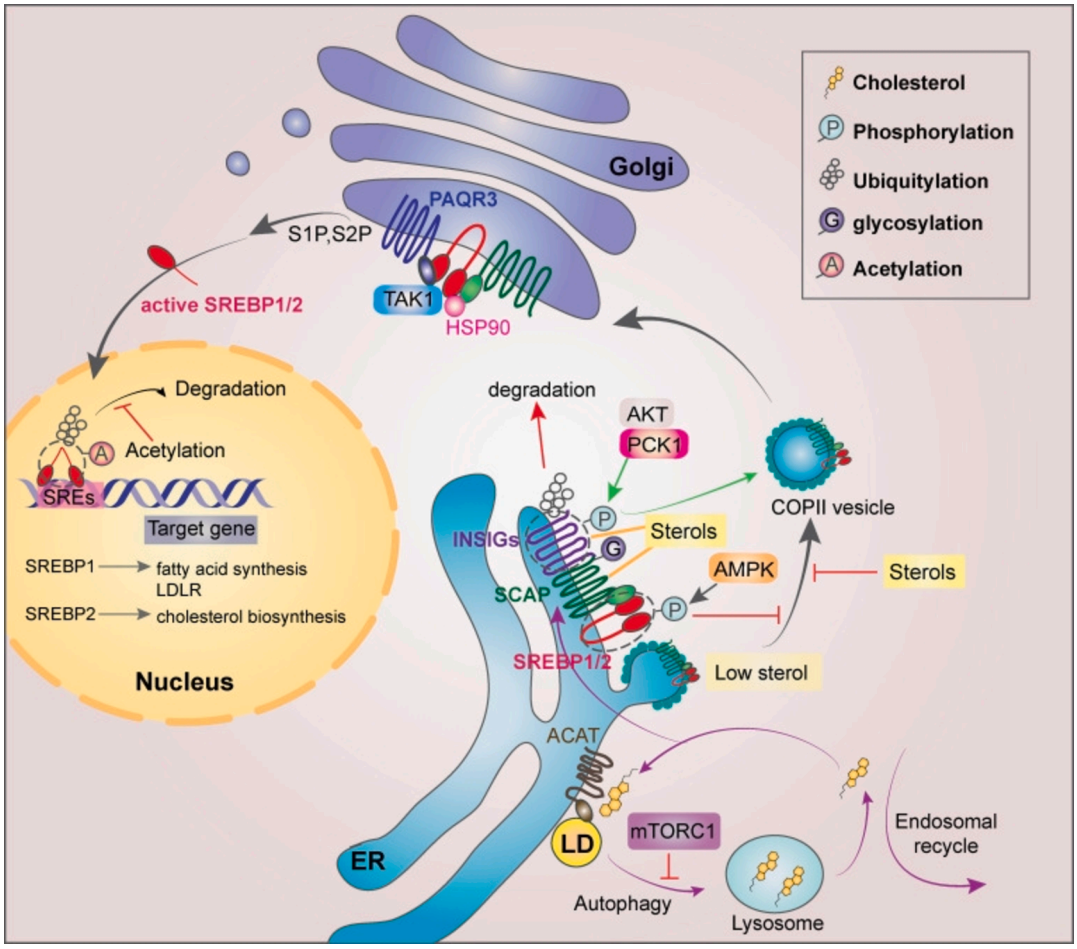

Fig. 3. Regulation of SREBP1/2 in cancer cells. SREBP activity can be regulated at multiple levels and at different subcellular localizations. In the ER, sterols bind to SCAP and disrupt the direct interaction between SCAP and COPII for the SREBP ER exit. When sterol level decreases, SCAP dissociates from INSIGs and facilitates the incorporation of SCAP/SREBP into COPII-coated vesicles. mTORC1 suppresses autophagy and subsequent cholesterol trafficking from the lysosome to the ER, leading to SREBP2 activation. Long-chain unsaturated FAs inhibit SREBP activation through inhibition of ubiquitylation of INSIG1. AKT-phosphorylated PCK1 phosphorylates INSIG1/2 and disrupts the bindings of oxysterols to INSIG1/2 for SREBP1/2 activation. In addition, activated AMPK can phosphorylate SREBP1/2 for their retention in the ER. EGFR activation enhances N-glycosylation of SCAP, triggering its dissociation from INSIG1. In the Golgi, SREBP1/2 are cleaved by S1P and S2P, releasing the transcriptionally active SREBP1/2. HSP90 facilitates the SREBP–SCAP complex transit from the ER to the Golgi. PAQR3 potentiates SREBP processing in the Golgi, whereas TAK1-mediated phosphorylation of SREBP1/2 inhibits SREBP. In the nucleus, truncated SREBP1/2 bind to SREs within the promoters of their target genes. GSK3-phosphorylated SREBP1/2 undergoes ubiquitylation and degradation, which can be counteracted by acetylation of the ubiquitylated Lys residues of SREBP1/2. LD, lipid droplet. Image from Bian X et al. 2020 [2] (open-access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited).

AKT can directly phosphorylate and activate SREBP, and mTORC1 can promote SREBP processing and nuclear translocation. Studies have found that miR-29, miR-185 and miR-342 can negatively regulate SREBP at the mRNA level [50]. In addition, the nucleotide transferase TUT1, which was significantly down-regulated in OS, could suppress the expression levels of PPAR-γ and SREBP-1c, two key regulators in adipogenesis, by up-regulating miRNA-24 and miRNA-29a, thereby inhibiting the development of OS [51].

