Ferroptosis in musculoskeletal disorders: Emerging mechanisms and therapeutic opportunities (Review)

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Abstract. Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, has emerged as a key mechanism underlying tissue degeneration and impaired regeneration in musculoskeletal disorders. Although ferroptosis is associated with conditions such as tendinopathy, sarcopenia, osteoarthritis and osteoporosis, systematic synthesis connecting molecular mechanisms with disease-specific contexts and translational implications remains limited. The present review summarizes the fundamental molecular mechanisms of ferroptosis, including iron metabolism dysregulation, lipid peroxidation processes and antioxidant defense systems centered on GPX4 and glutathione. Subsequently, the involvement of ferroptosis across major musculoskeletal diseases was investigated, highlighting how iron imbalance, oxidative stress and age-related alterations collectively contribute to tissue dysfunction and degeneration. Particular emphasis is placed on aging-associated changes in iron homeostasis and antioxidant capacity as potential amplifiers of ferroptotic vulnerability in musculoskeletal tissues. Experimental modeling strategies and pharmacological modulation approaches used to investigate ferroptosis in musculoskeletal research are further discussed and their mechanistic relevance and translational challenges are analyzed. Finally, the present review outlines emerging therapeutic perspectives and future research directions aimed at improving the understanding and potential clinical targeting of ferroptosis in musculoskeletal disorders. By providing a structured and integrative synthesis, the present review clarifies the role of ferroptosis at the intersection of iron dysregulation, redox imbalance and musculoskeletal decline.

Contents

1. Introduction of ferroptosis

Musculoskeletal disorders, including tendinopathy, sarcopenia, osteoarthritis and osteoporosis, represent a major and growing global health burden, with osteoarthritis affecting 32.5 million adults in the United States, osteoporosis affecting 8.4-17.7% of middle-aged and elderly adults and nearly half of skeletal muscle mass being lost by the age of 80 years due to sarcopenia (1,2), particularly in aging populations (3). These conditions are characterized by progressive tissue degeneration, impaired regenerative capacity and limited therapeutic options capable of restoring structural and functional integrity. Despite advances in understanding inflammatory signaling and mechanical stress-related injury, several aspects of musculoskeletal degeneration remain insufficiently explained at the level of regulated cell death and metabolic vulnerability (4,5). This gap suggests that additional mechanisms may underlie the progressive loss of tissue homeostasis observed in these disorders. Previous studies have identified ferroptosis, an iron-dependent form of regulated cell death driven by lipid

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peroxidation, as a potential contributor to tissue degeneration in multiple organ systems (6,7). Increasing evidence indicates that ferroptosis may intersect with iron dysregulation, oxidative stress and aging-associated metabolic alterations, features that are highly relevant to musculoskeletal tissues (8-11). These findings raise the possibility that ferroptosis represents a previously underappreciated mechanism in musculoskeletal decline (Fig. 1).

Ferroptosis, first identified in 2012 (7), is a regulated form of iron-dependent cell death characterized by excessive lipid peroxidation and failure of antioxidant defense systems. It is driven by intracellular iron accumulation, depletion of glutathione (GSH), inactivation of GSH peroxidase 4 (GPX4) and subsequent oxidative damage to membrane phospholipids (11-14). Unlike necrosis or apoptosis, ferroptosis is associated with cellular metabolic state and redox homeostasis, forming a self-amplifying cycle among iron overload, reactive oxygen species (ROS) generation and lipid peroxidation (12,15). At the molecular level, dysregulation of iron-handling proteins, including transferrin receptor (TFRC), ferritin and ferroportin, contributes to free iron accumulation and promotes Fenton chemistry-mediated ROS production (16-23). Lipid peroxidation of polyunsaturated fatty acids, particularly in cellular membranes, represents a hallmark event of ferroptosis, while GPX4 and the system the cystine/glutamate antiporter (Xc^-/) GSH axis serve as central antioxidant defenses that counteract this process (24-28). Mitochondrial dysfunction and oxidative stress further amplify ferroptotic signaling, as altered membrane potential, ROS overproduction and ferritinophagy-mediated iron release accelerate lipid damage and cell death (Fig. 2) (29-33).

Musculoskeletal tissues possess unique metabolic and structural characteristics that may render them particularly susceptible to ferroptotic injury (4). Tendons and cartilage are relatively avascular and rely heavily on tightly regulated redox balance, while skeletal muscle exhibits high metabolic demand and mitochondrial activity (34). Moreover, aging-associated alterations in iron homeostasis, stem cell function and antioxidant capacity may further amplify ferroptotic vulnerability across these tissues (34). These features suggest that ferroptosis could represent a convergent mechanism underlying degeneration and impaired regeneration in the musculoskeletal system.

The present review aims to provide a comprehensive and disease-oriented synthesis of current evidence regarding ferroptosis in musculoskeletal disorders. The fundamental molecular mechanisms of ferroptosis is first summarized followed by examination of its involvement in major musculoskeletal conditions, including tendinopathy, sarcopenia, osteoarthritis and osteoporosis. The present review further discuss aging-related modulation, experimental modeling strategies and emerging therapeutic perspectives to clarify the potential translational significance of targeting ferroptosis in musculoskeletal disease.

2. Application of ferroptosis in the musculoskeletal system

Musculoskeletal tissues exhibit distinct metabolic and structural characteristics that may influence their susceptibility to ferroptotic injury. Skeletal muscle is highly metabolically active and relies on robust mitochondrial function to sustain contractile activity. This high oxidative demand renders muscle fibers and muscle stem cells particularly sensitive to redox imbalance and iron-mediated lipid peroxidation (35-38). Notably, activation of ferroptosis in muscle stem cells has been shown to impair regenerative capacity by disrupting intracellular iron homeostasis and antioxidant defenses, leading to excessive lipid peroxidation and mitochondrial dysfunction. These alterations compromise satellite cell viability and functional maintenance, thereby contributing to accelerated muscle aging (39). Tendons, by contrast, are relatively avascular connective tissues with limited intrinsic antioxidant capacity (40,41). Their restricted blood supply may compromise redox buffering under stress conditions, potentially increasing vulnerability to iron accumulation and lipid peroxidation. Aging-associated dysfunction of tendon-derived stem cells further contributes to impaired repair, and emerging research suggests that ferroptosis may participate in this degenerative process (9,42,43). However, the interaction between cellular senescence, iron metabolism and ferroptosis remains complex and may vary depending on ferritinophagy status and intracellular iron handling (44). Bone tissue undergoes continuous remodeling through tightly regulated interactions between osteoblasts, osteoclasts and osteocytes (45). This dynamic process involves substantial metabolic activity and iron flux. A recent study have identified ferroptosis as a potential mechanism contributing to osteocyte loss and cortical bone degeneration during aging (46). Collectively, these tissue-specific characteristics suggest that ferroptosis may represent a convergent mechanism associating metabolic stress, iron dysregulation and impaired regeneration across the musculoskeletal system.

To provide a comparative overview of ferroptosis involvement across musculoskeletal tissues and diseases, the present review systematically summarizes key ferroptosis-related biomarkers reported in tendinopathy, muscle degeneration, sarcopenia, osteoporosis and other degenerative conditions, highlighting shared molecular signatures and conserved regulatory pathways (Table I).

The occurrence of ferroptosis in tendinopathy. Tendinopathy is commonly defined as unexplained tendon pain and may be associated with tears, inflammatory entheses or chronic degenerative lesions. It is a prevalent sports injury, with varying incidence rates across athletic populations: The rate of achilles tendon rupture reaches 52% in former elite runners, 24% in competitive athletes and 18% in athletes under 45 years of age; patellar tendinopathy affects 45% of volleyball players and 32% of basketball players (47), and chronic tendinopathy is often observed alongside more severe conditions, such as tendon damage or rupture (48), although causal relationships remain to be fully established. In 2022, a study suggested a potential association between ferroptosis and tendinopathy. In particular, Wu *et al* (49) reported that treatment with Farrerol (FA) was associated with a reduction in collagenase-induced tendinopathy, potentially involving modulation of ferroptosis. The study observed that tendinopathy is associated with iron accumulation in tendon cells and that FA treatment coincided with reduced lipid peroxidation, increased GSH levels and decreased iron accumulation, consistent with reduced ferroptosis. However, the study also observed that FA treatment

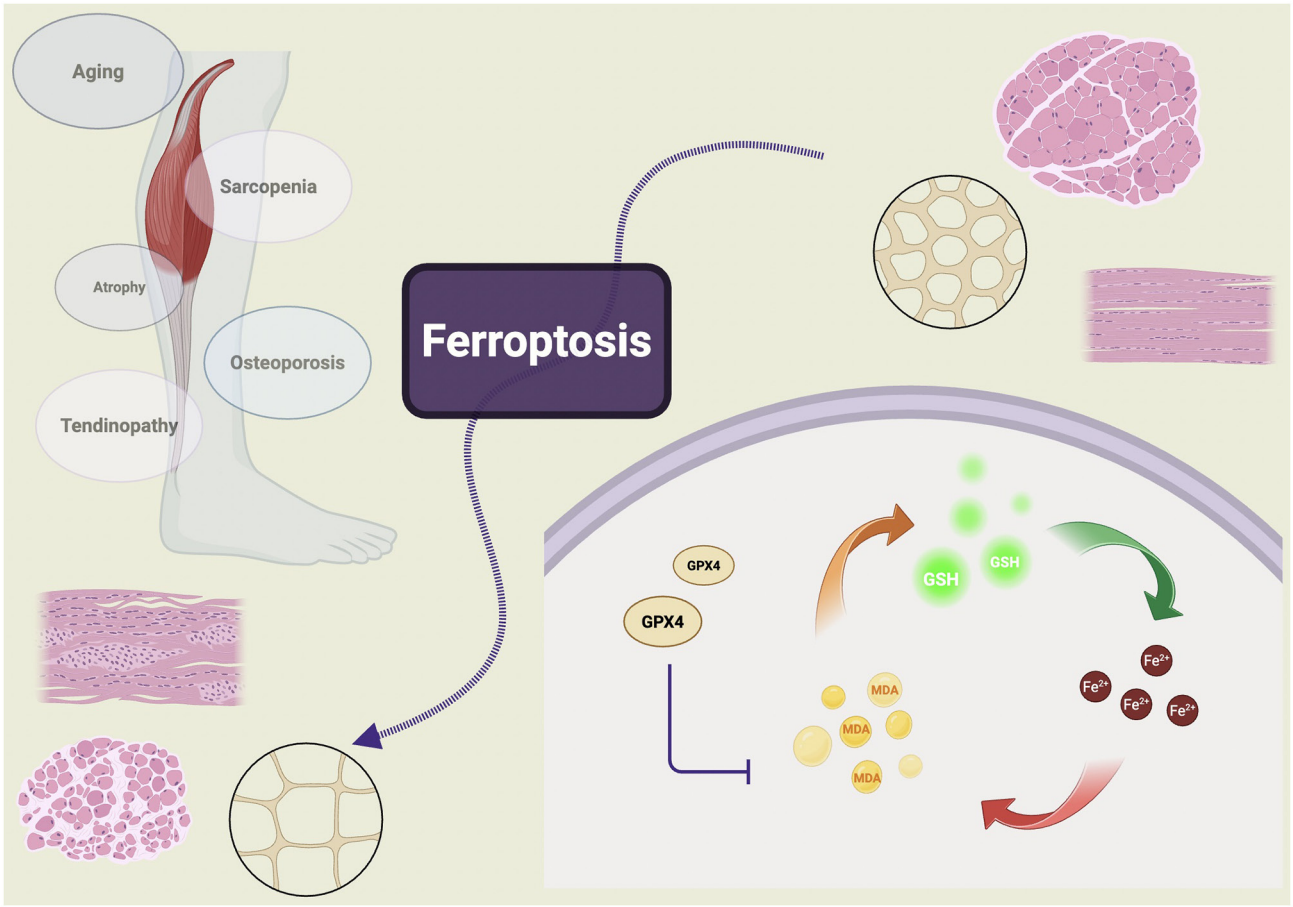

Figure 1. Graphical abstract illustrating the role of ferroptosis in musculoskeletal disorders. The diagram summarizes the core mechanisms of ferroptosis, including iron metabolism dysregulation, lipid peroxidation and impairment of antioxidant defense systems such as GPX4. These processes contribute to tissue degeneration across skeletal muscle, tendon, cartilage, intervertebral disc and bone. GSH, glutathione; GPX4, glutathione peroxidase 4; MDA, malondialdehyde.

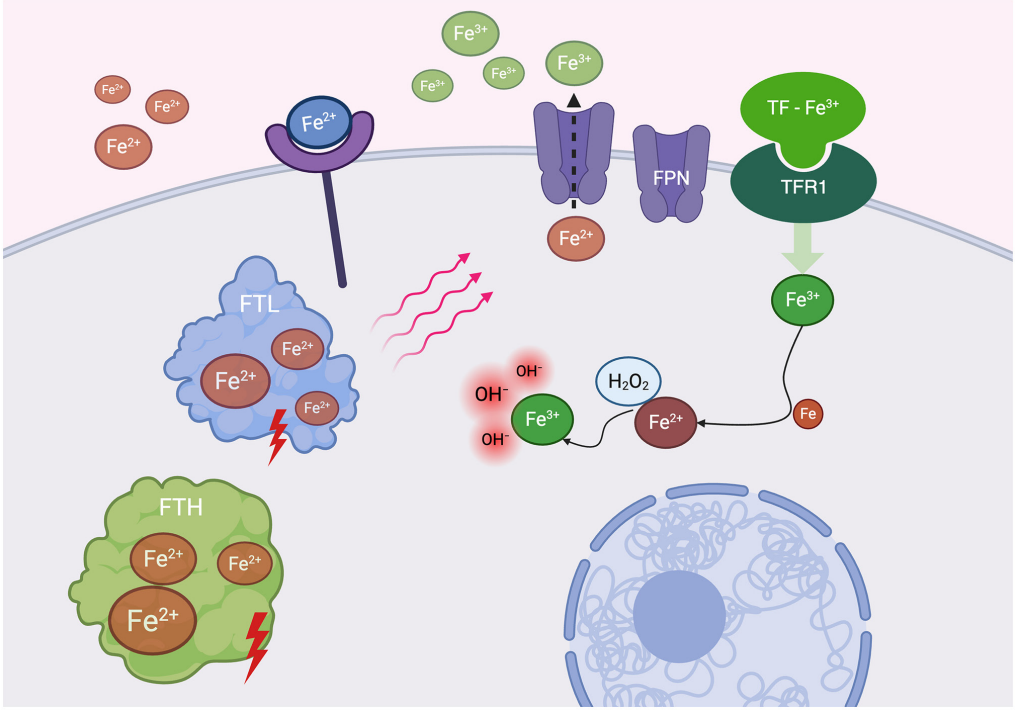

Figure 2. Schematic illustration of ferritin-mediated regulation of iron homeostasis in ferroptosis. Ferritin maintains intracellular iron balance by storing excess iron in a non-toxic form. Disruption of ferritin turnover, particularly via ferritinophagy, leads to increased release of labile iron, enhanced Fenton reaction-mediated reactive oxygen species production and subsequent lipid peroxidation, thereby facilitating ferroptotic cell death. TFR1, transferrin receptor 1; FPN, ferroportin; FTL, ferritin light chain; FTH, ferritin heavy chain.

Table I. Important biomarker of ferroptosis in musculoskeletal system related diseases.

