Mitochondria-driven ferroptosis in intervertebral disc degeneration: A novel target in age-related spinal diseases (Review)

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Abstract. Ferroptosis, an iron-dependent form of programmed cell death driven by lipid peroxidation and reactive oxygen species (ROS), has emerged as a key mechanism in the progression of intervertebral disc degeneration (IDD). Mitochondria serve a central role in this process by regulating iron metabolism, ROS production and energy homeostasis. In IDD, mitochondrial dysfunction leads to increased lipid ROS levels, decreased glutathione peroxidase 4 (GPX4) activity and impaired antioxidant defenses, contributing to extracellular matrix degradation and nucleus pulposus cell death. The present review summarizes the core molecular mechanisms underlying ferroptosis and highlights the mitochondrial pathways that mediate ferroptosis in IDD. Furthermore, the advances in mitochondria-targeted therapeutic strategies are discussed, including antioxidants, iron chelators, GPX4 activators, mitophagy modulators and nanotechnology-based interventions. These approaches provide promising avenues for preventing ferroptosis-induced disc degeneration and preserving the viability of disc cells. Understanding the interplay between mitochondrial dysfunction and ferroptosis may offer novel insights for the development of precise and effective treatments for IDD.

Contents

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1. Introduction

Ferroptosis is a programmed cell death process dependent on iron ions and reactive oxygen species (ROS), which is primarily characterized by an imbalance in iron homeostasis, inactivation of glutathione peroxidase 4 (GPX4) and lipid peroxidation damage (1). Unlike apoptosis, necrosis and autophagy, ferroptosis exhibits unique metabolic and oxidative stress-driven characteristics (2). In previous years, ferroptosis has been shown to serve a key role in numerous pathological processes, including neurodegenerative diseases, cancer and inflammation-related disorders (3). Within the context of spinal degenerative diseases, increasing evidence suggests that ferroptosis is a key contributor to intervertebral disc degeneration (IDD) (4-6).

Mitochondria, the central organelles for cellular energy metabolism and oxidative stress regulation, serve a key role in ferroptosis (7). Firstly, mitochondria serve as notable sites for iron storage and utilization, and the disruption of iron homeostasis directly leads to mitochondrial dysfunction (8). Secondly, mitochondria generate marked amounts of ROS, which promote ferroptosis through lipid peroxidation pathways (9). Furthermore, mitochondrial membrane potential ($\Delta\Psi m$) decline, increased mitochondrial outer membrane permeability and mitochondrial DNA (mtDNA) damage have been identified as key regulatory factors in ferroptosis (10,11). Collectively, these mitochondrial dysfunction-associated events contribute to ferroptosis-related nucleus pulposus cell injury and extracellular matrix degradation in IDD, thereby suggesting that targeting mitochondrial dysfunction may represent a potential therapeutic strategy for IDD.

IDD is a leading cause of chronic lower back pain with pathological mechanisms involving nucleus pulposus cell (NPC) apoptosis, extracellular matrix (ECM) degradation, an imbalanced inflammatory microenvironment and oxidative stress damage (12,13). Recent studies have suggested that ferroptosis-related molecules are abnormally expressed in the intervertebral disc tissues of patients with IDD, with marked downregulation of GPX4, iron ion accumulation and increased

lipid peroxidation levels (14,15). Additionally, research has demonstrated that interventions targeting mitochondrial function, oxidative stress suppression or iron homeostasis modulation may mitigate IDD progression (16). Consequently, therapeutic strategies targeting mitochondria-mediated ferroptosis, including antioxidants, iron chelators and mitochondrial protective agents, have gained attention.

Ferroptosis appears to be uniquely associated with age-related spinal degeneration. Unlike other forms of cell death, such as apoptosis, necroptosis and autophagy-dependent cell death, ferroptosis integrates imbalances in iron metabolism, oxidative stress and mitochondrial dysfunction, all of which progressively accumulate with age. Therefore, ferroptosis is not only a driver of disc cell loss but also a key process linking aging biology to spinal degenerative diseases (3,13). This unique contribution underscores the necessity of developing ferroptosis-targeted interventions for age-related IDD.

Overall, ferroptosis is a form of cell death that has garnered attention regarding its potential role in IDD pathology, with mitochondria being key regulators of this process. Therefore, the present review explores the functional mechanisms of mitochondria in ferroptosis and discusses therapeutic strategies targeting mitochondria-mediated ferroptosis for IDD treatment, aiming to provide novel insights for clinical intervention.

2. Molecular mechanisms of mitochondria and ferroptosis

Core mechanisms of ferroptosis. Mitochondria serve a key role in ferroptosis by acting as central regulators of cellular redox balance, iron metabolism, lipid peroxidation and ROS production.

Ferroptosis involves three key processes consisting of iron metabolism dysregulation, lipid peroxidation and an imbalance in the antioxidant system. Within iron metabolism regulation, iron is taken up by the transferrin receptor 1 (TfR1) pathway and stored in ferritin, whereas ferroportin is responsible for iron export. When ferritinophagy, mediated by nuclear receptor coactivator 4 (NCOA4), is enhanced, the stored iron is released, leading to the accumulation of intracellular free iron. This free iron undergoes the Fenton reaction, generating hydroxyl radicals (OH·) that induce ferroptosis (17,18).