However, the use of drugs directly inhibit SREBPs remains challenging, because transcription factors are not always easy to target. More promising methods may be inhibiting SREBP from ER to golgi body displacement [5]. SREBP-2 mainly adjusts this enzyme, inhibition of SREBP-2 has been explored for anticancer therapy [4]. But previous study have expounded statins inhibit cholesterol synthesis can cause SREBPs feedback activation, and did not have effective inhibit SREBP-2 drugs. So all of a variety of reasons, we would still need a further research in order to realize the transcription level of targeted therapy.

3.3. Lipid storage

In OS, elevated lipid uptake and increased endogenous synthesis inevitably lead to the accumulation of lipid pools. These pools originate from two primary pathways: first, acyl-CoA acyltransferase (ACAT) converts free cholesterol into cholesteryl esters (CE) in the endoplasmic reticulum (ER). Second, excessive fatty acids are ultimately converted into TAGs by diacylglycerol O-acyltransferase (DGAT). Both pathways culminate in the formation of lipid droplets (LDs), which help mitigate potential cellular damage from lipid peroxidation caused by an excess of free lipids [52,53](Fig. 1). When tumor cells face energy stress, fatty acids stored in LDs can be mobilized through β-oxidation to generate acetyl-CoA. Additionally, LDs serve as critical reservoirs for unsaturated fatty acids (UFAs), and the balance of monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs) within LDs may directly influence cell survival, including the regulation of ferroptosis. [54].

3.4. Fatty acid oxidation (FAO)

In lipid metabolism, FAO (fatty acid oxidation) is predominantly mediated through β-oxidation. First, fatty acids are activated into acyl-CoA by acyl-CoA synthetases located on the endoplasmic reticulum and outer mitochondrial membrane. These acyl-CoA molecules are then transported into the mitochondrial matrix via carnitine palmitoyltransferase 1 (CPT1) on the outer mitochondrial membrane and carnitine palmitoyltransferase 2 (CPT2) on the inner mitochondrial membrane. Once inside the mitochondrial matrix, a series of dehydrogenation, hydration, another dehydrogenation, and thiolysis reactions result in the production of acetyl-CoA, which enters the TCA cycle to generate ATP. Simultaneously, NADH and FADH2 produced during the oxidation process undergo oxidative phosphorylation, contributing further to energy production [2,6].

In normal cells, fatty acids are a vital energy source for cell growth and survival, especially under nutrient-limited conditions. Similarly, in OS, fatty acid catabolism is often elevated in response to high fatty acid uptake and synthesis. Evidence indicates that tumors upregulate CPT1 expression, which is associated with heightened FAO activity. Additionally, increased CPT1 expression promotes epithelial-mesenchymal transition (EMT) and stemness, thereby positively influencing tumor progression [55]. However, more research is needed to fully understand the alterations in FAO and its therapeutic potential in OS.

3.5. Reprogramming of lipid metabolism in the tumor microenvironment

It is well established that the tumor microenvironment (TME) is primarily characterized by hypoxic conditions due to oxygen deficiency, as well as an acidotic environment resulting from the accumulation of lactic acid metabolites from tumor cells and other cellular populations. Tumor cells adapt to limited nutrient availability and increased metabolic stress by modulating their own lipid metabolism and that of other cell populations within the TME. Simultaneously, changes in the microenvironment reciprocally influence cellular metabolism. This intricate relationship both advances our understanding of tumor metabolism and presents new opportunities for targeted therapeutic strategies.

3.5.1. Lipid metabolism in osteosarcoma under hypoxia and acidosis

In hypoxic conditions, OS cells exhibit increased dependence on fatty acid (FA) uptake, while the function of key lipid metabolic enzymes is affected. For instance, SCD1 requires oxygen to catalyze the formation of carbon double bonds for FA desaturation. Consequently, saturated fatty acids (SFAs) accumulate under hypoxic conditions due to impaired unsaturated fatty acid (UFA) formation. Tumor cells enhance UFA uptake and release from lipid droplets (LDs) to restore the SFA/UFA balance. However, hypoxia also increases SCD1 expression through SREBP1 regulation [56,57]. As previously mentioned, under hypoxic stress, a PI3K/AKT pathway-mediated positive feedback loop exists between HIF-2α and SCD1, ensuring sufficient endogenous fatty acid synthesis [42]. This apparent “contradiction” actually reflects the temporal differences and adaptive responses of tumor cells at both transcriptional regulation and functional execution levels. In the short term, due to limited SCD1 activity, tumor cells quickly restore SFA/UFA balance by enhancing exogenous UFA uptake and releasing UFAs from lipid droplets. Long-term, the HIF-2α/SREBP1 signaling axis upregulates SCD1 expression to ensure sustained endogenous UFA synthesis. This demonstrates the dynamic adaptation process of tumor cells from acute to chronic hypoxia.

