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Research Progress on the Common Mechanisms of the DLAT Gene in Osteoarthritis and Osteoporosis

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Abstract: ***Osteoarthritis (OA) and osteoporosis (OP) are two prevalent skeletal diseases that severely impair patients' health and quality of life. In recent years, studies have found that the DLAT gene may share common mechanisms in both diseases. Dihydrolipoamide acetyltransferase, encoded by the DLAT gene, is a key enzyme in the tricarboxylic acid cycle, participating in cellular energy metabolism and maintenance of cellular function. Research indicates that DLAT plays a critical role in multiple mechanisms, including cuproptosis, metabolic reprogramming, crosstalk regulation of immune inflammation, and epigenetic modification. These mechanisms collectively contribute to the onset and progression of OA and OP. This review summarizes the mechanisms of the DLAT gene in OA and OP, explores its potential as a diagnostic biomarker and therapeutic target, and provides a theoretical basis for future research and clinical applications.***

Keywords: DLAT, Osteoarthritis, Osteoporosis, Cuproptosis, Metabolic Reprogramming, Common Mechanisms**.**

1. Introduction

Osteoarthritis (OA) and osteoporosis (OP) are two common skeletal diseases, characterized by articular cartilage degeneration and hyperosteogeny (OA), as well as decreased bone mass and disrupted bone microarchitecture (OP), respectively. They severely affect the health and quality of life of hundreds of millions of people worldwide. According to Tang et al. [1], OA is one of the leading causes of disability globally, affecting approximately 300 million people worldwide, with a significantly increased prevalence with age. A systematic review and meta-analysis by Xiao et al. [2] reported that OP is even more prevalent, affecting over 200 million people globally, with postmenopausal women and elderly men being high-risk groups.

In terms of pathophysiological mechanisms, although OA and OP differ in pathological processes, both involve abnormal bone metabolism and may share common molecular pathways. OA primarily involves an imbalance between degradation and repair of articular cartilage, synovial inflammation, subchondral bone remodeling, and osteophyte formation [3]. OP is mainly manifested as a disrupted dynamic balance between bone formation and bone resorption, with bone resorption exceeding bone formation, leading to decreased bone mass and damaged bone microarchitecture [4]. Despite distinct pathological processes, both OA and OP involve abnormal bone metabolism and may share common molecular pathways. Clinically, the diagnosis and treatment of these two diseases face challenges. In recent years, molecular biology and genetic studies have shown that certain genes play important roles in pathogenesis. As a key enzyme in the tricarboxylic acid cycle, the DLAT gene may influence bone tissue homeostasis and repair by regulating energy metabolism and cellular function. However, its specific mechanisms in these two diseases remain unclear and require further investigation.

Studying the mechanisms of the DLAT gene in OA and OP can enhance our understanding of the molecular pathological basis of the diseases and provide targets for developing new therapeutic strategies. Elucidating its regulatory networks and signaling pathways in both diseases contributes to understanding bone metabolism mechanisms and offers new insights for clinical diagnosis and treatment.

2. Structure and Biological Functions of DLAT

Dihydrolipoamide acetyltransferase (DLAT), encoded by the DLAT gene, is a key enzyme and a core metabolic enzyme in the mitochondrial matrix, playing a pivotal role in cellular energy metabolism [5]. The DLAT protein consists of multiple subunits, each containing a conserved lipoamide-binding domain and a catalytic domain. The lipoamide-binding domain binds lipoamide coenzymes, while the catalytic domain catalyzes acetyl group transfer reactions. These two domains collectively ensure the normal function of DLAT. As a coenzyme, lipoamide participates in acetyl group transfer reactions through disulfide bonds and amide groups at its active site [6]. The structure of the DLAT protein is highly conserved, and specific amino acid residues in its active center are critical for substrate binding and catalytic reactions. As a component of the pyruvate dehydrogenase complex (PDC), DLAT catalyzes acetyl group transfer in the tricarboxylic acid (TCA) cycle to generate acetyl-CoA, linking glycolysis and the TCA cycle. Additionally, in the α-ketoglutarate dehydrogenase complex (KDC), DLAT converts α-ketoglutarate to succinyl-CoA, driving the progression of the TCA cycle [5]. These reactions not only supply energy for cells but also produce various metabolic intermediates for biosynthesis. In the regulation of cellular energy metabolism, DLAT influences energy production efficiency by controlling the rate of pyruvate entry into the TCA cycle. Furthermore, DLAT regulates the balance between fatty acid synthesis and oxidation, affecting energy storage and utilization. In terms of oxidative stress regulation, DLAT promotes the production of NADH and $FADH_2$, driving the electron transport chain and ATP generation.