Lipid peroxidation is a key process in ferroptosis. Polyunsaturated fatty acids (PUFAs) are oxidized by acyl-CoA synthetase long-chain family member 4 (ACSL4) and arachidonate 15-lipoxygenase (ALOX15), whereas GPX4 uses glutathione (GSH) to inhibit this process. When GPX4 is inactivated, the excessive accumulation of lipid peroxides disrupts membrane integrity, ultimately resulting in cell death (19).

Furthermore, the antioxidant system serves an important role in inhibiting ferroptosis. Solute carrier family 7 member 11 (SLC7A11, also known as xCT) maintains cellular antioxidant capacity by synthesizing GSH, whereas the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway activates downstream genes, such as GPX4, SLC7A11 and heme oxygenase 1 to suppress ferroptosis (20,21). Additionally, the ferroptosis suppressor protein 1/coenzyme Q10 pathway functions independently of GPX4 to protect cells from ferroptosis (22).

Role of mitochondria in ferroptosis. Mitochondria serve as central regulators of cellular iron metabolism, synthesizing iron-sulfur (Fe-S) clusters and heme while maintaining iron homeostasis. Mitochondrial iron transport proteins such as sideroflexin 1 import iron into the mitochondria, whereas the ATP-binding cassette transporter ABCB7 facilitates iron export. Excessive iron accumulation generates OH·, resulting in oxidative damage and exacerbating ferroptosis (23,24).

Mitochondria are the primary sources of cellular ROS. Superoxide anions ($O_2^{\cdot-}$) are produced at complexes I and III of the electron transport chain and are converted to hydrogen peroxide (H_2O_2) by superoxide dismutase 2 (SOD2). H_2O_2 further reacts with Fe^{2+} to generate OH·, promoting lipid peroxidation. In mitochondrial dysfunction, increased ROS levels further inhibit GPX4 activity, accelerate PUFA oxidation and ultimately induce ferroptosis (25-27).

The dysregulation of energy metabolism also serves a notable role in ferroptosis. The tricarboxylic acid cycle in the mitochondria regulates nicotinamide adenine dinucleotide phosphate (NADPH) levels, which are key for GSH regeneration. When NADPH is depleted, GSH levels decrease, leading to GPX4 inactivation and promoting ferroptosis (26). Moreover, reduced ATP synthesis impairs the function of SLC7A11, hindering GSH synthesis and increasing cellular susceptibility to ferroptosis (28).

Mitochondrial autophagy (mitophagy) is an important protective mechanism that removes damaged mitochondria, and reduces oxidative stress and iron accumulation. Moderate mitophagy lowers the risk of ferroptosis; however, excessive mitophagy exacerbates the cellular damage and promotes ferroptosis. For example, PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy, while removing damaged mitochondria, can lead to excessive mitochondrial loss, impairing cellular energy metabolism and indirectly enhancing ferroptotic signaling (29,30). Additionally, mitophagy mediated by NIX/BCL2-interacting protein 3, which is activated under hypoxic or metabolic stress, may influence ferroptosis by regulating iron homeostasis (31).

Stage-specific dynamics of mitochondrial dysfunction and ferroptosis in IDD. Emerging evidence has suggested that mitochondrial dysfunction and ferroptosis are not uniformly engaged across the course of IDD but instead display stage-dependent features (32,33).

Early IDD (radiographically mild degeneration or early symptomatic discs) is characterized by subtle bioenergetic stress with a mild decline in $\Delta\Psi m$ and increased mitochondrial ROS (MitoROS), preceding overt cell loss and ECM collapse. In NPCs, SOD2-dependent redox imbalance sensitizes cells to lipid peroxidation, whereas compensatory mitophagy is detectable but often insufficient to fully restore mitochondrial quality control (34). In parallel, iron-handling disturbances (such as labile iron accumulation and ferritinophagy-mediated iron release) initiate a pre-ferroptotic state, lowering the threshold for ferroptotic execution upon inflammatory or mechanical insults (13,14).