Regarding lipid metabolism, acidic conditions mediate FA transport through CD36 and promote PUFA storage in LDs, thereby increasing lipid accumulation in tumor cells [58]. Cortini et al. demonstrated lipid accumulation in acidotic OS cells and in sarcoma tissues expressing the acid-related biomarker LAMP2 near tumors. Interestingly, this acid-induced lipid droplet accumulation serves cell survival rather than higher energy demands [58]. Specifically, this lipid accumulation is essential for OS to reduce oxidative stress and lipid peroxidation caused by acidosis [59]. Mechanistically, increased secretion of the signaling lipid sphingosine-1-phosphate (S1P) mediates acid-induced tumor survival and migration. Furthermore, treatment combining the S1P receptor modulator FTY720 (Fingolimod) with a low serine/glycine diet significantly inhibited both lipid accumulation and tumor growth, suggesting promising prospects for anti-S1P strategies. Additionally, acid-sensing receptors on tumor cell membranes, such as G protein-coupled receptor 1 (OGR1), can detect low pH and induce LD formation to counter acidosis-related cellular damage, further indicating that lipid accumulation in OS is an adaptive survival strategy [60].Moreover, under prolonged acidic pH conditions, the SIRT1/HIF2α axis reshapes tumor metabolism by regulating the expression of lactate transporters and glutamine metabolism-related genes, reducing glucose metabolism while enhancing glutamine metabolism, and altering cellular responses to metabolic-targeted therapies [61]. Acidic environments also exacerbate lipid peroxidation of ω-3 and ω-6 PUFAs, increasing PUFA toxicity and tumor cell sensitivity to ferroptosis [62]. At the transcriptional level, low pH regulates the expression of SREBP2 target genes, such as HMGCR and ACAT, and increases cholesterol biosynthesis [63]. Studies also report that acidic TME weakens anti-tumor immunity by altering macrophage polarization, reducing natural killer cell activity, promoting pro-tumor phenotype transformation of neutrophils, and impeding dendritic cell antigen presentation function, while enhancing cancer immune evasion capabilities [57]. Nevertheless, specific molecular mechanisms and signaling pathways, particularly how lactate regulates OS cell metabolism and the interaction between metabolism and immune regulation, remain understudied. Most current research remains at descriptive and correlative levels, indicating that more effort needs to be invested in exploring these mechanisms.

3.5.2. Metabolic Crosstalk between osteosarcoma and other cells

In exploring lipid metabolism changes within the tumor microenvironment, metabolic alterations in cell populations beyond OS cells are both complex and significant. For instance, tumor cells have been found to induce lipolysis in adjacent adipocytes, and fatty acids derived from adipocytes and cancer-associated fibroblasts (CAFs) can be utilized and stored by cancer cells [64]. Through integrated transcriptome analysis, researchers discovered that the fatty acid metabolism family member C1QBP is highly expressed in OS and correlates with tumor drug resistance and patient prognosis. A complex interaction network exists between OS cells and non-tumor cells. Multiple enriched signaling pathways are closely associated with fatty acid metabolism, tumor progression, drug resistance, and macrophage polarization [65].

Notably, different macrophage subpopulations exhibit distinct roles in OS progression: M1-type demonstrates anti-tumor activity, while M2-type (including tumor-associated macrophages) promotes tumor growth, invasion, and mediates immune evasion. Additionally, researchers identified pro-inflammatory M3-type macrophage (FABP4 +) infiltration in pulmonary metastatic OS lesions. In-depth transcriptome analysis further revealed elevated C1QBP expression in M2 and M3-type macrophages but reduced levels in M1-type, suggesting C1QBP's potential involvement in OS progression through macrophage polarization regulation. Similarly, Lin et al. found that pre-differentiated macrophages highly express lipid metabolism-related genes such as CD36, APOE, and APOC1, a pattern closely associated with poor treatment response and drug tolerance [66].

The impact of lipid accumulation due to abnormal lipid metabolism on tumor-microenvironment dendritic cells may partially account for poor prognosis. Previous studies have shown that lipid-containing dendritic cells fail to present tumor-associated antigens [67]. Abnormal lipid accumulation suppresses dendritic cells' ability to promote anti-tumor T cells [68]. In glucose-deficient TME, CD8 + T cells can enhance their effector functions by upregulating fatty acid catabolism to provide necessary energy for maintaining their effector functions.

As primary stromal cells in the TME, the metabolic interaction between CAFs and tumor cells is commonly referred to as the "reverse Warburg effect." This terminology stems from CAFs' participation in aerobic glycolysis and lactate secretion, while tumor cells utilize these metabolic products, creating a "reverse" relationship to the tumor cells' own Warburg effect. Furthermore, CAFs can promote glutamine synthesis, which is subsequently taken up and utilized by tumor cells to maintain nucleotide synthesis and OXPHOS. Research indicates that this metabolic interaction significantly impacts tumor cell proliferation, invasion, and metastasis [69]. Regrettably, despite numerous researchers exploring lipid metabolism patterns in the OS TME through experimental or bioinformatic approaches, related studies remain limited, potentially providing important insights for future research directions.

4. Regulation of ferroptosis by lipid metabolism

Ferroptosis is a form of programmed cell death driven by iron-dependent lipid peroxidation. This process involves several key mechanisms:

(a) Antioxidant system imbalance: Under normal conditions, cells possess multiple protective mechanisms against ferroptosis, with glutathione peroxidase 4 (GPX4) playing a central role. Cells import cystine from the extracellular environment via the cystine-glutamate antiporter (System Xc-), which is crucial for the intracellular synthesis of glutathione (GSH). GPX4 uses GSH as a substrate to reduce PL-OOH to PL-OH, limiting the accumulation of lipid peroxides. When this antioxidant system is disrupted, the plasma membrane becomes vulnerable, leading to ferroptosis.

(b) Iron overload and reactive oxygen species (ROS) accumulation: Iron overload in cells results in excessive ROS production. In the bloodstream, Fe^{3+} binds to transferrin and enters cells via transferrin receptor 1. Once inside, Fe^{3+} is reduced to Fe^{2+} and released into the cytoplasmic labile iron pool (LIP). Fe^{2+}, being highly reactive, generates hydroxyl radicals through the Fenton reaction, which in turn react with polyunsaturated fatty acids (PUFAs) in membranes, producing lipid ROS that induce cell death.