Diseases	Biomarkers	(Refs.)
Tendinopathy	GPX4, SLC7A11, FSP1	(49)
Tendinopathy	ACSL4, GPX4, TfR1	(42)
Tendinopathy	GPX4, SLC7A11	(43)
Aged tendon	GPX4, ACSL4	(9)
Aged skeletal muscle	TfR1, SLC39A14, GPX4, FTH	(39)
Sarcopenia	SLC7A11, GPX4	(57)
Muscle wasting	ACSL4, GPX4	(57)
Muscle aging	FTH, GPX4, SLC7A11, FTL	(56)
Muscle aging	ACSL4, GPX4	(61)
Osteoporosis	GPX4, ACSL4	(101)
Osteoporosis	TFR1, FPN, GPX4, SLC7A11	(120)
Postmenopausal osteoporosis	GPX4, SLC7A11	(102)
Intervertebral disc degeneration	ACSL4, GPX4, FTH	(115,123)
Intervertebral disc degeneration	ACSL4, GPX4	(113)
Osteoarthritis	FTH, GPX4	(122)

ACSL4, acyl-CoA synthetase long-chain family member 4; FPN1, ferroportin 1; GPX4, glutathione peroxidase 4; TfR1, transferrin receptor protein 1; FTH, ferritin heavy polypeptide 1; FTL, ferritin light polypeptide; SLC7A11, solute carrier family 7 member 11.

was associated with reduced inflammatory cell response and infiltration (49), suggesting a potential association between ferroptosis and inflammation. Differential gene expression analysis from RNA sequencing of rotator cuff injury samples treated with the anti-inflammatory agents celecoxib and lactoferrin showed an association with ferroptosis (50). Subsequent analysis of differential genes in rotator cuff injury identified key ferroptosis-related genes, such as Acsl3, Cybb, Ascl4, Flt3, and Sat1 and further confirmed that ferroptosis is indeed interconnected with inflammation in rotator cuff tears. This finding indicated a possible association between ferroptosis inhibition and reduced inflammatory markers (51), though causality remains to be determined. Ferroptosis is also frequently associated with metabolic diseases, with diabetes being a typical example. A Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of differential genes in rotator cuff tear samples from diabetic and non-diabetic patients revealed an association with the ferroptosis signaling pathway (52). In a study on the db/db mouse model of diabetes, changes in the cellular microenvironment were found to make the mice more prone to tendinopathy, which was associated with ferroptosis (42). In the study by Wang *et al* (42), YAP, a key transcription factor in the Hippo signaling pathway known to be involved in various types of cancer (53), was found to associate with ACSL4 expression. Both YAP and ACSL4 levels were elevated in the diabetic microenvironment, coinciding with increased markers of ferroptosis, suggesting a potential regulatory association between YAP, ACSL4 and ferroptosis. The study observed that ferroptosis inhibitors were associated with reduced signs of diabetes-induced tendinopathy (42). The occurrence of tendinopathy is accompanied by the aging of tendon stem cells, which is triggered by oxidative stress. Gao *et al* (43) reported that hydrogen peroxide-induced oxidative stress in tendon stem cells activates the cGAS-STING signaling pathway in parallel with mitochondrial damage, mitophagy dysregulation and ferroptosis-related molecular alterations, ultimately contributing to tendinopathy-associated pathological phenotypes. Mechanistically, these findings support the cGAS-STING pathway as a stress-responsive damage-sensing signaling axis activated under oxidative stress conditions, rather than as a primary upstream driver of ferroptosis initiation. Within this framework, cGAS-STING is more appropriately positioned as a downstream modulatory and signal-amplifying node within the oxidative stress-mitochondrial dysfunction-ferroptosis regulatory network in tendon stem cells. Its activation may enhance inflammatory signaling and ferroptosis susceptibility through feedback regulation and pathway cross-talk, thereby contributing to degenerative progression. Further studies are warranted to clarify its hierarchical positioning and regulatory interactions in tendon degeneration. Another study on tendon stem cell aging and ferroptosis found that ferroptosis could promote tendon stem cell aging, leading to tendon degeneration and aging, while also affecting tendon-bone healing and mechanical strength (9). Therefore, tendon stem cell aging may be triggered by ferroptosis, which occurs concurrently with tendinopathy. Additionally, a bioinformatics analysis of sequencing data from patients with frozen shoulder revealed an association with ferroptosis. Ferroptosis influences the pathological processes of frozen shoulder and Il-6, Hmox1 and Tlr4 genes have been identified as potential therapeutic targets for this condition (54), as supported by transcriptomic and computational analyses conducted using established bioinformatics frameworks.

Current research associating ferroptosis to tendon stem cell aging and impaired regeneration is primarily derived from indirect indicators, including alterations in molecular expression profiles, increased oxidative stress levels, dysregulated

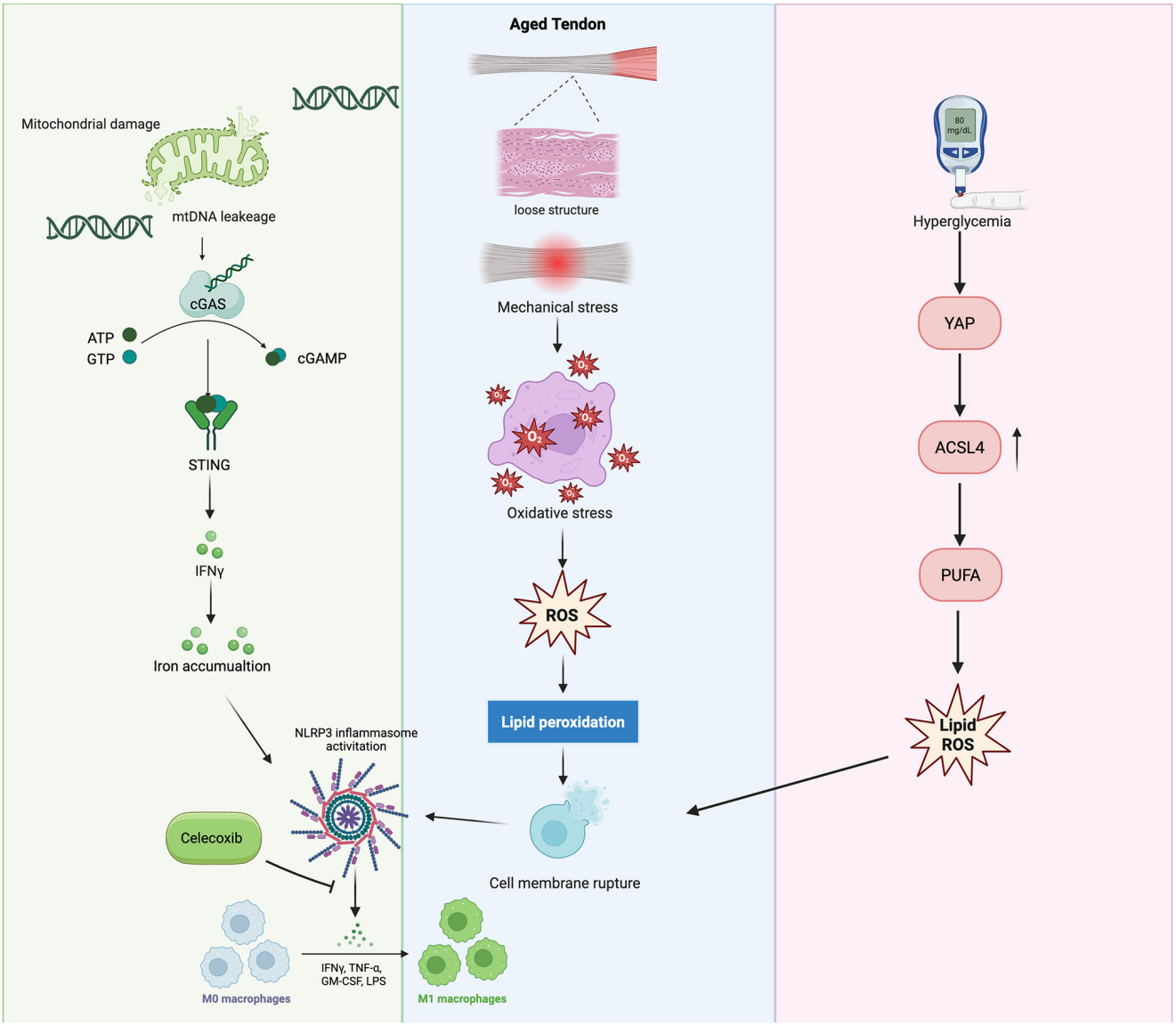

Figure 3. Ferroptosis in tendon-related diseases. Mitochondrial damage activates the cGAS-STING pathway, leading to iron accumulation and inflammatory responses. Mechanical stress induces ROS production and lipid peroxidation, resulting in membrane damage. In addition, hyperglycemia activates the YAP-ACSL4 axis, enhancing PUFA-dependent lipid ROS generation. These pathways collectively promote ferroptotic cell death and contribute to tendon degeneration. GM-CSF, granulocyte-macrophage colony-stimulating factor; LPS, lipopolysaccharide; YAP, Yes-associated protein 1; ACSL4, acyl-CoA synthetase long-chain family member 4; PUFA, polyunsaturated fatty acid.

iron metabolism and activation of ferroptosis-related signaling pathways. These findings mainly support associations and mechanistic inferences, while direct causal validation at the level of cell lineage and fate determination remains lacking. Future studies integrating lineage tracing models, single-cell transcriptomic analyses and spatial mapping of ferroptosis-specific markers in human tendon tissues will be essential to systematically validate the causal role of ferroptosis in tendon stem cell aging and regenerative decline. Such approaches will enable mechanistic dissection at the levels of cell fate determination, cellular subpopulation heterogeneity and tissue microenvironmental regulation, thereby establishing a more mechanistically robust and translationally relevant theoretical framework. Collectively, these studies indicate that ferroptosis is deeply integrated into the pathophysiological processes of tendinopathy through coordinated interactions among oxidative stress, inflammatory signaling, metabolic dysregulation and tendon stem cell aging (9,42,49). These interconnected mechanisms converge on iron accumulation, lipid peroxidation and membrane damage, ultimately driving ferroptotic cell death and tendon degeneration. the present review integrates these multi-axis regulatory pathways into a unified mechanistic framework, illustrating how mitochondrial damage-associated inflammatory signaling, mechanical stress-induced oxidative injury and metabolic reprogramming-driven lipid peroxidation collectively contribute to ferroptosis in tendon pathology (Fig. 3).

The occurrence of ferroptosis in muscle-related diseases. Iron metabolism plays a key role in muscle diseases, and the occurrence of ferroptosis can lead to muscle-related disorders (55-58). It is possible that ferroptosis not only promotes muscle aging but also contributes to muscle atrophy. Sarcopenia, which is a clinical manifestation of this process,

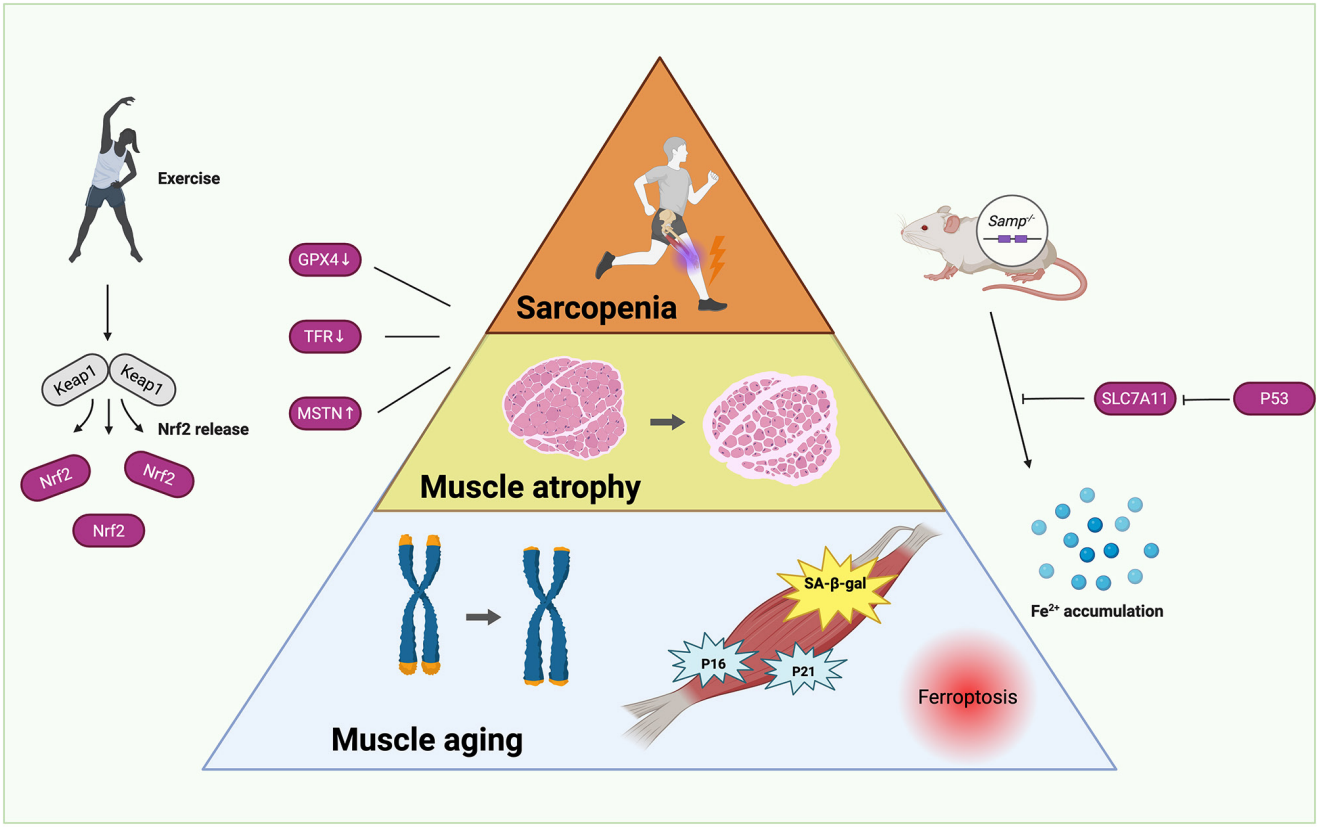

Figure 4. Role of ferroptosis in muscle-related diseases. The diagram summarizes key mechanisms involved in skeletal muscle aging, sarcopenia and muscle atrophy, including iron dysregulation, mitochondrial dysfunction and impaired antioxidant defense. Ferroptosis contributes to reduced muscle regeneration, stem cell dysfunction and loss of muscle mass and function. KEAP1, Kelch-like ECH-associated protein 1; NRF2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; TFR, transferrin receptor; MSTN, myostatin; SLC7A11, solute carrier family 7 member 11; p53, tumor protein p53; p16, cyclin-dependent kinase inhibitor 2A; p21, cyclin-dependent kinase inhibitor 1A.

can further lead to muscle wasting, and both conditions are associated with the occurrence of ferroptosis (Fig. 4).