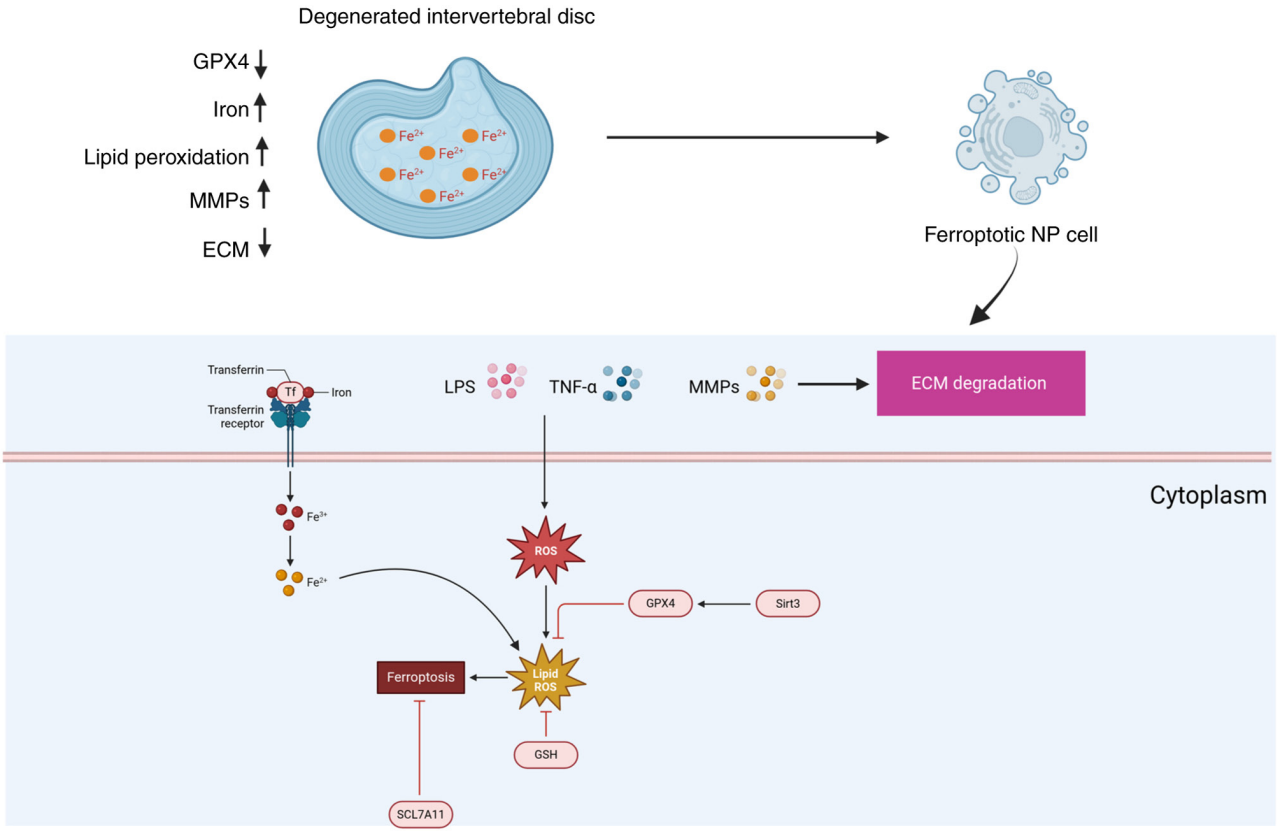

Figure 1. Mitochondria-mediated ferroptosis promotes extracellular matrix degradation in intervertebral disc degeneration. Mitochondrial dysfunction, triggered by iron overload and oxidative stress, leads to the accumulation of MitoROS and the activation of ferroptosis in nucleus pulposus cells (NPCs). Excess iron accumulates through mechanisms such as TfR upregulation and FTH1 downregulation, promoting lipid peroxidation and ROS generation. These processes result in cell death and the subsequent release of inflammatory mediators that exacerbate intervertebral disc degeneration. Furthermore, mitochondrial dysfunction impairs GPX4 activity, leading to reduced antioxidant capacity and increased oxidative damage. This cascade of events ultimately accelerates ECM degradation, contributing to the progression of IDD. GPX4, glutathione peroxidase 4; ECM, extracellular matrix; NP, nucleus pulposus; LPS, lipopolysaccharide; Tf, transferrin; Sirt3, sirtuin 3; ROS, reactive oxygen species; GSH, glutathione; SCL7A11, solute carrier family 7 member 11.

During the intermediate stage, cumulative oxidative injury amplifies lipid peroxidation through ACSL4/ALOX15-dependent pathways, whereas GSH depletion limits GPX4 activity. Concomitantly, impaired PINK1/Parkin-mediated mitophagy allows damaged mitochondria and mtDNA to persist, reinforcing the ROS-lipid peroxide feed-forward loops. Iron dysregulation becomes more evident, with NCOA4-driven ferritinophagy exacerbating oxidative injury and inflammatory cytokines (such as TNF-α and IL-1β) suppressing SLC7A11/GPX4 expression, further priming ferroptosis (14).

In advanced IDD, ferroptosis switches from a permissive state to a dominant execution program in subsets of disc cells. Profound ΔΨm collapse, extensive mitochondrial morphological damage, iron overload and persistent mitophagy insufficiency co-occur with ECM disintegration and cell depletion. At this stage, mitochondria-directed interventions [such as mitochondria-targeted coenzyme Q10 (MitoQ) and SkQ1] can still attenuate oxidative injury but may require combination strategies (iron chelation, GPX4 preservation and mitophagy rebalancing) to achieve structural benefits (35).

Together, these data support a temporal model in which mitochondrial stress and iron abnormalities appear early, intensify at the mid-stage and culminate in overt ferroptosis with structural failure in late-stage IDD.

3. Ferroptosis and IDD

Within recent research, the role of ferroptosis in IDD has gained increasing attention. The core pathological features of IDD include ECM degradation, NP and annulus fibrosus cell death, as well as oxidative stress and inflammatory responses. Mitochondrial dysfunction and ferroptosis have been suggested as key drivers of IDD progression, with mitochondria mediating this process of ferroptosis in IDD (Fig. 1).