(c) Lipid peroxide accumulation: The synthesis and accumulation of lipid peroxides are critical for ferroptosis. Acyl-CoA synthetase long-chain family member 4 (ACSL4) catalyzes the conversion of arachidonic acid (AA) and adrenic acid (AdA) into their CoA derivatives. These are then esterified into phosphatidylethanolamines (PEs) by lysophosphatidylcholine acyltransferase 3 (LPCAT3), forming AA-PE and AdA-PE. Subsequently, these lipids undergo oxidation by lipoxygenases (LOXs) to produce lipid peroxides. Ultimately, the accumulation of lipid peroxides leads to plasma membrane damage, a hallmark of ferroptosis. Disruptions in lipid metabolism can alter cellular lipid composition and increase susceptibility to ferroptosis [54,6](Fig. 4).

In summary, ferroptosis depends on lipid peroxidation and membrane damage, with metabolic reprogramming affecting cellular vulnerability. The role of lipid metabolism and lipid-modifying enzymes in ferroptosis will be explored next, particularly in the context of OS.

4.1. Lipids in ferroptosis

Just as shown in Fig. 5, polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) play opposing roles in regulating ferroptosis. PUFAs, particularly arachidonic acid (AA) and adrenic acid (AdA), contain multiple double bonds, making them highly susceptible to oxidation by reactive oxygen species (ROS). This vulnerability makes phospholipids containing PUFAs key targets for ferroptosis. The incorporation of PUFAs into membrane phospholipids involves several enzymatic steps. First, ACSL4 catalyzes the conversion of PUFA to PUFA-CoA by linking it to coenzyme A. Next, LPCAT3 facilitates its esterification into phosphatidylethanolamine, forming PUFA-PL. Finally, LOXs generate oxidized PUFA-PL-OOH, promoting ferroptosis.

In contrast, MUFAs, which have fewer double bonds, are less prone to peroxidation [70]. MUFAs suppress ferroptosis by replacing more oxidizable PUFAs in membrane phospholipids. As mentioned earlier, SCD1, the enzyme responsible for MUFA synthesis, is significantly upregulated in OS. Thus, it is evident that OS cells exploit the modulation of the key enzyme SCD1 to increase intracellular MUFAs, thereby reducing their sensitivity to ferroptosis. This change highlights the importance of metabolic reprogramming. Therefore, investigating the metabolic balance between PUFAs and MUFAs is crucial for understanding lipid metabolism-related ferroptosis.

Additionally, CoQ10, an important endogenous antioxidant produced via the mevalonate pathway, can be regenerated in its reduced form (CoQ10-H2) by ferroptosis suppressor protein 1 (FSP1) at the plasma membrane. In OS, active cholesterol synthesis promotes the generation of CoQ10-H2, with both CoQ10-H2 and cholesterol playing synergistic roles in tumor adaptation to the microenvironment [71].

4.2. Lipid metabolic enzymes in ferroptosis

(1) ACSL4(acyl-CoA synthetase long-chain family member 4):

ACSL4 is a key enzyme responsible for maintaining lipid homeostasis and is implicated in the pathogenesis of several cancers, including OS [72,73]. Researches have shown that ACSL4 expression is upregulated in OS, with higher levels correlating with increased tumor malignancy. In the context of ferroptosis, ACSL4 exhibits a dual function. On one hand,