Skeletal muscle aging. Skeletal muscle aging is a physiological phenomenon that is often accompanied by the onset of sarcopenia and other related diseases such as osteoporosis and osteoarthritis (59). Different subtypes of muscle stem cells contribute to distinct aging phenotypes (60). Compared with young mice, aged mice exhibit markedly reduced expression of GPX4 in skeletal muscle. Moreover, defects in cystathionine γ-lyase (CSE) exacerbate GPX4 reduction, thereby inducing ferroptosis in skeletal muscle (61). As aging progresses, the expression of TFRC declines in both skeletal muscle and satellite cells. The loss of TFRC triggers ferroptosis, impairing skeletal muscle regeneration (39). In a study utilizing Tfr1-specific knockout mice, Tfr1 depletion resulted in an ~60% irreversible reduction in satellite cell population, along with defects in proliferation and differentiation capacity, further promoting ferroptosis (39). The C2C12 cell line, derived from murine satellite cells, is frequently used as an *in vitro* model for muscle differentiation and regeneration (62,63). When appropriately stimulated, these myoblasts can differentiate into mature myofibers (64). Liu *et al* (55) discovered that ferroptosis in C2C12 myoblasts accelerates skeletal muscle aging, with a notable reduction in the redox-active metabolite taurine, leading to iron metabolism dysregulation. This suggests that aging and ferroptosis may form a vicious cycle that mutually reinforces each other, although the underlying mechanisms require further investigation. Grevendonk *et al* (65) found that regular exercise training enhances physical activity levels and considerably counteracts aging, potentially through mechanisms associated with mitochondrial function decline, although ferroptosis was not explicitly addressed. However, Wang *et al* (56) demonstrated that lifelong aerobic exercise mitigates oxidative stress in aging skeletal muscle by activating the Keap1/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, thereby enhancing antioxidant enzyme activity. Conversely, detraining inhibits this pathway, resulting in increased oxidative stress and ferroptosis, ultimately compromising muscle mass and function, leading to muscle atrophy. These effects are particularly pronounced during the aging process. Furthermore, skeletal muscle dysfunction may also arise from various pathological conditions. For instance, chronic obstructive pulmonary disease (COPD), which commonly develops with aging, contributes to sarcopenia and skeletal muscle impairment (66). In a cigarette smoke-induced COPD mouse model, Myostatin expression was upregulated and induced ferroptosis in skeletal muscle cells via hypoxia inducible factor (HIF) 2 α (67). Therefore, the investigation of ferroptosis in skeletal muscle should not be limited to primary ferroptotic events within muscle tissue but should also consider ferroptosis induced by aging, systemic diseases and other physiological conditions. Collectively, research suggests that skeletal muscle aging is accompanied by increased

susceptibility to ferroptosis, characterized by reduced GPX4 expression, altered iron handling (including TFRC decline) and heightened oxidative stress (39). Both intrinsic aging processes and external stressors, such as chronic disease and impaired antioxidant signaling, appear to converge on redox imbalance and mitochondrial dysfunction (68). Disruption of iron homeostasis and antioxidant defense may impair satellite cell maintenance and regenerative capacity, thereby contributing to age-related muscle decline (39). However, the majority of existing data are derived from animal models and *in vitro* systems, and direct validation in human aging muscle remains limited. Further studies are required to clarify whether ferroptosis represents a primary driver of muscle aging or a downstream consequence of systemic metabolic stress (39,68).

Sarcopenia. Sarcopenia is a systemic syndrome characterized by muscle atrophy, which is associated with an age-related decline in muscle mass and function. It is recognized as one of the leading causes of disability in the elderly (69), while also increasing the risk of falls and mortality (70). In a differential gene expression analysis comparing sarcopenic and normal muscle tissues, 46 ferroptosis-related genes were identified and found to be functionally enriched in key biological processes and KEGG signaling pathways, particularly those related to steroid hormone and glucocorticoid responses, carbon metabolism, ferroptosis and the glyoxylate metabolic pathway in sarcopenia. A total of 11 hub genes, Cdkn1a, Cs, DLD, Foxo1, Hspb1, Ldha, Mdh2 and Ywhaz, demonstrated high sensitivity and specificity for diagnosing sarcopenia, as derived from transcriptomic and network-based bioinformatics analyses conducted using established analytical frameworks (71). In a study by Huang *et al* (57) on ferroptosis in sarcopenia, the SAMP8 mouse model of accelerated aging was used, the study found that aged SAMP8 mice exhibited notable reductions in muscle mass and fiber density, along with an increased expression of ferroptosis-related markers in skeletal muscle. Moreover, iron overload was shown to induce ferroptosis, impairing the differentiation of C2C12 myoblasts into myotubes, reducing cell viability and promoting the accumulation of lipid peroxidation products. Mechanistically, this process was mediated by the p53-SLC7A11 signaling pathway (57). SLC7A11, a member of the solute carrier family 7, functions as an amino acid transporter involved in GSH biosynthesis (72). Iron overload upregulates p53 expression, which in turn inhibits SLC7A11 protein levels, leading to the accumulation of lipid peroxides and the induction of ferroptosis in muscle cells (57). Sarcopenia is frequently associated with various comorbidities. For instance, COPD is often accompanied by sarcopenia. A bioinformatics analysis identified SAA1 as a potential hub gene in COPD-associated sarcopenia, while the NF-κB signaling pathway was implicated in the underlying mechanism. Additionally, oxidative phosphorylation and ferroptosis were suggested to play key roles in the development of this comorbidity, based on published transcriptomic and computational analyses using standardized bioinformatics pipelines (73). Furthermore, studies have indicated that patients with multiple sclerosis may develop sarcopenia due to gut microbiota dysbiosis caused by hemodialysis (74). This suggests a considerable role for gut microbiota in the progression of sarcopenia. Recent research has also demonstrated that temperature fluctuations may influence gut microbiota, leading to increased serum levels of homocitrulline, which exacerbates ferroptosis and results in mitochondrial dysfunction in muscle cells (75,76). Notably, activation of the Nrf2 pathway was shown to mitigate heat exposure-induced ferroptosis-associated muscle atrophy (75). Additionally, a study by Liu *et al* (77) proposed that temperature fluctuations may impact muscle function via the gut-muscle axis, thereby contributing to sarcopenia progression. Taken together, emerging data indicate that ferroptosis may participate in the pathophysiology of sarcopenia through coordinated alterations in iron metabolism, p53-SLC7A11 signaling and mitochondrial oxidative stress. Transcriptomic analyses consistently identify ferroptosis-related gene enrichment in sarcopenic muscle, although these findings largely reflect associative bioinformatics evidence rather than direct functional validation. Moreover, comorbid conditions such as COPD, gut microbiota dysbiosis and environmental stress may amplify ferroptotic susceptibility, suggesting that sarcopenia represents a multifactorial state in which ferroptosis intersects with inflammatory and metabolic signaling. Future studies integrating human tissue validation and mechanistic intervention models are necessary to determine whether ferroptosis is a primary driver or a secondary consequence of muscle degeneration.

Skeletal muscle atrophy. Skeletal muscle atrophy is a systemic pathological condition that may result from multiple factors (77). The occurrence of muscle atrophy is characterized by a reduction in skeletal muscle size and thinning of muscle fibers (78). It can be broadly classified into two types: neurogenic and myogenic (79). Regardless of the type, muscle atrophy is invariably associated with a decline in muscle strength and mass, ultimately affecting patients' quality of life. Muscle atrophy is not an independent disease but rather a pathological condition that accompanies the progression of various diseases. Aging (80), immobilization (81), cancer (82), metabolic disorders (83) and neurodegenerative diseases have all been shown to contribute to muscle atrophy, often accompanied by the loss of collagen fibrin (84). Additionally, immobilization due to pain or postoperative recovery can lead to muscle atrophy (85). Following nerve injury, the control and nutritional support provided by nerves to muscles become impaired, further inducing muscle atrophy (86). Given that muscle atrophy frequently accompanies the onset and prognosis of various diseases, Ni *et al* (58) established a chronic kidney disease (CKD) mouse model and observed skeletal muscle dysfunction and atrophy, which was found to be associated with ferroptosis. In CKD, skeletal muscle atrophy, a common complication, has been found to be mitigated by caffeic acid, a natural phenolic compound, through inhibition of the TLR4/MYD88/NF-κB signaling pathway and ferroptosis (87). Moreover, Shenshuai Yingyang Jiaonang, a traditional Chinese herbal medicine, has been demonstrated to alleviate CKD-induced muscle atrophy by activating the HIF-1α/SLC7A11 pathway to inhibit ferroptosis (88). In patients with cancer undergoing cisplatin chemotherapy, although cisplatin effectively targets tumor cells, it has severe side effects, including muscle atrophy (89), which compromises muscle function. Programmed cell death protein 1 (PD-1), a membrane protein expressed on immune cells, plays a key role

in immune responses and autoimmunity. Knockout of PD-1 induces considerable skeletal muscle atrophy and following chemotherapy, PD-1-deficient mice exhibit exacerbated muscle atrophy accompanied by inflammation and oxidative stress. Notably, genes related to ferroptosis and autophagy were notably upregulated in these models (90). Inflammation and oxidative stress are recognized as major risk factors for muscle atrophy. In a study by Sheng *et al* (91), sepsis was found to induce muscle atrophy and weakness. Microarray dataset analysis revealed notable enrichment of genes related to muscle function, ferroptosis and the p53 signaling pathway, based on published transcriptomic analyses using standardized bioinformatics pipelines. Additionally, targeting the inhibition of STAT6 was shown to ameliorate mitochondrial dysfunction, ferroptosis and CHI3L1-mediated satellite cell damage, thereby improving muscle atrophy and weakness. Furthermore, treatment with dihydromyricetin was found to restore muscle mass and function. The underlying mechanism primarily involved inhibiting excessive E3 ubiquitin-protein ligase activity, reducing malondialdehyde (MDA) levels and restoring superoxide dismutase and GPX activity. This led to a reduction in oxidative stress and ferroptosis, ultimately improving muscle atrophy (89). As muscle atrophy is a common complication in various diseases, research on its association with ferroptosis remains limited. While emerging evidence suggests a potential association between ferroptosis and muscle atrophy, further investigations are needed to elucidate their precise. Overall, available evidence suggests that ferroptosis may contribute to skeletal muscle atrophy across diverse pathological contexts, including CKD, chemotherapy, sepsis and inflammatory states. A recurring theme involves oxidative stress amplification, dysregulation of antioxidant defense systems and activation of ferroptosis-related signaling pathways. However, the several studies rely on transcriptomic enrichment analyses or pharmacological intervention models, and the temporal relationship between ferroptosis activation and muscle fiber loss remains incompletely defined (92-94). Clarifying whether ferroptosis acts as an initiating event or a downstream amplifier of muscle atrophy will be key for determining its therapeutic relevance.

Bone-related disorders and ferroptosis. Osteoporosis, osteoarthritis and lumbar IVD represent three interrelated degenerative skeletal disorders, all of which are closely linked to aging, altered mechanical loading and hormonal changes. Osteoporosis has been shown to accelerate the progression of both osteoarthritis and IVD. Conversely, the reduced mobility and mechanical unloading resulting from joint and disc degeneration can further exacerbate bone loss and promote the development of osteoporosis (Fig. 5).

Osteoporosis. Osteoporosis is a major risk factor for fractures, particularly in elderly individuals. It is characterized by reduced bone mineral density resulting from alterations in bone microarchitecture, rendering bones susceptible to fractures even under relatively low-impact forces. Although aging and decreased levels of sex hormones are well-known contributors to osteoporosis, it may also occur secondary to various pathological conditions (95-97). Thus, osteoporosis is not limited solely to the elderly population (98). Ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation, has been identified as a key mechanism underlying osteoblast impairment in osteoporosis (99). Smoking is a recognized risk factor for osteoporosis and has been associated with ferroptosis-related bone homeostasis disruption. Jing *et al* (100) demonstrated that smoking increases ROS levels in bone marrow mesenchymal stem cells (BMSCs), leading to activation of the AMPK signaling pathway. This, in turn, promotes NCOA4-mediated ferritinophagy, resulting in elevated intracellular iron levels and lipid peroxidation, ultimately triggering ferroptosis and contributing to osteoporotic pathology. Ferroptosis in BMSCs may impair their osteogenic differentiation potential and simultaneously enhance osteoclast activation, further increasing the risk of osteoporosis. Enhanced osteoclastogenesis and bone resorption, processes frequently observed in osteoporosis, have also been associated with ferroptotic mechanisms (101). During aging, activating ATF3 promotes iron uptake by upregulating TFR1 and inhibits cystine import through suppression of SLC7A11, leading to iron overload and lipid peroxidation. This culminates in ferroptosis of osteocytes, cortical bone loss and ultimately contributes to osteoporosis development (46). Keap1 has been shown to modulate osteoblast ferroptosis through activation of the Nrf2/SLC7A11/GPX4 signaling axis, providing a potential therapeutic avenue for osteoporosis (99). Estrogen deficiency, particularly postmenopause, promotes iron accumulation in bone tissue and induces ferroptosis in osteocytes, making ferroptosis a promising therapeutic target for postmenopausal osteoporosis (102). Moreover, osteoporosis is a notable complication in patients with diabetes. Recent studies have revealed that elevated levels of ferroptosis in diabetic conditions impair the osteogenic commitment and differentiation of BMSCs, leading to marked skeletal abnormalities (103-105). Collectively, ferroptosis has been implicated to varying extents in osteoporosis of diverse etiologies, highlighting its potential as a mechanistic focus for future research into osteoporosis pathogenesis. Current research indicates that ferroptosis participates in osteoporosis across diverse etiologies, including aging, estrogen deficiency, smoking exposure and diabetes-associated metabolic dysfunction. A recurring mechanistic pattern involves iron accumulation, ferritinophagy activation, oxidative stress amplification and impairment of osteoblast or osteocyte viability. However, the majority of studies are based on animal models or *in vitro* BMSC systems, and the temporal relationship between ferroptosis activation and structural bone loss remains to be fully established (106,107). Whether ferroptosis represents a primary pathogenic driver or a secondary response to metabolic and hormonal imbalance warrants further investigation.

IVDD. IVDD is one of the most prevalent degenerative conditions affecting the spine and is considered a major contributor to various lumbar disorders, with a prevalence of 71% in men and 77% in women <50 years of age and >90% in individuals aged 50 years and older (108). Among these, lumbar disc herniation (LDH) represents a typical manifestation (109). The senescence of fibrochondrocytes within the intervertebral disc and the consequent reduction in proteoglycan synthesis led to disc dehydration and collapse. This structural deterioration increases the mechanical stress on the annulus fibrosus,