Major mechanisms of IDD. The pathogenesis of IDD is complex, involving a number of biological processes. A key feature is ECM degradation, which results from the upregulation of MMPs and ADAMTSs, leading to the breakdown of proteoglycans and collagen, ultimately causing structural damage to the intervertebral disc (36,37). Inflammatory activation serves a notable role in this process, as M1 macrophage infiltration and the release of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6, accelerate ECM degradation and promote cell death (38).

Oxidative stress is another key factor, whereby the accumulation of ROS damages cellular components, particularly the mitochondria. Oxidative damage triggers numerous forms of programmed cell death, including apoptosis, pyroptosis and ferroptosis (39). Within the context of ferroptosis, increasing evidence has suggested that iron metabolism dysregulation

contributes to IDD pathology. Studies have shown that ferroptosis-related genes, including GPX4, SLC7A11, ferritin heavy chain 1 (FTH1) and ACSL4, exhibit abnormal expression patterns in IDD tissues (40,41). These changes indicate a diminished ability to counteract oxidative damage and increased susceptibility to lipid peroxidation, further exacerbating disc degeneration.

The interplay among ECM degradation, inflammatory responses, oxidative stress and ferroptosis highlights the multifactorial nature of IDD and underscores the importance of targeting these mechanisms to develop potential therapeutic strategies.

Role of ferroptosis in IDD progression. Recent studies have highlighted ferroptosis as a key component of IDD progression (32,33). Ferroptosis-related genes exhibit abnormal expression in IDD tissues, with the downregulation of GPX4 and SLC7A11 reducing antioxidant capacity and inducing ferroptosis. By contrast, the upregulation of ACSL4, ALOX15, and NCOA4 promotes lipid peroxidation and intracellular iron accumulation, exacerbating cell death (42-45). Elevated iron levels in IDD tissues further intensify oxidative stress through the Fenton reaction, contributing to ECM degradation and the loss of disc structural integrity. *In vitro* studies have demonstrated that the iron overload induced by ferric ammonium citrate triggers ferroptosis in NPCs and increases MMP expression, accelerating ECM breakdown (5,33). Conversely, ferroptosis inhibitors, such as iron chelators, including deferoxamine (DFO), or GPX4 activators, have been shown to mitigate IDD progression, suggesting a potential therapeutic approach (4,46).

Additionally, inflammatory cytokines such as TNF-α and IL-1β serve an important role in ferroptosis-mediated IDD. These cytokines suppress the expression of GPX4 and SLC7A11, leading to enhanced lipid peroxidation and increased sensitivity to ferroptosis in IDD cells (42). Lipopolysaccharide stimulation further amplifies this effect by promoting ROS accumulation, making NPCs more vulnerable to ferroptosis (47). In addition to TNF-α and IL-1β, recent studies have suggested that IL-6 contributes to ferroptosis by impairing antioxidant defense and altering iron metabolism (48,49). These cytokines upregulate TfR1 and downregulate FTH1, thereby promoting intracellular iron overload and ROS generation, which directly sensitize NPCs to ferroptotic death (50). These findings indicate that the inflammatory microenvironment not only accelerates ECM degradation but also directly regulates ferroptosis pathways in IDD.

Although ferroptosis is considered an irreversible form of programmed cell death, accumulating evidence has suggested that its early stages are reversible or modifiable. Ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1, iron chelators (including DFO) and Nrf2 activators have demonstrated the ability to restore GPX4 activity, scavenge lipid peroxides and rescue NPCs from ferroptotic damage (51-55). This suggests that ferroptosis can be effectively attenuated if the intervention occurs before extensive mitochondrial collapse and lipid peroxidation. However, once the oxidative injury surpasses a specific threshold, ferroptosis becomes irreversible, ultimately leading to disc cell death. These findings highlight the existence of a therapeutic window in which ferroptosis-targeting strategies may halt or even reverse the progression of IDD.

The role of mitochondrial regulation in ferroptosis has also been demonstrated, particularly through the mitochondrial deacetylase sirtuin 3 (Sirt3). Sirt3 expression is markedly reduced in IDD tissues, and is associated with lower GPX4 levels and increased ferroptosis. Experimental activation of Sirt3 using nicotinamide riboside has been shown to restore GPX4 expression and protect IDD cells from ferroptosis, further reinforcing the role of mitochondria in IDD pathology (56).

Mitochondrial mediation of ferroptosis in IDD. Mitochondria serve a pivotal role in IDD by regulating oxidative stress, iron homeostasis and autophagy, all of which are closely linked to ferroptosis. Mitochondria are a major source of ROS and excessive MitoROS can damage lipid membranes and promote lipid peroxidation, a key feature of ferroptosis (1). In IDD cells, $\Delta\Psi m$ decreases while MitoROS levels increase, indicating mitochondrial dysfunction (57,58). Antioxidants such as MitoQ and SkQ1 can reduce MitoROS accumulation and inhibit ferroptosis, suggesting that targeting mitochondrial oxidative stress is a viable therapeutic approach (59-61).