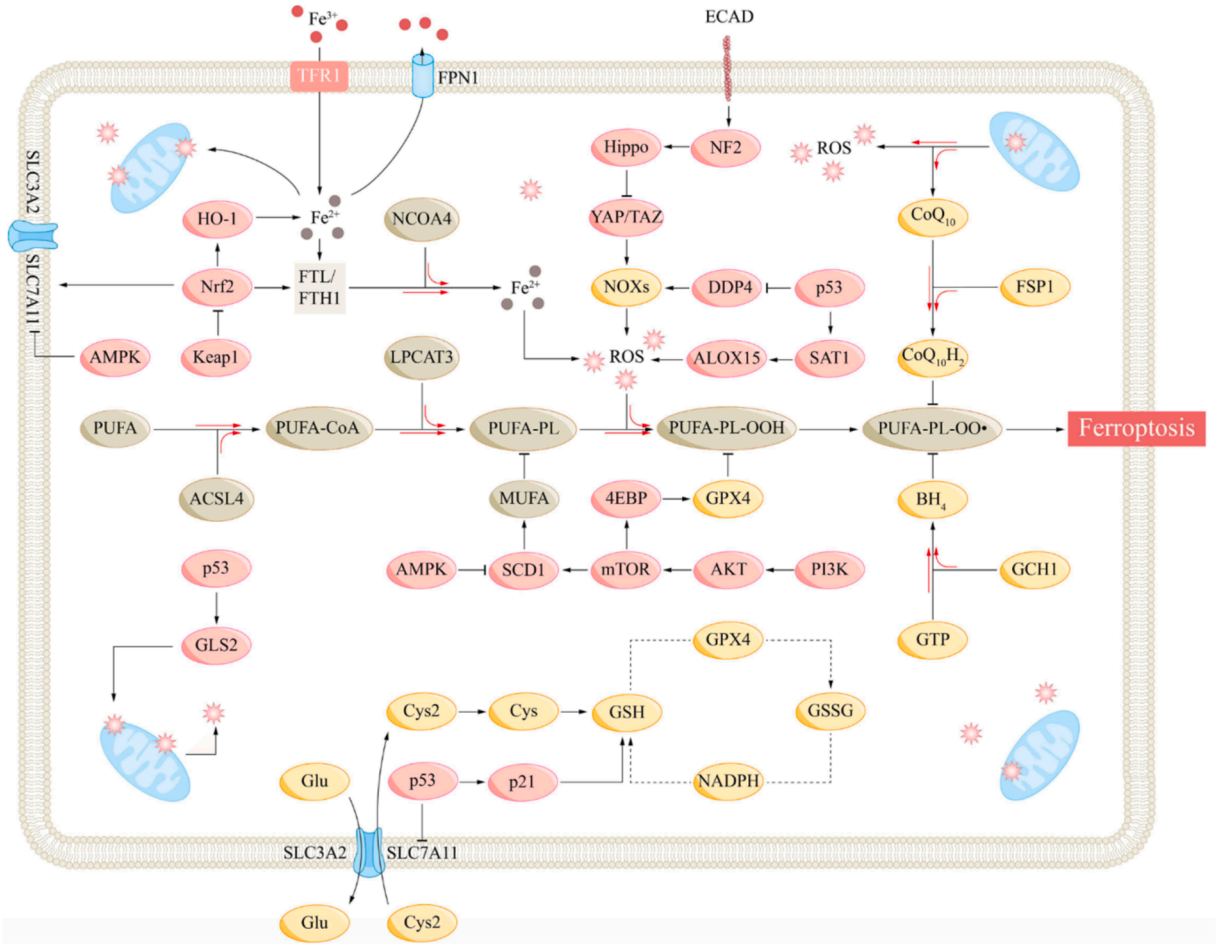

Fig. 4. Mechanisms and important regulatory signaling pathways of ferroptosis. Image from Chen H et al. 2023 [71] (open-access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited).

it promotes OS cell proliferation via the TGF-β/Smad2 signaling pathway [74]. On the other hand, as a key enzyme in lipid peroxidation, ACSL4 mediates the production of lipid peroxides (LPO), thereby increasing the sensitivity of OS cells to ferroptosis.

(2) ACSL3(acyl-CoA synthetase long-chain family member 3):

Unlike ACSL4, ACSL3 converts monounsaturated fatty acids (MUFAs) synthesized by SCD1 into acyl-CoA esters, which are then incorporated into membrane phospholipids, protecting tumor cells from ferroptosis [54]. However, it has been found that OS cells are often exposed to energy stress due to their rapid growth and limited oxygen supply, which inhibits mTOR signaling activity and weakens ACSL3 expression through BRD4-SRPK2-SRSF2 axis, thereby reducing erastin-induced ferroptosis [75]. Such accidental phenomenon is to reflect the tumor cells in the bad environment policy: in the process of a variety of metabolic balance, the ultimate goal to meet its survival.

5. Therapeutic strategies targeting lipid metabolism and ferroptosis in OS

5.1. Targeted therapies in fatty acid metabolism pathways

Targeting the fatty acid metabolism pathway offers a promising strategy for the treatment of OS. One approach involves targeting fatty acid uptake pathways, such as fatty acid transporters or receptors, to prevent cancer cells from absorbing exogenous fatty acids. Another strategy focuses on inhibiting enzymes involved in fatty acid synthesis to disrupt the production of lipids essential for tumor growth. For the former, it was previously demonstrated that the deletion of CD36 in the prostate of PTEN-/- mice, which are prone to cancer, significantly reduced fatty acid absorption, thereby decreasing the abundance of oncogenic lipid signals and attenuating cancer progression [76,77]. Furthermore, sulfo-N-succinimidyl oleate (SSO), a fatty acid analog, inhibits the uptake of long-chain fatty acids and oxidized low-density lipoproteins (oxLDL) by competitively binding to CD36. SSO is commonly used in vitro to disrupt CD36 activity. However, research on the in vivo safety of SSO has produced conflicting results [78]. Additionally, no studies have yet explored the inhibition of fatty acid uptake as a therapeutic strategy for OS. Even if in vitro experiments demonstrate successful blockage, the clinical translation of this approach may be hindered by off-target effects or systemic toxicity.

Targeting enzymes for therapeutic strategies has recently focused on ACLY, FASN, and SCD1. Research on ACLY has demonstrated that miRNA-mediated interference with ACLY synthesis effectively suppresses its expression, leading to a reduction in the proliferative and invasive capacities of OS cells while promoting cell apoptosis. Specifically, miR-22 has been identified as a key post-transcriptional regulator of ACLY. Not only in OS but also in prostate cancer, cervical cancer, and lung cancer, miR-22 has shown promising therapeutic potential [79].