However, abnormal activity may lead to increased reactive oxygen species (ROS), impairing the antioxidant defense system [7].

3. Mechanisms of DLAT in OA

3.1 Cuproptosis Pathway

In chondrocytes, activation of the cuproptosis pathway may profoundly impact cellular function and cartilage matrix homeostasis. Chondrocytes are highly specialized cells responsible for synthesizing and maintaining the cartilage matrix, including key components such as collagen and proteoglycans [8]. Upon cuproptosis activation, chondrocytes affect cartilage function through the following mechanisms: First, cuproptosis induces mitochondrial dysfunction, primarily by interfering with lipoylated DLAT proteins in mitochondria, reducing ATP production and thereby impairing the anabolic function of chondrocytes. Second, damage-associated molecular patterns (DAMPs) released during cuproptosis may trigger local inflammatory responses, further exacerbating cartilage damage. Finally, cuproptosis may reduce chondrocyte numbers, indirectly impairing the maintenance and repair capacity of the cartilage matrix [9]. A complex interaction exists between cuproptosis and cartilage matrix degradation. Cuproptosis-induced inflammation upregulates the expression of matrix-degrading enzymes, while cellular contents released after chondrocyte death may directly activate matrix degradation pathways [10].

3.2 Inflammatory and Immune Regulation

Inflammatory responses and immune dysregulation play key roles in the pathogenesis of OA. Gonzalo et al. [11] revealed that DLAT participates in the conversion of pyruvate (a glycolytic intermediate) to acetyl-CoA, potentially regulating inflammatory responses and immune cell function by influencing lactate metabolism. Studies have shown that lactate promotes the polarization of pro-inflammatory macrophages (M1 type) to anti-inflammatory macrophages (M2 type), thereby inhibiting inflammation [12, 13]. As a key enzyme in pyruvate metabolism, DLAT expression directly affects lactate production. Altered lactate metabolism influences immune cell recruitment and activation, thereby regulating the intensity of inflammatory responses. In the pathological process of OA, infiltration and activation of immune cells are critical drivers of joint destruction. Immune cells regulate osteoclast formation and bone metabolism through multiple mechanisms, particularly in inflammatory bone resorption diseases [14]. DLAT may influence immune cell recruitment and activation by modulating lactate metabolism. Manoharan et al. [15, 16] demonstrated that lactate-dependent regulation can alter the effector functions of dendritic cells and macrophages, shaping immune responses in the tissue microenvironment. This regulation of the metabolism-immune axis may serve as a key mechanism by which DLAT influences OA inflammation.

3.3 Metabolic Reprogramming

Metabolic reprogramming is a critical mechanism for cells to adapt to different physiological and pathological states and is essential for OA progression. In OA, chondrocytes undergo significant metabolic changes, including reprogramming of glucose, lipid, and amino acid metabolism. In terms of glucose metabolism, DLAT participates in the conversion of pyruvate to acetyl-CoA, a key step linking glycolysis and the TCA cycle. In OA chondrocytes, glucose metabolism undergoes substantial reprogramming, characterized by enhanced glycolysis and reduced oxidative phosphorylation [17]. This metabolic shift leads to lactate accumulation and an acidic microenvironment, further promoting cartilage matrix degradation and inflammation. Altered DLAT expression directly affects the efficiency of pyruvate entry into the TCA cycle, thereby influencing energy production and biosynthetic capacity of chondrocytes. Impaired DLAT function disrupts pyruvate metabolism, causing accumulation of glycolytic intermediates, activating the HIF-1α signaling pathway, and promoting a catabolic phenotype in chondrocytes [18]. Lipid metabolic reprogramming is another hallmark of OA chondrocyte metabolism. DLAT affects the balance between fatty acid synthesis and oxidation by regulating acetyl-CoA production. In normal chondrocytes, lipid metabolism remains relatively stable, providing essential lipid components for cell membranes and energy reserves. However, under OA conditions, chondrocytes exhibit lipid accumulation and enhanced fatty acid oxidation [19]. Dysregulated DLAT function disrupts the acetyl-CoA pool, altering the expression of lipid metabolism-related genes such as PPARγ and SREBP1. These transcription factors regulate fatty acid synthase expression, promoting lipid accumulation, exacerbating endoplasmic reticulum stress and oxidative stress, and ultimately leading to chondrocyte dysfunction and death [20]. Amino acid metabolism also plays a critical role in chondrocyte metabolic reprogramming. DLAT indirectly regulates amino acid metabolism by influencing TCA cycle intermediate production. Glutamine, an important energy and nitrogen source for chondrocytes, undergoes significant metabolic changes during OA. Studies have shown that glutaminolysis is enhanced in OA chondrocytes, generating α-ketoglutarate to enter the TCA cycle and compensate for energy deficiency [21].