Mitochondria also serve as a central hub for cellular iron metabolism and participate in the synthesis of Fe-S clusters and heme (62). In IDD tissues, FTH1 expression is reduced, thereby disrupting iron homeostasis and increasing ferroptosis. Imbalances in mitochondrial iron metabolism contribute to iron overload, exacerbating oxidative damage and lipid peroxidation (1,33).

Additionally, mitophagy is important in the removal of damaged mitochondria and the maintenance of cellular health. However, IDD cells exhibit impaired PINK1/Parkin-mediated mitophagy, thereby resulting in the accumulation of dysfunctional mitochondria and further promotion of ferroptosis (63,64). The pharmacological activation of mitophagy, particularly through pathways such as PINK1/Parkin and Nrf2 signaling, mitigates ferroptosis-induced cellular damage and slows the progression of IDD by preserving NPC viability and reducing oxidative stress (56,65).

4. Mitochondria-targeted regulation of ferroptosis as a therapeutic strategy for IDD

Through research into the mechanisms of ferroptosis, mitochondria have been recognized as key regulatory centers, making them potential therapeutic targets. Therefore, strategies for mitochondria-mediated ferroptosis in IDD exhibit notable research and application potential (Fig. 2).

Mitochondria-targeted antioxidant strategies. Oxidative stress is a major driver of ferroptosis, with excessive MitoROS accumulation leading to lipid peroxidation and the exacerbation of IDD. Targeting mitochondria using antioxidant strategies has emerged as a promising intervention for mitigating these effects. One such approach involves the use of MitoQ, which effectively reduces MitoROS production, inhibits lipid peroxidation and disrupts ferroptosis signaling pathways (66). MitoQ alleviates oxidative damage in intervertebral disc cells, enhances ECM synthesis and slows IDD progression (67,68).