In the therapy of tumor lipid metabolism, FASN inhibitors are one of the first strategies in this field [80]. Studies have found that miR-195 negatively regulates the oncogene FASN by binding to a specific site on its 3′-UTR [34]. Additionally, α-linolenic acid also downregulated the

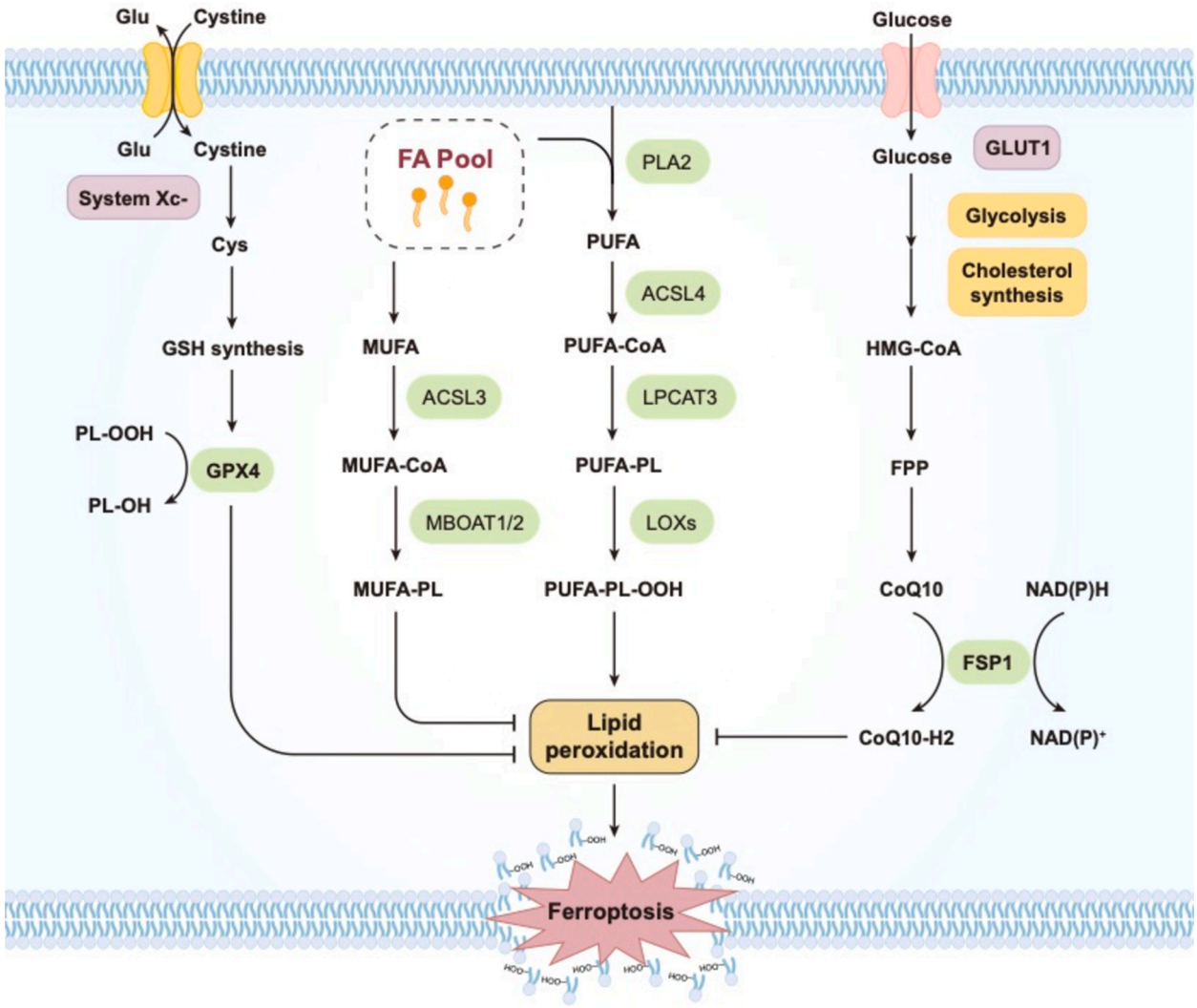

Fig. 5. Peroxidation of specific lipid components of lipid metabolism is a central driving mechanism of ferroptosis. In lipid metabolism, the proportion of various fatty acids has a significant effect on ferroptosis. Only PUFAs present on lipid substances such as phospholipids (PUFA-PL), but not free PUFAs, can activate the ferroptosis mechanism when they are peroxidized after catalysis by enzymes such as ACSL4 and LPCAT3 (PUFA-PL-OOH). However, because MUFA contains only one double bond compared with PUFA, it is not easy to be oxidized, and it can reduce the content of PUFA in the plasma membrane by replacing PUFA, thereby resisting ferroptotic death. In addition, the classical System XC-GSH-GPX4 system and NAD(P)H/FSP1/CoQ10 system are also defense mechanisms against ferroptosis.

expression of FASN and inhibited the proliferation and migration of OS cells in a dose-dependent manner [81]. In contrast, upregulation of miR-424 targeted FASN to inhibit OS cell migration and invasion [35]. LY294002, the PI3K family specific inhibitor, inhibits the malignant phenotype of OS cells in vitro by regulating the PI3K/Akt/FASN signaling pathway [81]. Meanwhile, lapatinib, a human epidermal growth factor receptor 2 (HER2) phosphorylation inhibitor, was also shown to inhibit this pathway to significantly reduce the migration and invasion abilities of OS cells in vitro [82]. Although the efficacy and mechanism of lapatinib in reducing the malignant phenotype of OS cells in vivo are not yet clear, the positive feedback loop between HER2 and FASN identified in this study provides promising information for the use of HER2 phosphorylation inhibitors in the treatment of OS. That is, it can break a hyperactive de novo fatty acid biogenesis. Moreover, oleic acid (OA), the primary MUFA in olive oil, which is a key component of the "Mediterranean diet", has recently been found to inhibit HER2 overexpression in tumor cells [83]. Specifically, studies show that exogenous supplementation of OA at physiological concentrations can significantly reduce the levels of the p185 (Her-2/neu) oncoprotein encoded by HER2 in tumor cells with natural HER gene amplification. This reduction in HER2 expression also impacts FASN levels. However, if HER2-amplified cancer cells do not express high levels of FASN, the OA-induced inhibition of HER2 promoter activity does not occur [84]. Fortunately, due to the positive feedback loop between HER2 and FASN in OS cells, the active form of HER2 protein is diminished in OS cells with low FASN expression [31]. This reduction limits their proliferative and metastatic potential. This characteristic compensates for the limitations of OA-enriched diets in improving the malignant phenotype of OS, making it a potentially valuable therapeutic strategy. At the transcriptional level, silencing of nuclear factor Y(NF-YA) significantly inhibited the migration and invasion of OS cells in vitro by reducing the expression of FASN. CircREOS inhibits HuR-mediated MYC activation to reduce FASN expression and lipid accumulation [85].