In summary, DLAT promotes OA progression by mediating cuproptosis, regulating inflammatory immune responses, and driving metabolic reprogramming. Its dysfunction leads to chondrocyte death, inflammatory factor release, and energy metabolism disorders, disrupting cartilage matrix homeostasis and ultimately accelerating joint degeneration. Targeting DLAT-related pathways may provide new strategies for OA treatment.

4. Mechanisms of DLAT in OP

4.1 Bone Metabolism Regulation

Bone metabolism is a dynamic balance of bone formation and resorption mediated by osteoblasts and osteoclasts, respectively, and is regulated by multiple factors. Cellular metabolism plays a key role in their differentiation and function, and metabolic reprogramming in bone metabolism regulation has become a research hotspot in recent years [17]. Osteoblasts are the primary executors of bone formation, and their differentiation requires substantial energy and metabolic intermediate support. Osteoblast differentiation is accompanied by significant metabolic reprogramming,

shifting from glycolysis-dominated energy acquisition to oxidative phosphorylation-dominated metabolism [22]. Osteoclasts are the main executors of bone resorption, and their differentiation and function are also tightly regulated by metabolism. Osteoclast differentiation relies on the synergistic action of glycolysis and mitochondrial oxidative phosphorylation [23, 24]. As a key node linking glucose metabolism and the TCA cycle, DLAT plays an important role in normal bone metabolism. In OP, dysfunction of DLAT may cause energy metabolism disorders, disrupting the balance between osteoblasts and osteoclasts. Immune cells also play a critical role in bone metabolism regulation, particularly in inflammatory bone diseases. Immune cells directly or indirectly influence osteoblast and osteoclast differentiation and function by secreting cytokines and chemokines [14].

4.2 Inflammasome Activation

The inflammasome is a key component of the innate immune system, and its activation is closely associated with multiple bone metabolic diseases. Sustained inflammasome activation in both OA and OP is considered an important driver of disease progression. As a key enzyme in the TCA cycle, DLAT may indirectly regulate inflammasome activation by influencing cellular metabolic status. Chondrocytes and osteoblasts undergo metabolic reprogramming from oxidative phosphorylation to glycolysis in an inflammatory microenvironment, a process tightly regulated by AMPK and mTOR pathways [25, 26]. Accumulation of metabolic intermediates, particularly lactate, significantly affects inflammasome activity. Aleksandra et al. [27] found that lactate, beyond acting as an energy substrate, regulates immune cell function through epigenetic modification, altering gene expression programs in pro-inflammatory T cells. This crosstalk between metabolism and immunity may be a key mechanism by which DLAT influences inflammasome activation. Adrian et al. [28] identified mitochondrial dysfunction as a critical link between metabolic abnormalities and inflammasome activation. Impaired mitochondrial function releases mitochondrial DNA and reactive oxygen species (ROS), directly activating the NLRP3 inflammasome. The mechanism of bone loss induced by inflammasome activation involves multiple cell types and molecular pathways. Galectin family members (e.g., Gal-1, -4, -7, and -8) are upregulated in inflammatory cartilage injury and positively correlate with cartilage erosion progression, suggesting their involvement in bone loss by regulating inflammasome activity [29].