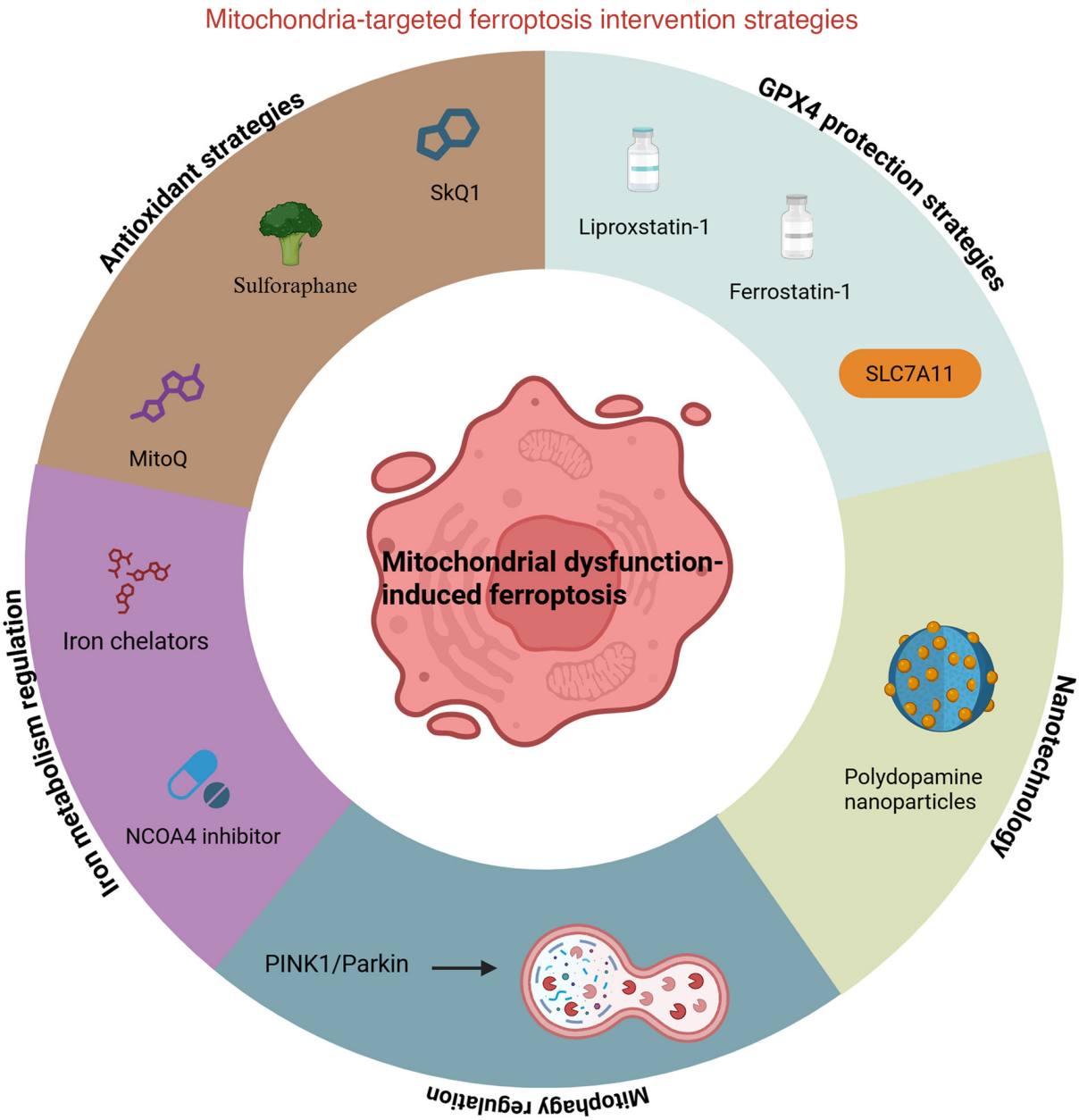

Figure 2. Therapeutic strategies targeting mitochondrial dysfunction-induced ferroptosis in intervertebral disc degeneration. SCL7A11, solute carrier family 7 member 11; PINK1, PTEN-induced kinase 1; NCOA4, nuclear receptor coactivator 4; MitoQ, mitochondria-targeted coenzyme Q10; GPX4, GPX4, glutathione peroxidase 4.

Similarly, SkQ1, another mitochondria-targeted antioxidant, exhibits potent free radical-scavenging capacity and acts directly within mitochondria to protect cells from ferroptosis-induced damage (69).

Furthermore, another key strategy involves activation of the Nrf2 signaling pathway, which serves a notable role in cellular antioxidant defense mechanisms (70). Compounds such as sulforaphane and bardoxolone function as Nrf2 activators, enhancing antioxidant capacity and increasing GPX4 activity, which leads to reduced lipid peroxidation and prevents ferroptosis (71,72). By boosting mitochondrial resilience against oxidative stress, mitochondria-targeted antioxidant strategies offer a promising option for therapeutic intervention in IDD. Although these compounds have demonstrated protective effects under other oxidative stress-related conditions, direct evidence for their application in IDD remains limited. However, given the established role of Nrf2 activation in IDD, as supported by existing research, sulforaphane and bardoxolone may exert similar protective effects in this context, yet further studies are required to validate the efficacy of IDD treatment.

Translating mitochondria-targeted antioxidant therapies into clinical applications faces a number of challenges. For example, MitoQ and SkQ1 exhibit poor stability, limited bioavailability and inefficient delivery to avascular disc tissues, which may reduce their therapeutic efficacy *in vivo* (73-75). Innovative drug delivery systems, such as nanoparticle encapsulation or hydrogel-based sustained-release platforms, are currently being explored with the aim of overcoming these challenges. However, clinical validation still remains

lacking. With regard to Nrf2 activators, such as sulforaphane and bardoxolone, the majority of evidence is currently derived from *in vitro* experiments or animal models of oxidative stress-related disorders, including osteoarthritis and IDD (72). Clinical trial data that directly evaluate their efficacy in IDD are also lacking, highlighting the gap between experimental findings and translational applications. Therefore, further preclinical optimization and early-phase clinical studies are required to establish their safety, pharmacokinetics and therapeutic potential in patients with IDD.

Iron metabolism-targeted drugs. Iron overload is an important trigger of ferroptosis as excessive free iron catalyzes the Fenton reaction, leading to increased ROS production and lipid peroxidation. Therefore, regulating iron homeostasis is key in mitigating ferroptosis and alleviating the progression of IDD. One widely studied approach involves iron chelators, such as DFO and deferiprone, which can effectively bind excess free iron, and reduce ROS generation and lipid peroxidation (33,76,77). DFO administration in IDD models helps alleviate oxidative stress, lowering inflammation and protecting NPCs from apoptosis (33).

An additional emerging approach involves targeting ferritinophagy, which regulates intracellular iron release by mediating the degradation of ferritin. NCOA4 inhibitors have been explored as potential therapeutic agents to prevent excessive ferritin degradation, thereby reducing intracellular free iron levels and minimizing the risk of ferroptosis (78,79). These inhibitors may delay IDD progression by stabilizing iron storage mechanisms and limiting iron availability for ROS generation.

Iron chelators and ferritinophagy modulators exert protective effects largely through mitochondrial mechanisms. These agents suppress the Fenton reaction within the mitochondria by reducing the mitochondrial labile iron pool, thereby limiting the formation of $OH^{\cdot}$ and preventing mitochondrial lipid peroxidation. Moreover, restoration of mitochondrial iron balance preserves electron transport chain function, stabilizes $\Delta\Psi m$ and decreases MitoROS accumulation, all of which collectively attenuate ferroptosis-induced mitochondrial injury in NPCs (80-82). Therefore, iron metabolism-targeted interventions not only modulate systemic iron homeostasis but also directly maintain mitochondrial integrity, providing a mechanistic basis for their therapeutic potential in IDD.

Regulation of mitophagy. Mitophagy, which is the selective degradation of damaged mitochondria, serves a notable role in maintaining mitochondrial homeostasis and regulating ferroptosis. Appropriate mitophagy clears dysfunctional mitochondria, reduces MitoROS accumulation and inhibits ferroptosis. However, excessive mitophagy may lead to mitochondrial depletion and metabolic dysfunction, further exacerbating IDD (81,83,84).