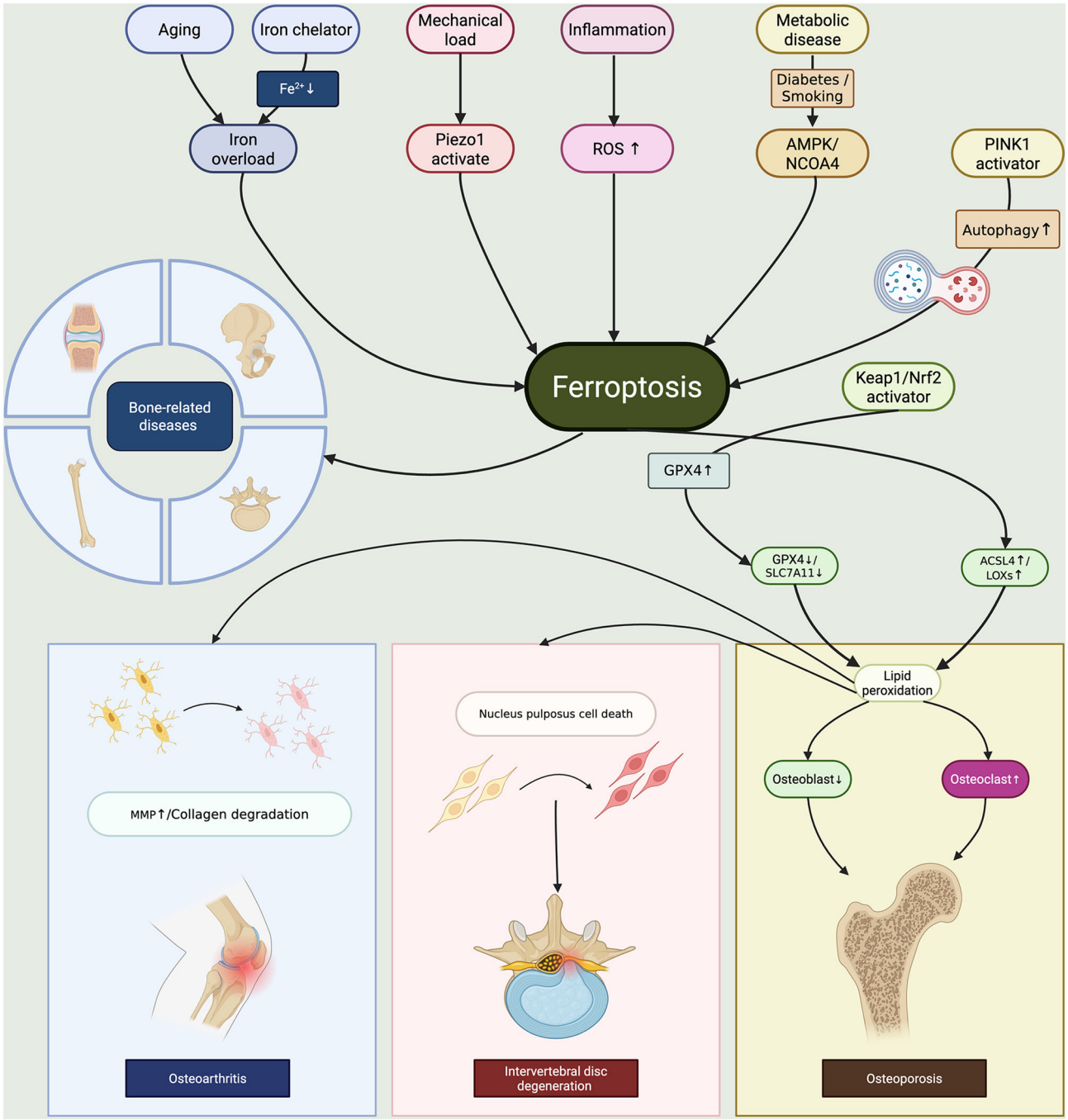

Figure 5. Ferroptosis in skeletal system diseases. The figure illustrates the involvement of ferroptosis in osteoporosis, osteoarthritis and intervertebral disc degeneration. Iron accumulation, oxidative stress and GPX4 inhibition promote osteocyte loss, chondrocyte dysfunction and extracellular matrix degradation, contributing to disease progression. ROS, reactive oxygen species; GPX4, glutathione peroxidase 4. MMP, mitochondrial membrane potential; Piezo1, Piezo-type mechanosensitive ion channel component 1; AMPK, AMP-activated protein kinase; NCOA4, nuclear receptor coactivator 4.

eventually causing the nucleus pulposus to herniate through annular fissures, thereby initiating LDH (110). Excessive mechanical loading is widely recognized as a key pathogenic factor in IVDD (111,112). Such loading activates the mechanosensitive ion channel Piezo1, located on the plasma and endoplasmic reticulum membranes, resulting in elevated intracellular Ca^{2+} levels. This, in turn, induces ferroptosis and endoplasmic reticulum stress (113). Xiang *et al* (114) further demonstrated an association between IVDD and ferroptosis, identifying key oxidative stress-related differentially expressed genes, including HMOX1, KEAP1, MAPK1, HSPA5, TXNRD1, IL6, PPARA, JUN, HIF1A and DUSP1. The principal signaling pathways implicated were the TNF signaling pathway, HIF-1 signaling pathway, NOD-like receptor signaling pathway and IL-17 signaling pathway. Additionally, a downregulation of sirtuin (SIRT) 3 expression has been observed during IVDD progression. An *in vivo* knockout study revealed that loss of SIRT3 exacerbates disc degeneration and pain symptoms (115). SIRT3 is considered to mitigate mitochondrial autophagy via the PINK1/Parkin signaling pathway and is closely associated with ubiquitination processes (115). While IVD is an age-related physiological process, proactive

strategies to delay or prevent disc degeneration may be effective in reducing the incidence and progression of related spinal disorders (116). Taken together, available studies suggest that ferroptosis may contribute to IVD through mechanisms involving mechanical stress-induced calcium influx, oxidative stress-related gene dysregulation and mitochondrial dysfunction (113). Activation of Piezo1 signaling and alterations in SIRT3 expression appear to represent important regulatory nodes linking mechanical loading to redox imbalance (117). Nevertheless, current evidence is largely derived from transcriptomic analyses and experimental models, and direct clinical validation in human disc tissue remains limited (118). Further studies are required to clarify the causal contribution of ferroptosis to disc structural failure and pain progression.

Osteoarthritis (OA). The pathogenesis of OA initially manifests at the level of articular cartilage. Early cartilage matrix degradation, particularly of collagen, prompts the proliferation and clustering of chondrocytes, leading to the formation of osteophytes (119). This is accompanied by the production of pro-inflammatory mediators and progressive cartilage erosion, ultimately resulting in joint destruction and the onset of OA (98). Iron homeostasis plays a pivotal role in maintaining the health of articular cartilage. Excessive iron accumulation induces oxidative stress and ferroptosis in chondrocytes, thereby contributing to the development of arthritis (120). Ferroptosis not only impairs chondrocyte function but also activates inflammatory signaling pathways, creating a vicious cycle that accelerates joint inflammation. Single-cell RNA sequencing comparing healthy cartilage and osteoarthritic cartilage revealed a considerable increase in both inflammatory and fibrocartilage-like chondrocyte populations in OA tissues, with enrichment of genes involved in ferroptosis pathways (121), based on published transcriptomic analyses using standardized bioinformatics pipelines. Furthermore, a study by Xie *et al* (122) demonstrated that the antioxidant compound JP4-039 attenuates OA progression by promoting PINK1/Parkin-dependent mitophagy, thereby protecting chondrocytes from ferroptotic cell death. Iron overload catalyzes the generation of ROS through mitochondrial dysfunction, which inhibits type II collagen expression and promotes the expression of matrix-degrading enzymes such as MMPs and ADAMTS. This enzymatic activity leads to the degradation of collagen and proteoglycans, compromising the structural integrity of cartilage (120). Excessive mechanical loading is also an important risk factor for OA, wherein the mechanosensitive ion channel Piezo1 contributes to disease progression by modulating ferroptosis in chondrocytes (5). Therefore, early therapeutic intervention targeting ferroptosis holds promise for the effective treatment of OA (123). Overall, current data support a contributory role of ferroptosis in osteoarthritis, particularly through iron-induced oxidative stress, mitochondrial dysfunction and inflammatory amplification in chondrocytes. Enrichment of ferroptosis-related genes in single-cell transcriptomic analyses and protective effects of ferroptosis-targeting interventions suggest mechanistic relevance. However, much of the evidence remains associative and the extent to which ferroptosis precedes or follows cartilage matrix degradation is not yet fully defined. Clarifying the sequence and cell-type specificity of ferroptotic events will be key for translating these findings into therapeutic strategies.

Aging is characterized by progressive dysregulation of both iron metabolism and antioxidant defenses, which together create a permissive environment for ferroptotic susceptibility in musculoskeletal tissues. Age-related increases in intracellular iron content have been observed in skeletal muscle and bone, which can promote oxidative damage through enhanced Fenton chemistry and lipid peroxidation, thereby impairing mitochondrial function and cellular homeostasis (124). Such iron accumulation is accompanied by a decline in GSH synthesis and activity of GPX4 and other endogenous antioxidant systems, weakening cellular capacity to neutralize ROS and lipid peroxides. In addition, age-associated impairment of iron export and storage mechanisms, such as reduced expression of ferroportin and altered ferritin dynamics, may further contribute to iron retention and redox imbalance. Together, these age-related changes in iron handling and antioxidant capacity may sensitize muscle cells, tendon-derived cells, chondrocytes and osteocytes to ferroptotic injury, thus intersecting with and potentially accelerating musculoskeletal decline (125).

3. Disease-oriented modeling and pharmacological modulation of ferroptosis in musculoskeletal systems

In vitro ferroptosis models are not merely experimental tools but represent essential platforms for understanding disease-specific mechanisms and evaluating therapeutic strategies in musculoskeletal disorders. In the context of tendon degeneration, muscle atrophy, cartilage degeneration and bone remodeling, ferroptosis-related cellular models provide key insights into how iron metabolism dysregulation, oxidative stress and lipid peroxidation contribute to tissue dysfunction, regenerative failure and progressive degeneration (126). Therefore, these models are discussed not as isolated experimental systems, but as disease-oriented platforms that integrate mechanistic investigation with translational relevance in musculoskeletal pathology.

At the level of pathological microenvironment modeling, ferroptosis can be induced by mimicking iron overload and oxidative stress conditions characteristic of degenerative musculoskeletal tissues. In the study conducted by Huang *et al* (57), ferric ammonium citrate was used to treat undifferentiated C2C12 myoblasts, differentiated C2C12 myotubes and cells undergoing differentiation, successfully inducing ferroptosis, thereby providing a model that reflects iron accumulation-driven cellular injury in muscle degeneration. Similarly, hydrogen peroxide (H_2O_2) is frequently used in oxidative stress and aging models relevant to musculoskeletal disorders. Importantly, studies have demonstrated that ferrostatin-1 (Fer-1) can effectively reverse cell death induced by H_2O_2, suggesting that H_2O_2-induced injury partially involves ferroptotic mechanisms (43). These models simulate disease-relevant microenvironmental stressors and provide a biologically meaningful context for studying ferroptosis in musculoskeletal degeneration.

At the level of molecular mechanism-oriented modeling, classical ferroptosis inducers target core regulatory nodes of ferroptotic signaling. Erastin, a commonly used ferroptosis

inducer, inhibits the Xc^- system, leading to reduced cystine uptake, depletion of intracellular GSH, impairment of antioxidant defenses and subsequent lipid peroxidation-driven cell death. In addition, erastin can induce ROS generation and activate p53 signaling, which further suppresses SLC7A11 expression, reinforcing Xc^- system inhibition and amplifying ferroptotic vulnerability (27). RSL3 represents another mechanistically distinct ferroptosis inducer. Although traditionally regarded as a GPX4 inhibitor, Dorian *et al* (127) demonstrated that RSL3 induces ferroptosis primarily through potent inhibition of thioredoxin reductase 1 (TXNRD1), thereby revealing an alternative redox regulatory axis in ferroptotic control. Together, these models enable precise dissection of ferroptosis-regulatory networks that are highly relevant to redox imbalance and metabolic dysregulation in musculoskeletal diseases.

At the level of pharmacological modulation, ferroptosis inhibitors provide essential tools for evaluating the therapeutic potential of ferroptosis-targeted interventions. Fer-1 is widely employed as a canonical ferroptosis inhibitor and acts by scavenging phospholipid hydroperoxyl radicals, thereby interrupting lipid peroxidation chain reactions and stabilizing membrane integrity. Comparative analyses by Miotto *et al* (128) demonstrated that although both Fer-1 and Trolox exhibit chain-breaking antioxidant activity, Fer-1 shows superior efficacy in inhibiting lipid peroxidation. Unlike conventional antioxidants that are consumed during redox reactions, Fer-1 forms a catalytic-like redox cycle through complex formation with Fe^{2+}, enabling sustained ferroptosis inhibition (118). Consistently, Rachid *et al* (129) reported that Fer-1 prevents ferroptotic cell death by protecting membrane lipids without interfering with mitochondrial ROS production or lysosomal membrane permeability, supporting its mechanistic specificity in ferroptosis modulation.

Importantly, the sensitivity of different cell types to ferroptosis inducers and inhibitors varies substantially, and their molecular targets are not universally conserved across tissues. This heterogeneity highlights the necessity of disease- and tissue-specific selection of experimental ferroptosis models and pharmacological agents, particularly in the musculoskeletal system, where cellular phenotypes, metabolic profiles and vascularization levels differ markedly among muscle, tendon, cartilage and bone tissues.

Collectively, these *in vitro* ferroptosis models should not be viewed as isolated experimental systems, but as disease-oriented platforms that bridge mechanistic research and translational application. While current ferroptosis inducers and inhibitors are indispensable for mechanistic dissection, the majority remain research-grade tools rather than clinically applicable agents. Their translational limitations include limited target specificity, poor bioavailability, lack of tissue-selective delivery and restricted applicability in low-vascularized musculoskeletal tissues such as tendons and cartilage. These challenges underscore the necessity of integrating disease-specific modeling with pharmacological optimization and targeted delivery strategies, thereby transforming experimental ferroptosis models into translational platforms for musculoskeletal therapy development (Table II).

While pharmacological inducers and inhibitors provide valuable tools for manipulating ferroptosis and exploring its therapeutic potential, these compounds primarily target downstream execution pathways, such as lipid peroxidation and antioxidant defense systems. However, ferroptosis is also tightly regulated at the post-translational level through dynamic modifications of key proteins involved in iron metabolism, redox balance and mitochondrial function. Understanding how post-translational modifications (PTMs) modulate ferroptosis-related signaling networks offers a deeper mechanistic perspective beyond compound-based intervention and provides insight into endogenous regulatory complexity. Therefore, the following section focuses on the role of PTMs in fine-tuning ferroptotic processes in musculoskeletal contexts.

4. Ferroptosis and post-translational modifications

PTMs represent a decisive regulatory layer that integrates upstream stress signals and determines ferroptotic cell fate through dynamic modulation of key proteins involved in iron metabolism, lipid peroxidation and antioxidant defense. Unlike transcriptional regulation, which alters gene expression at the mRNA level, PTMs provide rapid, reversible and spatially restricted control over protein stability, enzymatic activity and subcellular localization. In musculoskeletal tissues, where mechanical loading, metabolic imbalance, inflammatory signaling and aging-related oxidative stress frequently intersect, PTM-mediated fine-tuning may function as a key checkpoint that dictates ferroptosis susceptibility. Therefore, PTMs should not be viewed merely as molecular decorations, but as core regulatory nodes that connect upstream pathological stimuli with downstream ferroptotic execution mechanisms (Fig. 6).

Ubiquitination. Ubiquitination is a key post-translational modification that regulates protein synthesis, stability and degradation, thereby influencing cellular sensitivity to ferroptosis. This process plays a vital role in maintaining bone cell function and skeletal metabolic homeostasis. MYSM1, a histone deubiquitinase, has been shown to promote osteogenic differentiation, its deficiency leads to increased osteoclast number and activity, disrupts hematopoietic stem cell (HSC) function and heightens HSC susceptibility to ferroptosis, contributing to bone marrow failure syndromes. Mechanistically, MYSM1 deficiency reduces the translational efficiency of GPX4, a key ferroptosis suppressor and may also impair the recruitment of essential transcription factors such as Gata2 and Runx1 (130). Ubiquitination also contributes to ferroptosis regulation in the context of arthritis. For example, P21 modulates the mono-ubiquitination level of GPX4, indirectly affecting chondrocyte sensitivity to ferroptosis (131). TRIM8, via its RING domain, facilitates the ubiquitination and subsequent degradation of YTHDF2, thereby influencing chondrocyte ferroptosis and modulating arthritis progression (132). In studies on IVDD, Zhu *et al* (115) reported that the deubiquitinase USP11 alleviates oxidative stress-induced ferroptosis through deubiquitination mechanisms. Similarly, Huang *et al* (105) found that BMP9 alleviates iron accumulation-induced osteoporosis by upregulating USP10, which removes K48-linked polyubiquitin chains from FOXO1. This action prevents excessive cytoplasmic ubiquitination of FOXO1 and promotes GPX4 expression, thereby reducing ferroptosis. Aberrant expression of E3 ubiquitin ligases is closely associated with ferroptosis

Table II. Ferroptosis related model (*in vitro*).