4.3 Cuproptosis and Oxidative Stress

DLAT plays a dual role in oxidative stress responses. On one hand, as a core component of the TCA cycle, DLAT maintains energy metabolism and redox balance. On the other hand, abnormally elevated intracellular copper levels trigger lipoylation and aggregation of DLAT. In bone cells, this abnormal DLAT aggregation disrupts mitochondrial function, increases reactive oxygen species (ROS) production, forming a vicious cycle that further exacerbates oxidative stress. Excess copper directly induces cuproptosis in bone cells, reducing osteoblast numbers and impairing function [30]. Additionally, copper indirectly affects bone resorption by influencing osteoclast differentiation and activity [31]. Metal toxicity also causes mitochondrial dysfunction, further increasing ROS production and forming a positive feedback loop that accelerates bone tissue destruction [32]. In OP models, environmental factors such as circadian rhythm disruption disrupt bone metabolism balance, reducing bone density and trabecular number and impairing bone mineralization capacity. Oxidative stress-related pathways are activated, and pro-inflammatory cytokines (e.g., IL-1β, IL-6, iNOS, and TNF-α) are upregulated, promoting inflammation and bone resorption [33]. These changes are consistent with the mechanism of cuproptosis-induced cell death, suggesting cuproptosis as a key link between oxidative stress and bone loss.

In summary, DLAT promotes OP progression through multiple mechanisms, including regulating bone metabolism balance, mediating inflammasome activation, and participating in cuproptosis and oxidative stress. Its dysfunction leads to energy metabolism disorders, pro-inflammatory factor release, and aggravated oxidative damage, disrupting the osteoblast-osteoclast balance and ultimately causing bone loss and structural degeneration.

Table 1: Comparison of DLAT Expression and Regulation in OA and OP

Disease	Expression Change	Major Regulatory Factors	Main Cell Types	References
OA	Significantly Upregulated	IL-1β, TNF-α, HIF-1α	Chondrocytes, Subchondral Bone Osteoblasts	[34, 35]
OP	Significantly Upregulated	Estrogen Deficiency, ROS, Glucocorticoids	Osteoblasts, Osteocytes	[36]

5. Common Mechanisms of DLAT in OA and OP

5.1 Core Role of Cuproptosis

Zhou et al. [37] found that the core mechanism of cuproptosis involves direct binding of copper ions to DLAT (dihydrolipoamide acetyltransferase), a key protein in the mitochondrial TCA cycle. This binding induces DLAT aggregation, disrupts the TCA cycle, and triggers cell death. As the center of energy metabolism and metal ion homeostasis, mitochondrial structural and functional damage causes abnormal metal ion distribution, accelerating cellular dysfunction and even death. In OA and OP, mitochondrial dysfunction activates copper-dependent cell death, accelerating tissue degeneration [38]. Additionally, copper ions are closely associated with the activity of inflammatory factors and matrix metalloproteinases (MMPs), which play critical roles in OA pathogenesis [39]. In OP, disrupted copper homeostasis impairs osteoblast differentiation and function, affecting bone formation. Cuproptosis reduces osteoblast numbers and function, decreasing bone formation and increasing fracture risk. Therefore, DLAT-mediated cuproptosis may be a key factor linking the common pathological mechanisms of OA and OP [40].

5.2 Metabolic and Energy Disorders

As a core component of the pyruvate dehydrogenase complex (PDHc), dihydrolipoamide acetyltransferase encoded by DLAT plays a pivotal role in cellular energy metabolism. It catalyzes the conversion of pyruvate to acetyl-CoA, linking glycolysis and the TCA cycle. This process is critical for maintaining cellular energy balance, and any disruption may lead to severe metabolic consequences [41]. Mitochondrial dysfunction is a common pathological feature of OA and OP. Normally, mitochondria generate ATP via oxidative phosphorylation to supply energy for cells. However, impaired DLAT function reduces pyruvate entry into mitochondria, blocking the TCA cycle and reducing ATP production [42]. Energy metabolism imbalance not only impairs the normal function of chondrocytes and osteoblasts but also triggers a series of pathological changes, including increased oxidative stress, activated inflammation, and apoptosis. In OA, chondrocytes have high energy demands and primarily rely on glycolysis for energy. Impaired mitochondrial metabolism forces chondrocytes to increase glycolysis rates, leading to lactate accumulation and intracellular acidification, further impairing cartilage matrix synthesis and repair [43]. Meanwhile, energy deficiency reduces chondrocyte responsiveness to growth factors and cytokines, disrupting normal extracellular matrix turnover. In OP, energy metabolism is equally critical for osteoblasts. Mitochondrial dysfunction-induced energy metabolism disorders inhibit osteoblast differentiation and function while promoting osteoclast formation and activity [44]. Abnormal mitochondrial function reduces ATP production, impairing osteoblast bone formation capacity and exacerbating bone damage via increased oxidative stress [45]. Metabolic and energy disorders directly impair cellular function and amplify disease progression through multiple mechanisms. Energy imbalance activates inflammasomes, promoting pro-inflammatory cytokine release and forming a chronic inflammatory microenvironment that accelerates cartilage and bone destruction [46]. Additionally, metabolic dysregulation impairs autophagy, reducing clearance of damaged organelles and proteins and exacerbating intracellular deterioration [47]. These findings support DLAT-mediated metabolic disorders as a common mechanism in both diseases.