The PINK1/Parkin pathway is a primary mechanism regulating mitophagy. Under oxidative stress, PINK1 accumulates on the outer mitochondrial membrane, recruiting Parkin to promote the ubiquitination and degradation of damaged mitochondria. This process eliminates dysfunctional mitochondria, thereby reducing ROS production and preventing ferroptosis-induced cellular damage (85). However, maintaining a balance in mitophagy activation is important as excessive mitochondrial clearance may lead to energy metabolism disorders, further aggravating IDD pathology (85).

A recent review has further elucidated the dynamic interplay between mitophagy and ferroptosis in IDD, primarily mediated by ROS as a key mediator and involving pathways such as AMPK/mTOR and Nrf2/Kelch-like ECH-associated protein 1 (86). Mechanical stress induces ferroptosis in NPCs through the Piezo1 channel, while regulation of mitophagy (through Sirt signaling and the PINK1/Parkin axis) can alleviate ROS accumulation and mitochondrial damage. This previous study proposed that interventions targeting these interacting pathways (such as modulating ROS levels) may represent a new direction for IDD treatment (86). This underscores the importance of balancing mitophagy in IDD to prevent excessive ferroptosis and provides a theoretical foundation for developing comprehensive therapies.

Urolithin A, a natural compound derived from polyphenols, is a mitophagy inducer with potential therapeutic effects on IDD. By promoting mitochondrial quality control, Urolithin A enhances mitochondrial function, reduces oxidative stress and mitigates ferroptosis-related cell damage. Furthermore, it can alleviate mitochondrial dysfunction and delay IDD progression by maintaining mitochondrial integrity (85,87).

GPX4 protection strategies. GPX4 serves a central role in inhibiting ferroptosis by reducing lipid peroxidation and preserving cell membrane integrity. Strategies aimed at enhancing GPX4 activity or modulating its associated pathways are promising therapeutic approaches for IDD. For example, one effective method involves the use of GPX4 activators, such as liproxstatin-1 and ferrostatin-1, which mitigate ferroptosis-induced damage in NPCs. Preclinical studies have indicated that these compounds markedly improve intervertebral disc structure and suppress inflammatory responses in animal models of IDD, highlighting their potential clinical applications (47,88).

In addition, one alternative approach focuses on the regulation of SLC7A11, an important component in GSH synthesis. As GPX4 activity is heavily dependent on GSH availability, upregulation of SLC7A11 enhances GPX4 function and prevents ferroptosis. Inhibitors of erastin, which negatively regulates SLC7A11, have been explored as potential therapeutic agents to elevate intracellular GSH levels and protect intervertebral disc cells from oxidative stress and lipid peroxidation (32,89).

Mechanistically, GPX4 protection directly affects mitochondrial homeostasis during ferroptosis. GPX4 localizes not only in the cytosol but also within the mitochondria, where it detoxifies the phospholipid hydroperoxides generated by MitoROS (90,91). The upregulation or pharmacological activation of GPX4 helps maintain mitochondrial membrane integrity, prevents mtDNA oxidation and sustains ATP production during oxidative stress (90). Additionally, enhanced SLC7A11-GSH-GPX4 signaling ensures sufficient antioxidant capacity to counteract MitoROS accumulation, thereby interrupting the self-amplifying cycle of mitochondrial oxidative injury and ferroptosis (91,92). Thus, GPX4-targeted therapies protect cytoplasmic and mitochondrial compartments, offering a dual-layer defense against ferroptotic degeneration in IDD.

Mitochondria-targeted nanotherapy. With the rapid advancement of nanomedicine, mitochondria-targeted nanotherapy has emerged as a promising approach for the precise and efficient treatment of IDD by modulating ferroptosis pathways and oxidative stress at the mitochondrial level. A particularly notable strategy in this field involves the use of polydopamine nanoparticles (PDA NPs), which effectively inhibit oxidative stress-induced ferroptosis in NPCs (93). PDA NPs exert their protective effects by scavenging ROS, chelating Fe^{2+} to mitigate iron overload and regulating iron storage proteins such as FTH and TfR (93). In addition, these nanoparticles colocalize with GPX4 around the mitochondria, preventing its ubiquitin-mediated degradation, which in turn enhances the clearance of phospholipid hydroperoxides and reduces lipid peroxidation (94). *In vivo* studies have further demonstrated that PDA NPs can alleviate puncture-induced disc degeneration by suppressing ferroptosis and restoring antioxidant defenses, offering a novel therapeutic strategy for IDD that directly targets ferroptosis-related damage at the mitochondrial level (94,95).

Furthermore, one recent study developed DFOM@-cerium (IV) oxide (CeO_2) nanoparticles, which reduce iron overload through the iron chelator DFOM and scavenge ROS through CeO_2 while simultaneously achieving mitochondrial functional reprogramming. These nanoparticles inhibit tert-butyl hydroperoxide- or erastin-induced ferroptosis *in vitro*, restoring the expression of mitochondrial respiratory chain complexes (such as NDUFB8 and UQCRC2 subunits) and GPX4. Within an *in vivo* IDD rat model, these nanoparticles outperformed single DFOM or CeO_2 treatments, preserving intervertebral disc height and reducing ECM degradation (96). This strategy highlights the potential of nanotechnology in integrating iron metabolism regulation and mitochondrial protection, offering a novel option for the precise treatment of IDD.