The strategy of targeting SCD1 appears to hold considerable promise. Utilizing siRNA to disrupt de novo synthesis of MUFAs in OS cells not only directly impairs the lipid energy supply but also alters the composition ratio of PUFAs to MUFA in phospholipids. This change indirectly increases the susceptibility of OS cells to ferroptosis. Moreover, SCD1 deficiency has been shown to induce cell death through the activation of the unfolded protein response (UPR) and CHOP pathway

[86]. Such SCD1-targeting approaches appears to be particularly effective in inducing cell death.

Overall, although significant challenges remain in targeting lipid uptake, there has been substantial progress in therapeutic strategies that focus on key enzymes. Clinical trials using either FASN inhibitors alone or in combination with chemotherapy have shown improved tumor survival rates, providing new avenues for treatment. Nonetheless, further theoretical and practical evidence needs to be presented.

5.2. Targeted therapies in cholesterol synthesis pathways

Targeting the cholesterol synthesis pathway provides an alternative approach for the treatment of OS. Inhibitors targeting key enzymes in cholesterol biosynthesis, such as HMG-CoA reductase, have been investigated for their anticancer effects. HMGCR inhibitors such as simvastatin, as a widely used drug targeting the cholesterol synthesis pathway, specifically inhibit HMG-CoA reductase (HMGCR), reduce the production of mevalonate, and then reduce the synthesis of cholesterol.

It has long been shown that statins can induce apoptosis in OS cells through RhoA inactivation. For example, inactivated RhoA inhibits the JNK-c-Jun signaling pathway thereby reducing MMP2 activity and OS cell invasion [49]. Inactivation of RhoA also reduced the levels of phospho-p42 / p44-mitogen-activated protein kinases (MAPKs) and Bcl-2 to induce apoptosis in OS cells [87,88]. In addition, simvastatin also induced apoptosis of OS cells by directly activating AMPK and p38 MAPK. Metformin could enhance this effect by further activating AMPK [89].

The existing statistics show that OS cells have a strong metastatic ability, and the 5-year survival rate of patients with distant metastasis is very low. Therefore, it is very important to find a therapeutic method for OS metastasis. It has been shown that simvastatin, an HMGCR inhibitor, inhibits the metastasis of OS by inhibiting YAP1 activity by inactivating RhoA. [39] Statins, which block the Ras/MEK/ERK and Ras/PI3K/Akt pathways, reduce the expression of bFGF, HGF, and TGF-β as angiogenic factors in OS [90].

In addition to its anti-tumor ability, simvastatin also has the potential to promote osteogenesis. Novel 3D-printed titanium alloy scaffolds loaded with simvastatin and temperature-sensitive polylactic acid-co-glycolic acid copolymer-polyethylene glycol-polylactic acid-co-glycolic acid copolymer (PLGA-PEG-PLGA) hydrogel induced ferroptosis of OS cells by up-regulating transferrin (TF) and NADPH oxidase 2 (NOX2) levels. This dual effect promotes anti-tumor activity and bone defect repair in vitro and in vivo [86]. Compared with the systemic delivery system, which requires a significant first metabolism, local delivery of simvastatin using a drug carrier such as hydrogel can ensure drug concentration and has good osteogenic and anti-tumor effects [49,91]. In the future, targeted local administration may become a trend in the treatment of OS. (Fig. 6).

Modulation of the MVA pathway by statins is easy to achieve, but its negative feedback leads to activation of SREBPs and increased expression of MVA pathway genes, and this effect may be amplified in cancer cells. SREBP activation, for example, can increase the expression of LDLR, resulting in exogenous cholesterol intake increased, the effect has been shown to promote the biological behavior of cancer cells [92], but there is no specific research in OS. As discussed above, there is currently no effective inhibition of cholesterol uptake in OS, so the anti-tumor effect of statins alone in patients with OS is limited. Combining drugs targeting SREBPs with statins may become a feasible strategy.

5.3. Targeted therapies in ferroptosis pathways

At present, the targeted therapy of OS based on the iron metabolism pathway and GSH-GPX4 pathway in ferroptosis has been explored, such as inhibiting FSP1 (inhibitor of ferroptosis protein 1) or GPX4 to increase OS cell death [93]. However, there are few studies on the lipid peroxidation pathway. As mentioned above, the role of enzymes in the lipid peroxidation pathway in the occurrence and development of OS is often multiple, so the purpose of improving tumor prognosis cannot be achieved by single inhibition or activation. Dierge etc. have found, however, beyond starving tumor cells through metabolic pathway