5.3 Crosstalk Regulation of Immune Inflammation

A close crosstalk exists between metabolism and immune responses, termed "immunometabolism", which plays a critical role in maintaining tissue homeostasis and disease pathogenesis [48]. Immune inflammation crosstalk is key to OA and OP pathogenesis, and DLAT, as a key enzyme in lactate metabolism, plays a pivotal role in this process. DLAT influences immune cell function and phenotypic transformation by regulating lactate metabolism. Long considered a harmless byproduct of glucose metabolism, lactate is now recognized as a complex immunomodulatory molecule that controls the effector functions of innate and adaptive immune cells [49]. In inflammatory microenvironments, lactate promotes polarization of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages, reducing pro-inflammatory cytokine production [16]. This phenotypic transformation is critical for timely inflammation resolution and tissue repair. In joint and bone microenvironments, DLAT-regulated lactate metabolism exerts dual effects on inflammation. On one hand, lactate accumulation exacerbates local inflammation under OA and OP pathological conditions. On the other hand, appropriate lactate levels regulate and resolve inflammation by promoting macrophage polarization and modulating T cell function [50]. Studies have shown that lactate regulates dendritic cell and macrophage function, influencing the initiation and regulation of adaptive immune responses [27]. This complex regulatory network establishes DLAT as a key factor linking metabolism and immune inflammation.

5.4 Epigenetic Regulation

Epigenetic regulation plays a critical role in gene expression, influencing gene activity without altering DNA sequences. DNA methylation, a major epigenetic modification, regulates gene expression by adding methyl groups to DNA, altering gene activity and cellular responsiveness to external stimuli [51]. In OA and OP, DNA methylation changes in the DLAT gene promoter or regulatory regions may affect its expression. Hypermethylation often silences genes, while hypomethylation promotes expression. Triggered by environmental or disease factors, these changes lead to abnormal DLAT expression, impair mitochondrial function and energy metabolism, and ultimately contribute to bone pathology. Dynamic changes in chromatin domains are key mechanisms of epigenetic regulation. Studies have shown that gene co-regulation primarily occurs in specific chromatin domains, typically located in less active B compartments and containing functionally similar genes [52]. The DLAT gene may reside in such domains, forming a co-regulatory network with other bone metabolism-related genes. Altered activation of these domains manifests as compartment switching and internal contact changes rather than large-scale boundary alterations. This chromatin reprogramming disrupts DLAT and related gene expression, impairing the balance between bone formation and resorption.

In summary, DLAT participates in the onset and progression of OA and OP through multiple mechanisms, including cuproptosis induction, energy metabolism disorders, immune inflammation regulation, and epigenetic changes. As a key target of cuproptosis and a core metabolic enzyme, DLAT influences cell death, energy supply, immune microenvironment, and gene expression regulation, providing a critical foundation for understanding the common pathogenesis of both diseases and developing intervention strategies.

Table 2: Summary of Common Mechanisms of OA and OP Mediated by DLAT

Common Mechanism	Role in OA	Role in OP	References
Mediating Cuproptosis	Induces chondrocyte death and cartilage degeneration	Induces osteoblast death and reduces bone formation	[39, 53]
Triggering Metabolic Reprogramming	Forces chondrocytes to shift to glycolysis, impairing function	Inhibits osteoblast mitochondrial metabolism, blocking differentiation	[25, 54]
Exacerbating Oxidative Stress	Generates excessive ROS, damaging chondrocytes	Generates excessive ROS, activating osteoclasts	[55, 56]

Driving Inflammatory Responses	Maintains chronic joint inflammation, destroying cartilage	Creates a pro-osteoclast inflammatory microenvironment, promoting bone resorption	[57]
Affecting Bone Remodeling	Induces abnormal subchondral bone remodeling, accelerating OA	Causes systemic bone remodeling imbalance, triggering OP	[33]