Future research directions. Mitochondria-targeted regulation of ferroptosis represents a promising approach for IDD treatment; however, notable challenges remain before clinical application can be achieved. Currently, the majority of research has used cellular and animal models, with mature clinical trial data lacking. Future studies should aim to focus on developing more representative animal models, including larger animal experiments, to further mimic the pathological characteristics of human IDD. Functional experiments using gene editing (such as CRISPR/Cas9) and pharmacological interventions may be key in validating the role of ferroptosis-related genes, including GPX4, SLC7A1 and NCOA4, as well as evaluating the effects of targeted therapies.

To optimize mitochondria-targeted therapies, enhancing drug specificity remains a priority, as existing antioxidants and iron chelators often exert systemic effects that may disrupt normal cellular functions. The development of mitochondria-targeted drug delivery systems should improve selectivity and therapeutic efficiency while minimizing unintended side effects. Additionally, long-term safety assessment of iron chelators and GPX4 activators is important, as they may disrupt normal iron metabolism and antioxidant balance. Furthermore, a combination therapy strategy, integrating antioxidants with iron chelators or leveraging mitochondria-targeted nanocarriers with gene-editing technologies, could further enhance treatment outcomes.

Despite this, a number of key knowledge gaps remain unaddressed. Firstly, it remains unclear whether ferroptosis is an initiating event or a secondary consequence of IDD progression. Moreover, identifying the precise temporal dynamics of ferroptosis during the early vs. late stages of disease is key. Secondly, the threshold at which ferroptosis becomes irreversible remains unclear, making it difficult to determine the optimal therapeutic window for intervention. Thirdly, the current preclinical studies lack standardized outcome measures, meaning more systematic *in vivo* studies are required to validate the efficacy and safety of mitochondria-targeted ferroptosis modulators. Addressing these knowledge gaps remains important for accelerating clinical translation.

Given the heterogeneity of patients with IDD, a personalized treatment approach appears necessary. The expression levels of ferroptosis-related molecules such as GPX4, ACSL4 and SLC7A11 in intervertebral disc tissues or peripheral blood can serve as biomarkers to guide therapeutic decisions. Advances in artificial intelligence and big data analytics, particularly single-cell sequencing and machine learning, may enable the development of molecular classification systems for patients with IDD, identifying those who would benefit the most from mitochondrial-targeted interventions. Within this context, precision medicine strategies should be emphasized to tailor therapeutic regimens based on patient-specific molecular profiles, genetic backgrounds and disease stages. Such individualized approaches will enhance therapeutic efficacy and reduce the risk of adverse effects from systemic treatments.

Nanomedicine and gene therapy represent another frontier of IDD treatment, with potential advancements in mitochondria-targeted nanoparticle design, such as TAT-PEG-MitoQ, to enhance drug delivery efficiency while reducing systemic toxicity. Gene editing tools, such as CRISPR/Cas9 and RNA interference, enable the precise regulation of ferroptosis-related genes in intervertebral disc cells, achieving long-term suppression of ferroptosis. Moreover, bioengineered intervertebral disc scaffolds loaded with mitochondria-targeted drugs enable controlled local drug release during surgical implantation, thereby improving treatment precision.

Finally, although the majority of the current research on ferroptosis in IDD has focused on disease progression, early intervention may exhibit a greater impact. Investigating the role of ferroptosis-related molecules in the early stages of disc degeneration and developing non-invasive diagnostic tools, such as MRI combined with molecular imaging, could facilitate early detection. Preventive strategies, including lifestyle modifications such as exercise and antioxidant supplementation, may also help mitigate the risk of ferroptosis in intervertebral disc cells, reducing the likelihood of early IDD onset.

5. Conclusions

In summary, mitochondria-driven ferroptosis serves a pivotal role in the pathogenesis of IDD by disrupting the redox balance, promoting lipid peroxidation and impairing cellular antioxidant defense. As the central hub for iron metabolism and ROS production, mitochondria not only initiate ferroptotic

signaling but also serve as promising therapeutic targets. Increasing evidence indicates that targeting mitochondrial dysfunction using antioxidants, iron chelators, GPX4 activators and mitophagy modulators effectively attenuates ferroptosis and preserves disc cell viability. These findings underscore the importance of mitochondrial health in disc homeostasis and provide novel insights into precise strategies for treating age-related degenerative spinal diseases. However, future studies focusing on mitochondria-based interventions may pave the way for more effective and targeted therapies for IDD.

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Authors' contributions

YH and LL drafted the initial manuscript. XY, DQ and JS performed the literature review, collected relevant references, and assisted in figure conceptualization and design. YG conceived the present study, provided critical intellectual input, extensively revised the manuscript and supervised the entire project. All authors critically reviewed the manuscript, and all authors read and approved the final manuscript. Data authentication is not applicable.

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.

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