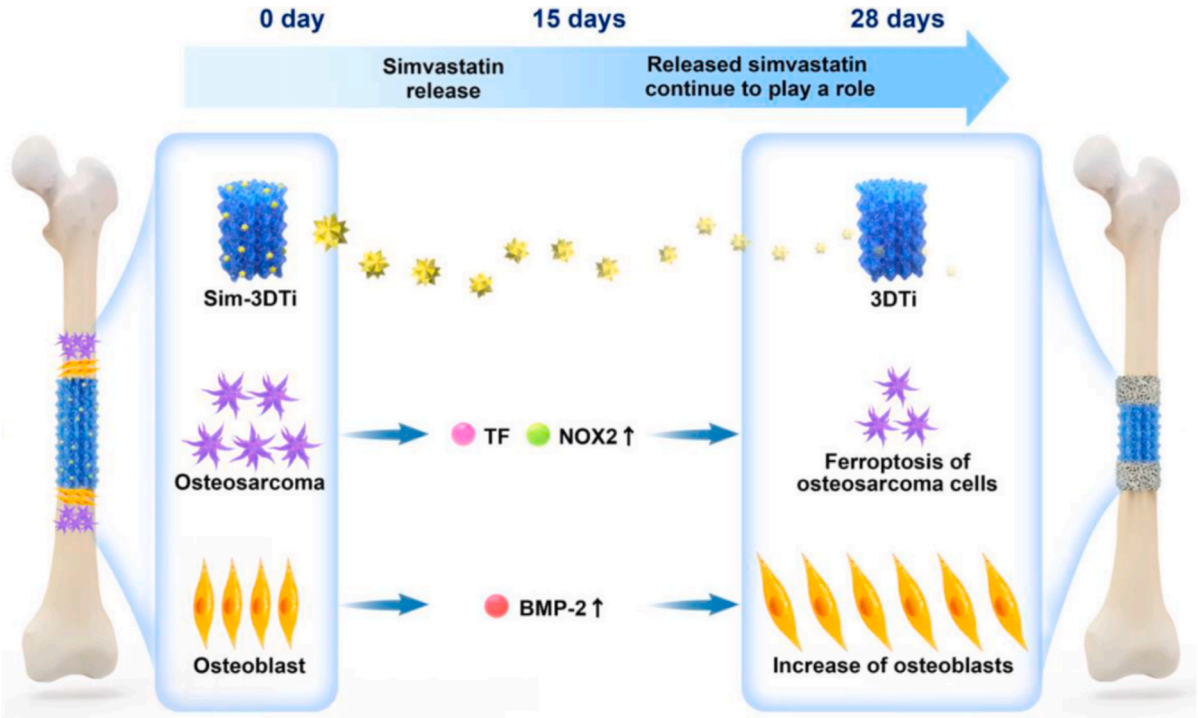

Fig. 6. Anti-osteosarcoma and osteogenic mechanisms of Sim-3DTi. Image from Jing Z et al. 2024 (open-access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited).

inhibition, the introduction of specific nutrients can also have detrimental effects, representing an underappreciated therapeutic vulnerability. By leveraging the tendency of tumor cells to accumulate lipids in acidic environments, they demonstrated that supplementing exogenous PUFAs could induce ferroptosis and slow tumor growth [63]. This provides us with a novel perspective of targeted therapy.

Despite the potential of the iron death in cancer treatment have been recognized, but the development of effective clinical drug remains challenging. Thus, to ultimately improve clinical outcome in patients with OS, many obstacles need to be overcome.

6. Conclusion

Lipid metabolic reprogramming in OS cells represents a complex and multifaceted phenomenon that significantly contributes to the tumor's malignant behavior. The upregulation of enzymes involved in lipid uptake and de novo synthesis, such as ACLY, ACSS2, FASN, and SCD1, not only supports the structural and functional demands of rapidly dividing OS cells but also confers resistance to ferroptosis. The mevalonate pathway, with HMGCR as a key enzyme, is highly activated in OS, further promoting tumor growth and metastasis.

Targeting lipid metabolism and ferroptosis pathways has emerged as a promising therapeutic strategy for OS. The use of FASN inhibitors, statins, and modulation of the MVA pathway presents a novel approach to disrupt the lipid metabolic reprogramming and induce ferroptosis in OS cells. However, the effectiveness of these therapies may be limited by compensatory mechanisms, acquired resistance, and potential off-target effects. Taking together the previously described approaches for targeting OS, we found the role of miRNA to be prominent, given that BMSCS-derived extracellular vesicles have been considerably investigated in tumor suppression. It is reasonable to speculate that targeting OS cells with extracellular vesicles carrying miRNAs that inhibit tumor progression and metastasis holds great promise.

Despite these challenges, the potential of lipid metabolism-targeted therapies in combination with existing treatments holds great promise for improving the clinical outcomes of OS patients. Future research should focus on elucidating the precise molecular mechanisms, identifying biomarkers for patient stratification, and developing combination therapies to overcome resistance. The exploration of ferroptosis as a therapeutic target also warrants further investigation, particularly in the context of lipid peroxidation pathways and their complex interplay with cellular metabolism. By harnessing the vulnerabilities exposed by lipid metabolic reprogramming and ferroptosis, we may pave the way for more efficacious and personalized treatment strategies for OS.

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8. Relationships

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9. Patents and Intellectual Property

There are no patents to disclose.

10. Other activities

There are no additional activities to disclose.

CRediT authorship contribution statement

Zhiyang Yin: Writing – review & editing, Writing – original draft, Software, Resources, Investigation, Data curation, Conceptualization. **Guanlu Shen:** Writing – review & editing, Writing – original draft. **Minjie Fan:** Writing – review & editing, Writing – original draft. **Pengfei Zheng:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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