A, Inducers

Authors, year	Cells	Compound	(Refs.)
Wu *et al*, 2022	Tenocytes	RSL3	(49)
Gao *et al*, 2024	TSPCs (tendon stem cells)	H_2O_2	(43)
Huang *et al*, 2021	C2C12 myoblasts, C2C12 myotubes	Ferric citrate, erastin	(57)
Ni *et al*, 2023	C2C12 myoblasts, C2C12 myotubes	Indolyl sulfate	(58)
Wang *et al*, 2021	C2C12 myoblasts	RSL3	(61)
Liu *et al*, 2022	BMSCs	Erastin, RSL3	(138)
Jiang *et al*, 2024	Ocy454 cell line	FAC	(102)
Wan *et al*, 2023	Chondrocyte	Erastin	(135)
Xie *et al*, 2025	Chondrocytes	Tert-Butyl Hydroperoxide, TBHP	(122)

B, Inhibitors

Authors, year	Cells	Compound	(Refs.)
Wang *et al*, 2023	Tendon-derived stem cells	Ferrostatin-1 (Fer-1)	(42)
Gao *et al*, 2024	Tendon stem/progenitor cells	Fer-1	(43)
Huang *et al*, 2021	C2C12 myoblasts, C2C12 myotubes	Fer-1, Deferoxamine	(57)
Ni *et al*, 2023	C2C12 myoblasts, C2C12 myotubes	Lobetyolin	(58)
Zhang *et al*, 2022	C2C12 myotubes	UAMC-3203	(67)
Jing *et al*, 2023	Bone marrow mesenchymal stem cells	Fer-1, DFO	(100)
Jiang *et al*, 2024	Ocy454 cell line	Lip-1, Fer-1	(102)

RSL3, RAS-selective lethal 3; H_2O_2, hydrogen peroxide; FAC, ferric ammonium citrate; TBHP, Tert-Butyl Hydroperoxide; Fer-1, ferrostatin-1; DFO, Deferoxamine; Lip-1, liproxstatin-1.

in musculoskeletal diseases (89), with PD-1 playing a regulatory role in this context (90). SMURF, identified as the E3 ligase for FTH1, activates ferroptosis signaling and inhibits myoblast differentiation into myotubes (133). Nestin, a cytoskeletal protein, has been recognized as a key regulator of the ferroptosis-autophagy crosstalk in skeletal muscle atrophy. It interacts with MAP1LC3B (LC3B) and catalyzes its polyubiquitination at lysine-51, reducing LC3B availability for autophagy and thereby suppressing ferroptotic cell death (134). Moreover, the transcription factor Nrf2, a master regulator of antioxidant responses, is itself regulated by Keap1-mediated ubiquitin-dependent degradation. This regulatory axis represents a promising direction for future investigations into ferroptosis-related musculoskeletal pathologies. Collectively, ubiquitination acts as a protein stability checkpoint that determines the turnover of key ferroptosis regulators such as GPX4, FTH1 and transcription factors. By controlling degradation dynamics, ubiquitination establishes a threshold for ferroptotic activation in musculoskeletal cells.

Phosphorylation. Phosphorylation, a post-translational modification in biological systems, wherein phosphate groups are covalently attached to proteins or other biomolecules under enzymatic catalysis. This modification profoundly influences protein activity, subcellular localization and interaction networks, thereby modulating numerous cellular pathways. In a study by Xue *et al* (101), inhibition of I-κB and p65 phosphorylation was shown to suppress activation of the NF-κB signaling pathway, indicating that phosphorylation plays a key regulatory role in inflammatory responses. Similarly, Chen *et al* (9) demonstrated that phosphorylation of AMPK is essential for regulating cellular energy metabolism, antioxidant defense and regeneration. By modulating the AMPK/Nrf2/GPX4 signaling axis, AMPK phosphorylation delays the senescence of TSPCs, inhibits ferroptosis and enhances tendon regeneration. Phosphorylation also plays a pivotal role in ferroptosis associated with IVDD. For instance, PDK4 phosphorylates the E1α subunit of the pyruvate dehydrogenase complex, thereby inhibiting pyruvate decarboxylation and regulating cellular energy metabolism and lipid biosynthesis (123). Wan *et al* (135) found that induction of AMPKα phosphorylation in chondrocytes enhances its stability and activity and that activation of the AMPK/Nrf2/HO-1 pathway attenuates ferroptosis, offering a potential therapeutic strategy for arthritis. Similarly, Zhou *et al* (136) reported that suppression of PI3K/Akt phosphorylation mitigates ferroptosis by enhancing antioxidant defenses through upregulation of GSH and GPX4, thereby preventing lipid peroxidation and relieving joint pain. In

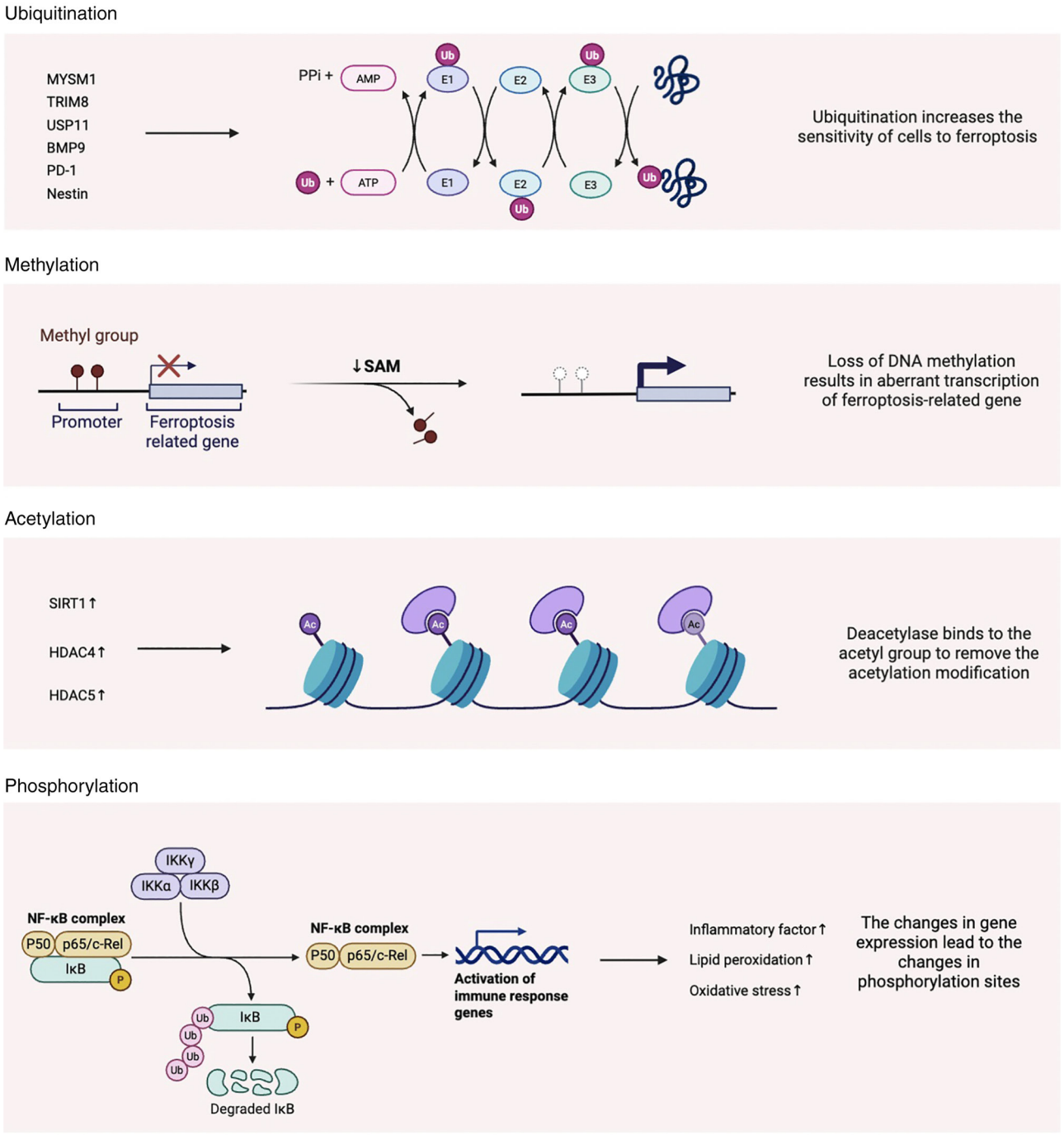

Figure 6. Post-translational modifications regulating ferroptosis in musculoskeletal disorders. The diagram highlights key post translation modifications, including ubiquitination, phosphorylation, methylation and acetylation, which modulate the stability, activity and localization of ferroptosis-related proteins. These modifications act as regulatory nodes linking upstream stress signals to ferroptotic cell death. MYSM1, Myb-like, SWIRM and MPN domain-containing protein 1; TRIM8, tripartite motif containing 8; USP11, ubiquitin specific peptidase 11; BMP9, bone morphogenetic protein 9; PD-1, programmed cell death protein 1; Nestin, neuroepithelial stem cell protein; SIRT1, sirtuin 1; HDAC4, histone deacetylase 4; HDAC5, histone deacetylase 5; p50, nuclear factor NF-kappa-B p50 subunit; p65, transcription factor p65.

another study, Hyeon *et al* (137) demonstrated that donepezil alleviates skeletal muscle insulin resistance in obese mice by inhibiting inflammation and ferroptosis via the AMPK/FGF21 pathway. This effect was mainly attributed to suppression of NF-κB phosphorylation and I-κB degradation, leading to reduced expression of pro-inflammatory markers. Moreover, mutations in genes encoding phosphorylation-related enzymes or phospho-sites can disrupt phosphorylation dynamics, resulting in aberrant signaling and contributing to disease pathogenesis in musculoskeletal tissues. Taken together, phosphorylation functions as a rapid signal transduction mechanism that links metabolic and inflammatory stimuli to ferroptosis-related antioxidant pathways, thereby modulating cellular susceptibility to ferroptotic stress.

Methylation. Methylation refers to the enzymatic transfer of a methyl group from a donor molecule to specific substrates, a process typically catalyzed by methyltransferases. This

epigenetic and epitranscriptomic modification plays a key role in gene expression regulation, RNA stability and cellular function, including the modulation of ferroptosis in musculoskeletal tissues. In a study by Liu (138), NSUN5, a member of the NOP2/Sun RNA methyltransferase family, was shown to play a pivotal role in regulating ferroptosis in BMSCs through the NSUN5-FTH1/FTL axis. Specifically, NSUN5 catalyzes 5-methylcytosine (m5C) modifications on the mRNA of FTH1 and FTL, and NSUN5 depletion results in a reduction of these modifications, subsequently leading to decreased expression of FTH1 and FTL, thereby promoting ferroptosis. Nrf2, a key regulator of antioxidant defense, also plays a central role in the modulation of ferroptosis in bone cells. Beyond its involvement in ubiquitination pathways, Nrf2 has been found to regulate DNA methylation of the receptor activator of nuclear factor κB ligand (RANKL) promoter via DNA methyltransferase 3a (Dnmt3a), thus influencing RANKL expression and osteoclastogenesis (102). Moreover, methyltransferase-like 3 (METTL3), an RNA N6-methyladenosine (m6A) methyltransferase, has emerged as a key modulator in chondrocyte ferroptosis. Depletion of METTL3 was shown to alleviate ferroptosis and cartilage damage, whereas its overexpression enhanced m6A methylation of HMGB1 mRNA, promoting ferroptotic responses (139). In models of diabetic osteoporosis induced by high glucose and high fat, METTL3 was found to activate the ASK1-p38 MAPK signaling pathway, thereby promoting ferroptosis in osteoblasts. Knockdown of METTL3 in MC3T3-E1 osteoblasts not only inhibited ASK1-p38 activation but also attenuated ferroptosis, highlighting METTL3 as a potential molecular target in diabetic bone loss (140). Furthermore, methylation directly impacts the expression and activity of ferroptosis-regulating enzymes. Inhibition of GPX4 methylation has been shown to mitigate ferroptosis in chondrocytes during arthritis progression (141). In ovariectomized mouse models of osteoporosis, reduced GPX4 expression was accompanied by hypermethylation of its promoter and elevated levels of DNA methyltransferases DNMT1, DNMT3a and DNMT3b (142). Although methylation has been widely studied in cancer and neurological diseases, its role in musculoskeletal disorders and ferroptosis is an emerging area of interest and warrants further exploration. Overall, methylation introduces an additional epigenetic and epitranscriptomic layer of regulation, influencing ferroptosis through long-term modulation of gene expression and mRNA stability, particularly in aging and metabolic disorders.

Acetylation. Acetylation is a form of post-translational protein modification involving the addition of an acetyl group to specific amino acid residues, most commonly lysine (143). This modification can considerably impact protein function, localization and interactions, thereby influencing diverse cellular processes, including ferroptosis. Recent studies have highlighted the regulatory role of acetylation in ferroptosis within musculoskeletal diseases (144,145). Overexpression of SIRT1, a class III histone deacetylase, promotes the expression of FTL by deacetylating it at lysine 181 (K181), which in turn suppresses ferroptosis in chondrocytes and attenuates the progression of arthritis (144,146). Histone deacetylases HDAC4 and HDAC5 also contribute to ferroptosis regulation by reducing acetylation of the tumor suppressor protein p53 at lysine 120 (K120). This deacetylation inhibits the activation of apoptotic and ferroptotic pathways, thereby preserving skeletal muscle cell viability and function under lipotoxic stress conditions (147). As such, acetylation-based regulatory mechanisms represent a promising avenue for future research in understanding and potentially targeting ferroptosis in musculoskeletal pathology. Acetylation-dependent regulation highlights the importance of metabolic-epigenetic crosstalk in ferroptosis control, suggesting that cellular acetyl-CoA availability and deacetylase activity may shape ferroptotic outcomes in musculoskeletal pathology.

Emerging PTMs such as SUMOylation, O-GlcNAcylation, lactylation and succinylation have recently been implicated in redox regulation and metabolic stress adaptation in other disease contexts. Although research associating these modifications to ferroptosis in musculoskeletal tissues remains limited, their established roles in regulating iron metabolism, mitochondrial function and antioxidant signaling suggest potential relevance. Future multi-omics and proteomics approaches may uncover additional PTM-mediated regulatory circuits that fine-tune ferroptotic susceptibility.

5. Therapeutic approaches for ferroptosis in muscular system disorders

Interorgan communication. Guan *et al* (148) demonstrated that the gut microbiota-derived metabolite capsiate (CAT) plays a regulatory role in ferroptosis induced by OA. Specifically, CAT targets HIF-1α to activate the expression of SLC2A1, thereby inhibiting ferroptosis and attenuating OA progression. This finding highlights the interorgan communication between the gut and the joints. Metabolites produced by the gut microbiota can reach joint tissues via the circulatory system or other pathways, thereby modulating the occurrence of ferroptosis in joint-resident cells. Despite its potential significance, research on interorgan communication in the context of ferroptosis and musculoskeletal diseases remains limited, particularly regarding the modulatory effects of gut microbial metabolites on musculoskeletal health.

Exosome therapy. Extracellular vesicles, also known as exosomes (EXOs), have been increasingly recognized as a promising tool for mitigating tendon aging, with potential applications in tissue regeneration and repair (9), and the purified exosomes can also improve the biomechanics of the rotator cuff (149). Platelet-derived EXOs exhibit anti-inflammatory properties and promote stem cell proliferation. In the study by Jin *et al* (150), it was found that systemic administration of bio-nanoparticles derived from human exfoliated deciduous teeth stem cell-derived EXOs (SHED-EXOs) effectively attenuated tendon degeneration in a naturally aging rat model and localized delivery of microspheres loaded with SHED-EXOs not only markedly reduced the accumulation of senescent cells and ectopic ossification but also restored the regenerative and reparative capacity of tendons in aged rats.