6. Potential of DLAT as a Diagnostic Biomarker and Therapeutic Target

6.1 Diagnostic Value

Biomarkers play a vital role in disease diagnosis, enabling assessment of biological processes, pathological processes, and drug responses. In the era of precision medicine, validated biomarkers are particularly critical for clinical decision-making. An ideal biomarker should exhibit high sensitivity, specificity, stability, accessibility, and cost-effectiveness, enabling early detection of abnormalities and providing opportunities for intervention. Dihydrolipoamide acetyltransferase encoded by the DLAT gene is a key enzyme in the TCA cycle, participating in energy metabolism and cellular function maintenance. Metabolic abnormalities are central to OA and OP pathogenesis, making DLAT a potential biomarker [58]. In OA, impaired chondrocyte energy metabolism drives disease progression; in OP, the balance between osteoblasts and osteoclasts is regulated by metabolic pathways. Thus, DLAT and its related metabolites may reflect changes in disease metabolic status. Biomarkers enable early disease detection in asymptomatic stages via monitoring DLAT expression or activity changes, providing opportunities for early intervention. Similar to DNA methylation in early cancer detection [59], DLAT-related metabolic profiling may serve as a screening tool for OA and OP. In particular, liquid biopsy, detecting changes in DLAT-related molecules in blood or other body fluids, enables non-invasive or minimally invasive disease monitoring. Prognostic assessment is a key application of biomarkers. DLAT expression or activity changes may correlate with disease progression, severity, and complication risk. Clinically, dynamic monitoring of biomarkers [60] enables assessment of disease progression and treatment response. Disease subtyping is the foundation of precision medicine, requiring distinct therapeutic strategies for different subtypes. Varied DLAT expression patterns in OA or OP patients may aid subtype classification, facilitating personalized treatment. Combined with multi-omics analysis, similar to enhanced early cancer detection via circulating tumor DNA testing [61], combined application of DLAT with other biomarkers may improve disease subtyping accuracy and clinical utility.

6.2 Therapeutic Strategies

With advancing understanding of DLAT function, multiple potential therapeutic approaches targeting the DLAT gene in OA and OP are being explored. Development of DLAT-targeted drugs primarily focuses on modulating its metabolic activity and influencing downstream signaling pathways. Leveraging DLAT's role as a key component of the pyruvate dehydrogenase complex, small molecules specifically regulating its activity can be developed [62]. Drug design requires consideration of DLAT structural features and functional domains to achieve precise regulation of metabolic pathways. Additionally, optimization of drug delivery systems, particularly bone-targeted delivery, enhances therapeutic efficacy and reduces systemic side effects. Gene therapy offers novel therapeutic avenues for DLAT-related diseases. Single-dose gene therapy may provide durable and curative benefits, offering hope for chronic diseases such as OA and OP [63]. Combination therapy is critical for enhancing efficacy. Given the complexity of OA and OP, single-target drugs often yield unsatisfactory outcomes. Thus, therapeutic implementation requires multidisciplinary collaboration among basic researchers, clinicians, and drug developers.

In summary, as a key enzyme in energy metabolism, DLAT exhibits dual potential as a diagnostic biomarker and therapeutic target in OA and OP. Its expression or activity changes reflect disease metabolic status, enabling early non-invasive screening, prognostic assessment, and disease subtyping. Therapeutically, DLAT can be targeted via small molecule modulators, gene therapy, and multidisciplinary strategies to intervene in metabolic pathways and enable personalized treatment.

7. Summary and Outlook

As a core molecule linking energy metabolism and cuproptosis, DLAT plays a pivotal role in the onset and progression of OA and OP. It participates in pathological processes such as chondrocyte degeneration and osteoblast-osteoclast imbalance through multiple mechanisms, including regulating cuproptosis, driving metabolic reprogramming, mediating immune inflammation crosstalk, and modulating epigenetic modification, highlighting its common molecular basis in both skeletal diseases. Changes in DLAT expression or activity not only have potential as biomarkers for early diagnosis, subtyping, and prognostic assessment of the diseases but also provide new directions for developing therapeutic strategies targeting the metabolism-immune microenvironment (e.g., small molecule drugs, gene intervention, and combination therapies).

Future research should further explore the dynamic regulatory mechanisms of DLAT across different disease stages and subtypes, clarify the association between its gene polymorphisms and disease susceptibility, and promote the clinical translation of DLAT-based precision diagnostic tools and multi-modal therapeutic strategies.

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