Pharmacological therapy. Celecoxib, a non-steroidal anti-inflammatory drug, has been reported to exert

ferroptosis-inhibitory effects (151). When combined with lactoferrin, celecoxib enhances tendon repair. Zhang *et al* (50) conducted gene identification and bioinformatics analysis to explore the underlying mechanisms and identified Slc40a1, Tfrc and Cryab as ferroptosis-related genes key for regulating tendon injury repair (50), as indicated by published bioinformatics analyses. Lobetyolin, an active compound in traditional Chinese medicine, has been found to alleviate skeletal muscle damage by activating the Hedgehog signaling pathway, particularly the transcription factor Gli1, thereby upregulating a series of ferroptosis-inhibitory factors (58). Taurine, a redox-specific metabolite (152), has been shown to prevent ferroptosis by markedly increasing intracellular GSH levels, reducing MDA and ROS production and restoring the vitality of impaired myogenic differentiation. Taurine is also essential for glycerophospholipid metabolism, playing a key role in cell membrane repair. Additionally, it enhances mitochondrial bioenergetics, increasing the energy reserves produced by muscle satellite cells (55). Aconine is a natural compound that suppresses osteoclast activity and reduces bone resorption. It exerts its effects by inhibiting the NF-κB signaling pathway and modulating the expression of GPX4 and ACSL4, thereby regulating ferroptosis in osteoclasts (101). Biotin A (BCA), a naturally occurring isoflavonoid isolated from Astragalus membranaceus, exhibits anti-inflammatory and antioxidant properties. It directly reduces intracellular iron levels by inhibiting TfR1 and promoting FPN expression. In addition, BCA targets the Nrf2/system Xc^-/GPX4 signaling pathway to scavenge free radicals and prevent lipid peroxidation (120). Selenium supplementation has been shown to alleviate endoplasmic reticulum stress by upregulating selenoprotein K (SelK) expression and reducing intracellular free Ca^{2+} concentrations. Through both the selenium-GPX4 and selenium-SelK axes, selenium mitigates ferroptosis induced by mechanical overload and contributes to the stabilization of the extracellular matrix (113).

Biomaterials and other approaches. Intramuscular injection of lentivirus expressing Tfr1 has been shown to mitigate Tfr1 deficiency-induced iron accumulation, thereby promoting skeletal muscle regeneration (39). Fer-1, a widely used ferroptosis inhibitor, upregulates CSE, thereby modulating the CSE/H_2S signaling pathway, scavenging ROS and preventing lipid peroxidation. Hydrogen sulfide (H_2S), a novel gaseous signaling molecule derived from CSE, is widely distributed across tissues and organs and plays a regulatory role in oxidative stress and lipid metabolism (61). Ferroptosis exhibits a dual role in cancer therapy. Zhang *et al* (153) designed a self-amplifying nanodrug (RCH NPs) using human serum albumin as a carrier to program the dual nature of ferroptosis. Within this system, ferric porphyrin-induced ferroptosis is coupled with celecoxib-mediated disruption of inflammation-related immune suppression, while roscovitine genetically blocks IFN-γ-induced PD-L1 upregulation. This strategy enhances the therapeutic potential of ferroptosis in tumor treatment. Regular physical exercise (65) and newly developed brain-muscle communication interventions that suppress detrimental central signals while stabilizing peripheral muscles to prevent muscle aging (154) may indirectly regulate ferroptosis, providing new directions for future research. In the study by Gao *et al* (155), a ROS-responsive injectable hydrogel, PVA-tsPBA@SLC7A11 modRNA, was developed to mitigate IVDD. Upon local injection into the degenerated disc, ROS-induced cleavage of the PVA-tsPBA hydrogel facilitated the release of encapsulated SLC7A11 modRNA, thereby suppressing ferroptosis in nucleus pulposus cells and ameliorating IVDD. In a separate study, Cit-AuNRs@Anti-TRPV1, a near-infrared (NIR)-activated nanoplatform, was shown to protect chondrocytes against ferroptosis under NIR irradiation and attenuate the progression of arthritis, offering a promising therapeutic strategy for joint diseases (156).

6. Future perspectives

Ferroptosis has emerged as a key pathogenic mechanism across a spectrum of musculoskeletal disorders, including skeletal muscle aging and atrophy, tendinopathy, osteoarthritis, IVDD and osteoporosis. Despite increasing research associating iron dysregulation, oxidative stress amplification and mitochondrial dysfunction to musculoskeletal tissue degeneration, several fundamental questions remain unresolved.

First, the temporal sequence of ferroptotic activation during tissue degeneration requires further clarification. It remains unclear whether ferroptosis functions as a primary driver of stem/progenitor cell dysfunction and extracellular matrix degradation or as a secondary amplifier of inflammatory and metabolic stress. Second, the interplay between ferroptosis and other cellular regulatory pathways, such as autophagy, warrants deeper investigation. For example, autophagy deficiency has been shown to mitigate erastin-induced ferroptosis (16), highlighting the importance of autophagy-dependent regulatory networks that may also be relevant in musculoskeletal tissues.

In addition, emerging evidence suggests potential crosstalk between ferroptosis and other forms of metal-associated regulated cell death. Xue *et al* (157) demonstrated that Cu^{2+} can enhance cellular susceptibility to ferroptosis by directly binding to GPX4 and promoting its ubiquitination and degradation. Although these findings were not limited to musculoskeletal models, they raise the possibility that metal homeostasis beyond iron may influence ferroptotic vulnerability in musculoskeletal pathology.

Future research should prioritize tissue-specific and stage-specific investigation of ferroptosis within the musculoskeletal system. Particular attention should be given to the interaction between mechanical loading, metabolic stress and ferroptotic signaling, as well as to the development of targeted therapeutic strategies for low-vascularized tissues such as tendon and cartilage. Integrating multi-omics approaches with functional validation in human tissues will be essential to translate ferroptosis-based interventions into clinically relevant therapies.

Overall, maintaining a focused mechanistic framework centered on musculoskeletal diseases will be critical for advancing both basic understanding and therapeutic innovation in this field.

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Availability of data and materials

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Authors' contributions

WG was responsible for the writing, original draft of the manuscript. TX, FL and LY contributed to the writing, review and editing of the manuscript. FL responsible for preparation of figures. HZ and YY provided supervision and conceptualization of the present study. GW contributed to the conceptualization of the research and the acquisition of funding.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Joy EA, Briesacher M and Wiegand B: Musculoskeletal failure. Am J Lifestyle Med 18: 826-829, 2024.
2. Leser JM, Harriot A, Buck HV, Ward CW and Stains JP: Aging, osteo-sarcopenia, and musculoskeletal mechano-transduction. Front Rehabil Sci 2: 782848, 2021.
3. Safiri S, Kolahi AA, Cross M, Hill C, Smith E, Carson-Chahhoud K, Mansournia MA, Almasi-Hashiani A, Ashrafi-Asgarabad A, Kaufman J, *et al*: Prevalence, deaths, and disability-adjusted life years due to musculoskeletal disorders for 195 countries and territories 1990-2017. Arthritis Rheumatol 73: 702-714, 2021.
4. Xiang W, Zhang T, Li B, Li S, Zhang B, Fang S, Chen L, Gong Y, Huang B, Feng D, *et al*: Senescent macrophages induce ferroptosis in skeletal muscle and accelerate osteoarthritis-related muscle atrophy. Nat Aging 5: 1295-1316, 2025.
5. Wang S, Li W, Zhang P, Wang Z, Ma X, Liu C, Vasilev K, Zhang L, Zhou X, Liu L, *et al*: Mechanical overloading induces GPX4-regulated chondrocyte ferroptosis in osteoarthritis via Piezo1 channel facilitated calcium influx. J Adv Res 41: 63-75, 2022.
6. Cui W, Liu D, Gu W and Chu B: Peroxisome-driven ether-linked phospholipids biosynthesis is essential for ferroptosis. Cell Death Differ 28: 2536-2551, 2021.
7. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
8. Fan Y, Chen Z, Wang H, Jiang M, Lu H, Wei Y, Hu Y, Mo L, Liu Y, Zhou C, *et al*: Isovitexin targets SIRT3 to prevent steroid-induced osteonecrosis of the femoral head by modulating mitophagy-mediated ferroptosis. Bone Res 13: 18, 2025.
9. Chen D, Tang Q, Song W and He Y: Platelet-derived exosomes alleviate tendon stem/progenitor cell senescence and ferroptosis by regulating AMPK/Nrf2/GPX4 signaling and improve tendon-bone junction regeneration in rats. J Orthop Surg Res 19: 382, 2024.
10. Lu X, Sharko OL, Shmanai VV, Shchepinov MS and Markworth JF: Deuterated polyunsaturated fatty acids alleviate in vitro skeletal muscle dysfunction induced by oxidative stress. Free Radic Biol Med 248: 222-237, 2026.
11. Bertrand RL: Iron accumulation, glutathione depletion, and lipid peroxidation must occur simultaneously during ferroptosis and are mutually amplifying events. Med Hypotheses 101: 69-74, 2017.
12. Riegman M, Sagie L, Galed C, Levin T, Steinberg N, Dixon SJ, Wiesner U, Bradbury MS, Niethammer P, Zaritsky A and Overholtzer M: Ferroptosis occurs through an osmotic mechanism and propagates independently of cell rupture. Nat Cell Biol 22: 1042-1048, 2020.
13. Brown CW, Amante JJ, Chhoy P, Elaimy AL, Liu H, Zhu LJ, Baer CE, Dixon SJ and Mercurio AM: Prominin2 drives ferroptosis resistance by stimulating iron export. Dev Cell 51: 575-586.e4, 2019.
14. Chen GH, Song CC, Pantopoulos K, Wei XL, Zheng H and Luo Z: Mitochondrial oxidative stress mediated Fe-induced ferroptosis via the NRF2-ARE pathway. Free Radic Biol Med 180: 95-107, 2022.
15. Li Y, Zeng X, Lu D, Yin M, Shan M and Gao Y: Erastin induces ferroptosis via ferroportin-mediated iron accumulation in endometriosis. Hum Reprod 36: 951-964, 2021.
16. Park E and Chung SW: ROS-mediated autophagy increases intracellular iron levels and ferroptosis by ferritin and transferrin receptor regulation. Cell Death Dis 10: 822, 2019.
17. Yu Y, Jiang L, Wang H, Shen Z, Cheng Q, Zhang P, Wang J, Wu Q, Fang X, Duan L, *et al*: Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis. Blood 136: 726-739, 2020.
18. Gao M, Monian P, Quadri N, Ramasamy R and Jiang X: Glutaminolysis and transferrin regulate ferroptosis. Mol Cell 59: 298-308, 2015.
19. Tian Y, Lu J, Hao X, Li H, Zhang G, Liu X, Li X, Zhao C, Kuang W, Chen D and Zhu M: FTH1 inhibits ferroptosis through ferritinophagy in the 6-OHDA model of Parkinson's disease. Neurotherapeutics 17: 1796-1812, 2020.
20. Yang X, Ding Y, Sun L, Shi M, Zhang P, Huang Z, Wang J, He A, Wang J, Wei J, *et al*: Ferritin light chain deficiency-induced ferroptosis is involved in preeclampsia pathophysiology by disturbing uterine spiral artery remodelling. Redox Biol 58: 102555, 2022.
21. Kim H, Villareal LB, Liu Z, Haneef M, Falcon DM, Martin DR, Lee HJ, Dame MK, Attili D, Chen Y, *et al*: Transferrin receptor-mediated iron uptake promotes colon tumorigenesis. Adv Sci (Weinh) 10: e2207693, 2023.
22. Feng H, Schorpp K, Jin J, Yozwiak CE, Hoffstrom BG, Decker AM, Rajbhandari P, Stokes ME, Bender HG, Csuka JM, *et al*: Transferrin receptor is a specific ferroptosis marker. Cell Rep 30: 3411-3423.e7, 2020.
23. Henning Y, Blind US, Larafa S, Matschke J and Fandrey J: Hypoxia aggravates ferroptosis in RPE cells by promoting the Fenton reaction. Cell Death Dis 13: 662, 2022.
24. Borchert A, Kalms J, Roth SR, Rademacher M, Schmidt A, Holzhutter HG, Kuhn H and Scheerer P: Crystal structure and functional characterization of selenocysteine-containing glutathione peroxidase 4 suggests an alternative mechanism of peroxide. Biochim Biophys Acta Mol Cell Biol Lipids 1863: 1095-1107, 2018.
25. Fang X, Wang H, Han D, Xie E, Yang X, Wei J, Gu S, Gao F, Zhu N, Yin X, *et al*: Ferroptosis as a target for protection against cardiomyopathy. Proc Natl Acad Sci USA 116: 2672-2680, 2019.
26. Conrad M and Friedmann Angeli JP: Glutathione peroxidase 4 (Gpx4) and ferroptosis: What's so special about it? Mol Cell Oncol 2: e995047, 2015.
27. Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, Thomas AG, Gleason CE, Tatonetti NP, Slusher BS and Stockwell BR: Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis. Elife 3: e02523, 2014.
28. Ingold I, Berndt C, Schmitt S, Doll S, Poschmann G, Buday K, Roveri A, Peng X, Porto Freitas F, Seibt T, *et al*: Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis. Cell 172: 409-422.e21, 2018.

29. Gao M, Yi J, Zhu J, Minikes AM, Monian P, Thompson CB and Jiang X: Role of mitochondria in ferroptosis. Mol Cell 73: 354-363.e3, 2019.
30. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, Herbach N, Aichler M, Walch A, Eggenhofer E, *et al*: Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat Cell Biol 16: 1180-1191, 2014.
31. Li Y, Feng D, Wang Z, Zhao Y, Sun R, Tian D, Liu D, Zhang F, Ning S, Yao J and Tian X: Ischemia-induced ACSL4 activation contributes to ferroptosis-mediated tissue injury in intestinal ischemia/reperfusion. Cell Death Differ 26: 2284-2299, 2019.
32. Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ III, Kang R and Tang D: Autophagy promotes ferroptosis by degradation of ferritin. Autophagy 12: 1425-1428, 2016.
33. Qiu B, Zandkarimi F, Bezjian CT, Reznik E, Soni RK, Gu W, Jiang X and Stockwell BR: Phospholipids with two polyunsaturated fatty acyl tails promote ferroptosis. Cell 187: 1177-1190.e18, 2024.
34. Blanc RS, Shah N, Hachmer S, Salama NAS, Meng FW, Mousaei A, Puri G, Hwang JH, Wacker EE, Yang BA, *et al*: Epigenetic erosion of H4K20me1 induced by inflammation drives aged stem cell ferroptosis. Nat Aging 5: 1491-1509, 2025.
35. Campbell NJ and Maani CV: Histology, muscle. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2026.
36. Braithwaite JP and Al Khalili Y: Physiology, muscle myocyte. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2026.
37. Kuang S, Kuroda K, Le Grand F and Rudnicki MA: Asymmetric self-renewal and commitment of satellite stem cells in muscle. Cell 129: 999-1010, 2007.
38. García-Prat L, Muñoz-Cánoves P and Martinez-Vicente M: Dysfunctional autophagy is a driver of muscle stem cell functional decline with aging. Autophagy 12: 612-613, 2016.
39. Ding H, Chen S, Pan X, Dai X, Pan G, Li Z, Mai X, Tian Y, Zhang S, Liu B, *et al*: Transferrin receptor 1 ablation in satellite cells impedes skeletal muscle regeneration through activation of ferroptosis. J Cachexia Sarcopenia Muscle 12: 746-768, 2021.
40. Thorpe CT, Peffers MJ, Simpson D, Halliwell E, Screen HR and Clegg PD: Anatomical heterogeneity of tendon: Fascicular and interfascicular tendon compartments have distinct proteomic composition. Sci Rep 6: 20455, 2016.
41. Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W, Li L, Leet AI, Seo BM, Zhang L, *et al*: Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat Med 13: 1219-1227, 2007.
42. Wang G, Wang S, Ouyang X, Wang H, Li X, Yao Z, Chen S and Fan C: Glycolipotoxicity conferred tendinopathy through ferroptosis dictation of tendon-derived stem cells by YAP activation. IUBMB Life 75: 1003-1016, 2023.
43. Gao Y, Sun W, Wang J, Zhao D, Tian H, Qiu Y, Ji S, Wang S, Fu Q, Zhang F, *et al*: Oxidative stress induces ferroptosis in tendon stem cells by regulating mitophagy through cGAS-STING pathway. Int Immunopharmacol 138: 112652, 2024.
44. Masaldan S, Clatworthy SAS, Gamell C, Meggyesy PM, Rigopoulos AT, Haupt S, Haupt Y, Denoyer D, Adlard PA, Bush AI and Cater MA: Iron accumulation in senescent cells is coupled with impaired ferritinophagy and inhibition of ferroptosis. Redox Biol 14: 100-115, 2018.
45. Kamel-ElSayed SA, Nezwek TA and Varacallo MA: Physiology. Bone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2026.
46. Yin Y, Chen GJ, Yang C, Wang JJ, Peng JF, Huang XF, Tang QM and Chen LL: Osteocyte ferroptosis induced by ATF3/TFR1 contributes to cortical bone loss during ageing. Cell Prolif 57: e13657, 2024.
47. Cushman DM, Stokes D, Vu L, Corcoran B, Fredericson M, Eby SF and Teramoto M: Ultrasound as a predictor of time-loss injury for the patellar tendon, Achilles tendon and plantar fascia in division I collegiate athletes. Br J Sports Med 59: 241-248, 2025.
48. Charnoff J, Ponnarasu S, Sina RE and Naqvi U: Tendinosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2026.
49. Wu Y, Qian J, Li K, Li W, Yin W and Jiang H: Farrerol alleviates collagenase-induced tendinopathy by inhibiting ferroptosis in rats. J Cell Mol Med 26: 3483-3494, 2022.
50. Zhang Y, Shi L, Wang F, Wang L, Min N, Wen L and Xue Q: Screening for autophagy/hypoxia/ferroptosis/pyroptosis-related genes of tendon injury and repair in a rat model after celecoxib and lactoferrin treatment. J Orthop Surg Res 18: 383, 2023.
51. Tong Z, Li H, Jin Y, Sheng L, Ying M, Liu Q, Wang C and Teng C: Mechanisms of ferroptosis with immune infiltration and inflammatory response in rotator cuff injury. Genomics 115: 110645, 2023.
52. Yuan Z, Zhu X, Dai Y, Shi L, Feng Z, Li Z, Diao N, Guo A, Yin H and Ma L: Analysis of differentially expressed genes in torn rotator cuff tendon tissues in diabetic patients through RNA-sequencing. BMC Musculoskelet Disord 25: 31, 2024.
53. Khalil AA, Smits D, Haughton PD, Koorman T, Jansen KA, Verhagen MP, van der Net M, van Zwieten K, Enserink L, Jansen L, *et al*: A YAP-centered mechanotransduction loop drives collective breast cancer cell invasion. Nat Commun 15: 4866, 2024.
54. Zhang H, Zhou J, Liu Z, Wang K and Jiang H: Bioinformatics analysis of ferroptosis in frozen shoulder. BMC Med Genomics 17: 234, 2024.
55. Liu X, Zhou Y, Qi Z, Huang C and Lin D: Taurine alleviates ferroptosis-induced metabolic impairments in C2C12 myoblasts by stabilizing the labile iron pool and improving redox homeostasis. J Proteome Res 23: 3444-3459, 2024.
56. Wang ZZ, Xu HC, Zhou HX, Zhang CK, Li BM, He JH, Ni PS, Yu XM, Liu YQ and Li FH: Long-term detraining reverses the improvement of lifelong exercise on skeletal muscle ferroptosis and inflammation in aging rats: Fiber-type dependence of the Keap1/Nrf2 pathway. Biogerontology 24: 753-769, 2023.
57. Huang Y, Wu B, Shen D, Chen J, Yu Z and Chen C: Ferroptosis in a sarcopenia model of senescence accelerated mouse prone 8 (SAMP8). Int J Biol Sci 17: 151-162, 2021.
58. Ni SH, Zhang XJ, OuYang XL, Ye TC, Li J, Li Y, Sun SN, Han XW, Long WJ, Wang LJ, *et al*: Lobetyolin alleviates ferroptosis of skeletal muscle in 5/6 nephrectomized mice via activation of hedgehog-GLI1 signaling. Phytomedicine 115: 154807, 2023.
59. Liu C, Zheng D, Zhang R, Li H, Tong X, Wu Y, Zhang G, Wang S, Chen H, Ren Z, *et al*: Transcriptional diversity in response to aging across skeletal muscles. Aging Cell 24: e70164, 2025.
60. Kedlian VR, Wang Y, Liu T, Chen X, Bolt L, Tudor C, Shen Z, Fasouli ES, Prigmore E, Kleshchevnikov V, *et al*: Human skeletal muscle aging atlas. Nat Aging 4: 727-744, 2024.
61. Wang Y, Yu R, Wu L and Yang G: Hydrogen sulfide guards myoblasts from ferroptosis by inhibiting ALOX12 acetylation. Cell Signal 78: 109870, 2021.
62. Nguyen NUN, Hsu CC, Ali SR and Wang HV: Actin-organizing protein palladin modulates C2C12 cell fate determination. Biochem Biophys Rep 39: 101762, 2024.
63. Sato S, Hanai T, Kanamoto T, Kawano F, Hikida M, Yokoi H, Take Y, Magome T, Ebina K, Mae T, *et al*: Vibration acceleration enhances proliferation, migration, and maturation of C2C12 cells and promotes regeneration of muscle injury in male rats. Physiol Rep 12: e15905, 2024.
64. Yaffe D and Saxel O: Serial passaging and differentiation of myogenic cells isolated from dystrophic mouse muscle. Nature 270: 725-727, 1977.
65. Grevendonk L, Connell NJ, McCrum C, Fealy CE, Bilet L, Bruls YMH, Mevenkamp J, Schrauwen-Hinderling VB, Jörgensen JA, Moonen-Kornips E, *et al*: Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. Nat Commun 12: 4773, 2021.
66. Kaluźniak-Szymanowska A, Talarska D, Tobis S, Styszyński A, Cofta S, Wieczorowska-Tobis K and Deskur-Śmielecka E: Body compositions phenotypes of older adults with COPD. Front Nutr 11: 1449189, 2024.
67. Zhang L, Li D, Chang C and Sun Y: Myostatin/HIF2α-mediated ferroptosis is involved in skeletal muscle dysfunction in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 17: 2383-2399, 2022.
68. Ji F, Rheem H, Lee H, Eom M and Kim JH: Multilevel regulation of skeletal muscle ferroptosis in aging: Sex- and exercise-dependent effects on histological, molecular, and genetic markers. Geroscience: Jan 10, 2026 (Epub ahead of print).
69. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM and Ferrucci L: Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. J Appl Physiol (1985) 95: 1851-1860, 2003.
70. Kirk B, Cawthon PM, Arai H, Ávila-Funes JA, Barazzoni R, Bhasin S, Binder EF, Bruyere O, Cederholm T, Chen LK, *et al*: The conceptual definition of sarcopenia: Delphi consensus from the global leadership initiative in sarcopenia (GLIS). Age Ageing 53: afae052, 2024.

71. Chen Y, Zhang Y, Zhang S and Ren H: Molecular insights into sarcopenia: Ferroptosis-related genes as diagnostic and therapeutic targets. J Biomol Struct Dyn 43: 7989-8007, 2025.
72. Yan Y, Teng H, Hang Q, Kondiparthi L, Lei G, Horbath A, Liu X, Mao C, Wu S, Zhuang L, *et al*: SLC7A11 expression level dictates differential responses to oxidative stress in cancer cells. Nat Commun 14: 3673, 2023.
73. Wang W, Ren W, Zhu L, Hu Y and Ye C: Identification of genes and key pathways underlying the pathophysiological association between sarcopenia and chronic obstructive pulmonary disease. Exp Gerontol 187: 112373, 2024.
74. Tang J, Zhang H, Yin L, Zhou Q and Zhang H: The gut microbiota from maintenance hemodialysis patients with sarcopenia influences muscle function in mice. Front Cell Infect Microbiol 13: 1225991, 2023.
75. Guo YF, Liu ZY, Zhou M, Kuang WH, Liu Y, Huang Y, Yin P and Xia ZY: Heat exposure promotes sarcopenia via gut microbiota-derived metabolites. Aging Cell 29: e14370, 2025.
76. Liu Y, Guo Y, Liu Z, Feng X, Zhou R, He Y, Zhou H, Peng H and Huang Y: Augmented temperature fluctuation aggravates muscular atrophy through the gut microbiota. Nat Commun 14: 3494, 2023.
77. Hesketh GE: Progressive muscular atrophy. Physiotherapy 33: 57-60, 1947.
78. Bean LA, Thomas C, Villa JF, Fitt AJ, Javier AJS, Agrawal A, Whitney H, Dos Santos GN, White KE, Huot JR and Welc SS: Klotho deficiency promotes skeletal muscle weakness and is associated with impaired motor unit connectivity. Int J Mol Sci 26: 7986, 2025.
79. Bao S and Lei Y: Motor unit activity and synaptic inputs to motoneurons in the caudal part of the injured spinal cord. J Neurophysiol 131: 187-197, 2024.
80. Wang HH, Zhang Y, Qu TQ, Sang XQ, Li YX, Ren FZ, Wen PC and Sun YN: Nobiletin improves D-galactose-induced aging mice skeletal muscle atrophy by regulating protein homeostasis. Nutrients 15: 1801, 2023.
81. Yokogawa H, Higashida K and Nakai N: Iron homeostasis disruption and lipid peroxidation in skeletal muscle during short-term immobilization. FEBS Open Bio: Mar 19, 2026 (Epub ahead of print).
82. Bhatt BJ, Ghosh S, Mazurak V, Brun AQ, Bathe O, Baracos VE and Damaraju S: Molecular subtypes of human skeletal muscle in cancer cachexia. Nature 646: 973-982, 2025.
83. Ma X, Rao Z, Jin Z, Lu Y, Sun Z and Zheng L: Resistance exercise counteracts skeletal muscle atrophy in T2DM mice by upregulating FGF21 and activating PI3K/Akt pathway. Biomolecules 16: 3, 2025.
84. Cohen S, Brault JJ, Gygi SP, Glass DJ, Valenzuela DM, Gartner C, Latres E and Goldberg AL: During muscle atrophy, thick, but not thin, filament components are degraded by MuRF1-dependent ubiquitylation. J Cell Biol 185: 1083-1095, 2009.
85. Lee J, Lee SH, Kim H and Chung SW: Effect of electrical muscle stimulation on the improvement of deltoid muscle atrophy in a rat shoulder immobilization model. J Orthop Res 42: 2634-2645, 2024.
86. Liu Z, Zeng X, Bian W, Li H, Tegeleqi B, Gao Z and Liu J: Exosomes from muscle-derived stem cells repair peripheral nerve injury by inhibiting ferroptosis via the Keap1-Nrf2-Ho-1 axis. J Cell Biochem 125: e30614, 2024.
87. He J, He Z, Wang H, Zhang C, Pei T, Yan S, Yan Y, Wang F, Chen Y, Yuan N, *et al*: Caffeic acid alleviates skeletal muscle atrophy in 5/6 nephrectomy rats through the TLR4/MYD88/NF-kB pathway. Biomed Pharmacother 174: 116556, 2024.
88. Ju L, Diao J, Zhang J, Dai F, Zhou H, Han Z, Hu R, Pei T, Wang F, He Z, *et al*: Shenshuai Yingyang Jiaonang ameliorates chronic kidney disease-associated muscle atrophy in rats by inhibiting ferroptosis mediated by the HIF-1α/SLC7A11 pathway. Heliyon 10: e29093, 2024.
89. You L: Dihydromyricetin inhibits ferroptosis to attenuate cisplatin-induced muscle atrophy. Physiol Res 73: 405-413, 2024.
90. Liu X, Xu M, Yu Y, Chen Y, Weng X and Zhu L: PD-1 alleviates cisplatin-induced muscle atrophy by regulating inflammation and oxidative stress. Antioxidants (Basel) 11: 1839, 2022.
91. Sheng Z, Yu Z, Wang M, Zhou R, Chen S, Yu X and Li F: Targeting STAT6 to mitigate sepsis-induced muscle atrophy and weakness: Modulation of mitochondrial dysfunction, ferroptosis, and CHI3L1-Mediated satellite cell loss. Biochem Biophys Rep 37: 101608, 2023.
92. Tran L, Xie B, Assaf E, Ferrari R, Pipinos II, Casale GP, Mota Alvidrez RI, Watkins S and Sachdev U: Transcriptomic profiling identifies ferroptosis-related gene signatures in ischemic muscle satellite cells affected by peripheral artery disease-brief report. Arterioscler Thromb Vasc Biol 43: 2023-2029, 2023.
93. Maimaiti Y, Abulitifu M, Ajimu Z, Su T, Zhang Z, Yu Z and Xu H: FOXO regulation of TXNIP induces ferroptosis in satellite cells by inhibiting glutathione metabolism, promoting sarcopenia. Cell Mol Life Sci 82: 81, 2025.
94. Co HKC, Wu CC, Lee YC and Chen SH: Emergence of large-scale cell death through ferroptotic trigger waves. Nature 631: 654-662, 2024.
95. Wáng YXJ, Xiao BH, Leung JCS, Griffith JF, Aparisi Gómez MP, Bazzocchi A, Diacinti D, Chan WP, Guermazi A and Kwok TCY: The observation that older men suffer from hip fracture at DXA T-scores higher than older women and a proposal of a new low BMD category, osteofrailia, for predicting fracture risk in older men. Skeletal Radiol 54: 925-936, 2025.
96. Florez H, Carrasco JL, Barberá M, Hernández-Rodríguez J, Muxi A, Mocritcaia A, Prieto-González S, Cid MC, Monegal A, Guañabens N and Peris P: Risk factors for glucocorticoid induced osteoporosis in young adults. Front Endocrinol (Lausanne) 16: 1528962, 2025.
97. Sornay-Rendu E, Duboeuf F and Chapurlat RD: Postmenopausal women with normal BMD who have fractures have deteriorated bone microarchitecture: A prospective analysis from The OFELY study. Bone 182: 117072, 2024.
98. Porter JL and Varacallo MA: Osteoporosis(archived). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2026.
99. Deng X, Lin B, Wang F, Xu P and Wang N: Mangiferin attenuates osteoporosis by inhibiting osteoblastic ferroptosis through Keap1/Nrf2/SLC7A11/GPX4 pathway. Phytomedicine 124: 155282, 2024.
100. Jing Z, Li Y, Zhang H, Chen T, Yu J, Xu X, Zou Y, Wang X, Xiang K, Gong X, *et al*: Tobacco toxins induce osteoporosis through ferroptosis. Redox Biol 67: 102922, 2023.
101. Xue C, Luo H, Wang L, Deng Q, Kui W, Da W, Chen L, Liu S, Xue Y, Yang J, *et al*: Aconine attenuates osteoclast-mediated bone resorption and ferroptosis to improve osteoporosis via inhibiting NF-κB signaling. Front Endocrinol (Lausanne) 14: 1234563, 2023.
102. Jiang Z, Qi G, He X, Yu Y, Cao Y, Zhang C, Zou W and Yuan H: Ferroptosis in osteocytes as a target for protection against postmenopausal osteoporosis. Adv Sci (Weinh) 11: e2307388, 2024.
103. Xu CY, Xu C, Xu YN, Du SQ, Dai ZH, Jin SQ, Zheng G, Xie CL and Fang WL: Poliumoside protects against type 2 diabetes-related osteoporosis by suppressing ferroptosis via activation of the Nrf2/GPX4 pathway. Phytomedicine 125: 155342, 2024.
104. Li Y, Cai Z, Ma W, Bai L, Luo E and Lin Y: A DNA tetrahedron-based ferroptosis-suppressing nanoparticle: Superior delivery of curcumin and alleviation of diabetic osteoporosis. Bone Res 12: 14, 2024.
105. Huang Y, Zhang J, Zhu Y, Zhao R, Xie Z, Qu X, Duan Y, Li N, Tang D and Luo X: BMP9 alleviates iron accumulation-induced osteoporosis via the USP10/FOXO1/GPX4 axis. J Adv Res 79: 953-972, 2026.
106. Zhang Y, Cong Y, Du J, Guo D, Huang J, Pan J, Liang Y, Zhang J, Ye Z, Liu Y and Zhou Y: Lif-deficiency promote systemic Iron metabolism disorders and increases the susceptibility of osteoblasts to ferroptosis. Bone 189: 117266, 2024.
107. Tang X, Yang M, Liu Y, Zhang H, Hong X, Deng M, Liu P, Sun Q, Tu X and Shao G: Inhibition of ferroptosis rescues BMP osteogenic differentiation impaired by iron overload in the osteoporotic microenvironment. Cell Signal 136: 112116, 2025.
108. Teraguchi M, Yoshimura N, Hashizume H, Muraki S, Yamada H, Minamide A, Oka H, Ishimoto Y, Nagata K, Kagotani R, *et al*: Prevalence and distribution of intervertebral disc degeneration over the entire spine in a population-based cohort: The Wakayama spine study. Osteoarthritis Cartilage 22: 104-110, 2014.
109. Li W, Djuric N, Mink C and Vleggeert-Lankamp CLA: Inflammation and macrophage polarization are associated with Modic change type in lumbar radiculopathy. Brain Spine 5: 104249, 2025.
110. Al Qaraghli MI and De Jesus O: Lumbar disc herniation. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, 2026.
111. Du J, Dong H, Huang M, Silberschmidt VV, Meng L and Miao J: Regional variations of mechanical responses of IVD to 7 different motions: An in vivo study combined with FEA and DFIS. J Mech Behav Biomed Mater 160: 106785, 2024.
112. Guo J, Ding Q and Sun L: Association between sarcopenia and intervertebral disc degeneration: A bidirectional two-sample Mendelian randomization. J Back Musculoskelet Rehabil 38: 902-913, 2025.

113. Jia C, Xiang Z, Zhang P, Liu L, Zhu X, Yu R, Liu Z, Wang S, Liu K, Wang Z, *et al*: Selenium-SelK-GPX4 axis protects nucleus pulposus cells against mechanical overloading-induced ferroptosis and attenuates senescence of intervertebral disc. Cell Mol Life Sci 81: 49, 2024.
114. Xiang Q, Zhao Y and Li W: Identification and validation of ferroptosis-related gene signature in intervertebral disc degeneration. Front Endocrinol (Lausanne) 14: 1089796, 2023.
115. Zhu J, Sun R, Sun K, Yan C, Jiang J, Kong F and Shi J: The deubiquitinase USP11 ameliorates intervertebral disc degeneration by regulating oxidative stress-induced ferroptosis via deubiquitinating and stabilizing Sirt3. Redox Biol 62: 102707, 2023.
116. Yao B, Cai Y, Wan L, Deng J, Zhao L, Wang W and Han Z: BACH1 promotes intervertebral disc degeneration by regulating HMOX1/GPX4 to mediate oxidative stress, ferroptosis, and lipid metabolism in nucleus pulposus cells. J Gene Med 25: e3488, 2023.
117. Xiang Z, Zhang P, Jia C, Xu R, Cao D, Xu Z, Lu T, Liu J, Wang X, Qiu C, *et al*: Piezo1 channel exaggerates ferroptosis of nucleus pulposus cells by mediating mechanical stress-induced iron influx. Bone Res 12: 20, 2024.
118. Zou M, Wu S, Wang J, Xue W, Sun X, Liu L, Yin P and Huang D: Bioinformatics analysis reveals hub genes linked to programmed cell death in intervertebral disc degeneration. Appl Biochem Biotechnol 197: 4475-4493, 2025.
119. Takemoto M, Sugishita Y, Takahashi-Suzuki Y, Fujiya H, Niki H and Yudoh K: Repetitive compressive loading down-regulates mitochondria function and upregulates the cartilage matrix degrading enzyme MMP-13 through the coactivation of NAD-dependent sirtuin 1 and Runx2 in osteoarthritic chondrocytes. Int J Mol Sci 26: 4967, 2025.
120. He Q, Yang J, Pan Z, Zhang G, Chen B, Li S, Xiao J, Tan F, Wang Z, Chen P and Wang H: Biochanin A protects against iron overload associated knee osteoarthritis via regulating iron levels and NRF2/System xc-/GPX4 axis. Biomed Pharmacother 157: 113915, 2023.
121. Li H, Jiang X, Xiao Y, Zhang Y, Zhang W, Doherty M, Nestor J, Li C, Ye J, Sha T, *et al*: Combining single-cell RNA sequencing and population-based studies reveals hand osteoarthritis-associated chondrocyte subpopulations and pathways. Bone Res 11: 58, 2023.
122. Xie Y, Lv Z, Li W, Lin J, Sun W, Guo H, Jin X, Liu Y, Jiang R, Fei Y, *et al*: JP4-039 protects chondrocytes from ferroptosis to attenuate osteoarthritis progression by promoting Pink1/Parkin-dependent mitophagy. J Orthop Translat 51: 132-144, 2025.
123. Chen W, Yang W, Meng B, Wang X, Duan H, Xu Q and Li H: Validation and the role of PDK4 relevant to ferroptosis in degenerative lumbar disc disease. J Orthop Surg Res 20: 30, 2025.
124. Seo AY, Xu J, Servais S, Hofer T, Marzetti E, Wohlgemuth SE, Knutson MD, Chung HY and Leeuwenburgh C: Mitochondrial iron accumulation with age and functional consequences. Aging Cell 7: 706-716, 2008.
125. Chen X, Zhang Y, Zhao Y, Zhou M, Cheng P, Yang H, Shu Y, Duan L, Wu Y, Sun Y, *et al*: SLC38A1 protects against aging-related oxidative stress and lipid peroxidation in C2C12 myoblasts: Implication of a ferroptosis-related regulator for skeletal muscle aging. Exp Gerontol 210: 112880, 2025.
126. Qiao C, Sun Z, Muhammad F, Gong W, Lin J, Lv J, Cheng X, Fei Y, Xu N, Xie Y, *et al*: Ruthenium oxide nanozyme for tendinopathy treatment via countering ferroptosis. Adv Healthc Mater 14: e2501035, 2025.
127. Cheff DM, Huang C, Scholzen KC, Gencheva R, Ronzetti MH, Cheng Q, Hall MD and Arnér ESJ: The ferroptosis inducing compounds RSL3 and ML162 are not direct inhibitors of GPX4 but of TXNRD1. Redox Biol 62: 102703, 2023.
128. Miotto G, Rossetto M, Di Paolo ML, Orian L, Venerando R, Roveri A, Vučković AM, Bosello Travain V, Zaccarin M, Zennaro L, *et al*: Insight into the mechanism of ferroptosis inhibition by ferrostatin-1. Redox Biol 28: 101328, 2020.
129. Skouta R, Dixon SJ, Wang J, Dunn DE, Orman M, Shimada K, Rosenberg PA, Lo DC, Weinberg JM, Linkermann A and Stockwell BR: Ferrostatins inhibit oxidative lipid damage and cell death in diverse disease models. J Am Chem Soc 136: 4551-4556, 2014.
130. Zhao J, Jia Y, Mahmut D, Deik AA, Jeanfavre S, Clish CB and Sankaran VG: Human hematopoietic stem cell vulnerability to ferroptosis. Cell 186: 732-747.e16, 2023.
131. Zheng Z, Shang X, Sun K, Hou Y, Zhang X, Xu J, Liu H, Ruan Z, Hou L, Guo Z, *et al*: P21 resists ferroptosis in osteoarthritic chondrocytes by regulating GPX4 protein stability. Free Radic Biol Med 212: 336-348, 2024.
132. Liu R, Xiao Y, Zhang G, Han P, Lin Z and Song H: TRIM8 enhances chondrocyte ferroptosis by inhibiting YTHDF2-m6A mediated SREBF2 mRNA degradation to promote OA progression. Int Immunopharmacol 152: 114441, 2025.
133. Xiong X, Li W, Yu C, Qiu M, Zhang Z, Hu C, Zhu S, Yang L, Pen H, Song X, *et al*: SMURF1-induced ubiquitination of FTH1 disrupts iron homeostasis and suppresses myogenesis. Int J Mol Sci 26: 1390, 2025.
134. Han S, Zhao X, Yu C, Cui C, Zhang Y, Zhu Q, Qiu M, Yang C and Yin H: Nestin regulates autophagy-dependent ferroptosis mediated skeletal muscle atrophy by ubiquitinating MAP 1LC3B. J Cachexia Sarcopenia Muscle 16: e13779, 2025.
135. Wan Y, Shen K, Yu H and Fan W: Baicalein limits osteoarthritis development by inhibiting chondrocyte ferroptosis. Free Radic Biol Med 196: 108-120, 2023.
136. Zhou X, Pan Y, Li J, Zhuang R, Tong P and Xia H: Notopterol mitigates osteoarthritis progression and relieves pain in mice by inhibiting PI3K/Akt/GPX4-mediated ferroptosis. Int Immunopharmacol 151: 114323, 2025.
137. Gwon HJ, Cho W, Choi SW, Lim DS, Tanriverdi EÇ, Abd El-Aty AM, Jeong JH and Jung TW: Donepezil improves skeletal muscle insulin resistance in obese mice via the AMPK/FGF21-mediated suppression of inflammation and ferroptosis. Arch Pharm Res 47: 940-953, 2024.
138. Liu J, Ren Z, Yang L, Zhu L, Li Y, Bie C, Liu H, Ji Y, Chen D, Zhu M and Kuang W: The NSUN5-FTH1/FTL pathway mediates ferroptosis in bone marrow-derived mesenchymal stem cells. Cell Death Discov 8: 99, 2022.
139. Bao T, Liao T, Cai X, Lu B, Dai G, Pei S, Zhang Y, Li Y and Xu B: METTL3 mediated ferroptosis in chondrocytes and promoted pain in KOA via HMGB1 m6A modification. Cell Biol Int 48: 1755-1765, 2024.
140. Lin Y, Shen X, Ke Y, Lan C, Chen X, Liang B, Zhang Y and Yan S: Activation of osteoblast ferroptosis via the METTL3/ASK1-p38 signaling pathway in high glucose and high fat (HGHF)-induced diabetic bone loss. FASEB J 36: e22147, 2022.
141. Shang J, Xiong C, Jiang W, Yu Z, Zhang J, Zhang Y, Han L, Miao K, Yu C, Huang Y and Zhou X: Gossypol acetic acid alleviates the ferroptosis of chondrocytes in osteoarthritis by inhibiting GPX4 methylation. Curr Med Chem 32: 2422-2439, 2025.
142. Ruan B, Dong J, Wei F, Huang Z, Yang B, Zhang L, Li C, Dong H, Cao W, Wang H and Wang Y: DNMT aberration-incurred GPX4 suppression prompts osteoblast ferroptosis and osteoporosis. Bone Res 12: 68, 2024.
143. Romanick SS, Godoy L, Lopez A, Matsumura A, Boc K, Stewart TJ, Baker JE and Ferguson BS: Skeletal muscle alpha actin acetylation enhances myosin binding and increases calcium sensitivity. Biophys Rep (N Y) 5: 100226, 2025.
144. Xiong X, Huang H, Wang N, Zhou K and Song X: Sirt1 overexpression inhibits chondrocyte ferroptosis via Ftl deacetylation to suppress the development of osteoarthritis. J Bone Miner Metab 43: 203-215, 2025.
145. Zhang Z, Zhang N, Li M, Ma X and Qiu Y: Sappanone a alleviates osteoarthritis progression by inhibiting chondrocyte ferroptosis via activating the SIRT1/Nrf2 signaling pathway. Naunyn Schmiedebergs Arch Pharmacol 397: 8759-8770, 2024.
146. Bai L, Wang T, Zheng J, Bian C, Zhang Y and Fan Y: SIRT1 mediated by baicalein and GFI1 promotes osteogenic differentiation and ameliorates osteoporosis by inhibiting ferroptosis in bone marrow mesenchymal stem cells. J Biochem Mol Toxicol 39: e70368, 2025.
147. Martin SD, Connor T, Sanigorski A, McEwen KA, Henstridge DC, Nijagal B, De Souza D, Tull DL, Meikle PJ, Kowalski GM, *et al*: Class IIa HDACs inhibit cell death pathways and protect muscle integrity in response to lipotoxicity. Cell Death Dis 14: 787, 2023.
148. Guan Z, Jin X, Guan Z, Liu S, Tao K and Luo L: The gut microbiota metabolite capsiate regulate SLC2A1 expression by targeting HIF-1α to inhibit knee osteoarthritis-induced ferroptosis. Aging Cell 22: e13807, 2023.
149. Ren Y, Zhang S, Wang Y, Jacobson DS, Reisdorf RL, Kuroiwa T, Behfar A, Moran SL, Steinmann SP and Zhao C: Effects of purified exosome product on rotator cuff tendon-bone healing in vitro and in vivo. Biomaterials 276: 121019, 2021.

150. Jin S, Wang Y, Wu X, Li Z, Zhu L, Niu Y, Zhou Y and Liu Y: Young exosome bio-nanoparticles restore aging-impaired tendon stem/progenitor cell function and reparative capacity. Adv Mater 35: e2211602, 2023.
151. Li Y, Ma M, Wang X, Li J, Fang Z, Li J, Yang B, Lu Y, Xu X and Li Y: Celecoxib alleviates the DSS-induced ulcerative colitis in mice by enhancing intestinal barrier function, inhibiting ferroptosis and suppressing apoptosis. Immunopharmacol Immunotoxicol 46: 240-254, 2024.
152. Liu C, He P, Guo Y, Tian Q, Wang J, Wang G, Zhang Z and Li M: Taurine attenuates neuronal ferroptosis by regulating $GABA_B$/AKT/GSK3β/β-catenin pathway after subarachnoid hemorrhage. Free Radic Biol Med 193: 795-807, 2022.
153. Zhang M, Qin X, Zhao Z, Du Q, Li Q, Jiang Y and Luan Y: A self-amplifying nanodrug to manipulate the Janus-faced nature of ferroptosis for tumor therapy. Nanoscale Horiz 7: 198-210, 2022.
154. Kumar A, Vaca-Dempere M, Mortimer T, Deryagin O, Smith JG, Petrus P, Koronowski KB, Greco CM, Segalés J, Andrés E, *et al*: Brain-muscle communication prevents muscle aging by maintaining daily physiology. Science 384: 563-572, 2024.
155. Gao T, Xu G, Ma T, Lu X, Chen K, Luo H, Chen G, Song J, Ma X, Fu W, *et al*: ROS-responsive injectable hydrogel loaded with SLC7A11-modRNA inhibits ferroptosis and mitigates intervertebral disc degeneration in rats. Adv Healthc Mater 13: e2401103, 2024.
156. Li W, Lv Z, Wang P, Xie Y, Sun W, Guo H, Jin X, Liu Y, Jiang R, Fei Y, *et al*: Near infrared responsive gold nanorods attenuate osteoarthritis progression by targeting TRPV1. Adv Sci (Weinh) 11: e2307683, 2024.
157. Xue Q, Yan D, Chen X, Li X, Kang R, Klionsky DJ, Kroemer G, Chen X, Tang D and Liu J: Copper-dependent autophagic degradation of GPX4 drives ferroptosis. Autophagy 19: 1982-1996, 2023.