Review

Targeting ferroptosis to enhance the efficacy of mesenchymal stem cell-based treatments for intervertebral disc degeneration

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Abstract

Although mesenchymal stromal cell (MSC) implantation shows promise for repairing intervertebral disc (IVD) degeneration (IVDD), their limited retention within degenerative IVDs compromises therapeutic efficacy. The oxidative stress in the microenvironment of degenerated IVDs induces a surge in reactive oxygen species production within MSCs, disrupting the balance between oxidation and antioxidation, and ultimately inducing ferroptosis. Recent evidence has suggested that targeting ferroptosis in MSCs could enhance MSC retention, extend the survival of transplanted MSCs, and markedly delay the pathological progression of IVDD. By targeting ferroptosis, a novel approach emerges to boost the efficacy of MSC transplantation therapy for IVDD. In this review, current research on targeting ferroptosis in MSCs is discussed from various perspectives, including the targeting of specific genes and pathways, drug preconditioning, and hydrogel encapsulation. A detailed discussion on the effects of targeting ferroptosis in MSCs on the transplantation repair of degenerated IVDs is provided. Insights that could guide improvements in stem cell transplantation therapies are also offered. Significantly, this review presents specific ideas for our future foundational research. These insights outline promising avenues for future clinical translation and will contribute to developing and optimizing treatment strategies for MSC transplantation therapy, maximizing benefits for patients with lumbar IVDD.

Keywords: Mesenchymal stem cell (MSC); MSC transplantation; Oxidative stress; Ferroptosis; Intervertebral disc degeneration (IVDD)

1. Introduction

The intervertebral disc (IVD) is a well-hydrated, fibro-cartilaginous tissue comprising a central, proteoglycan-rich nucleus pulposus (NP), an outer annulus fibrosus, and a cartilage endplate [1]. It is critical for spinal mobility and stability [2]. Located within the inner disc, NP cells (NPCs) are primarily responsible for synthesizing and maintaining the extracellular matrix (ECM) [3]. The onset and acceleration of intervertebral disc degeneration (IVDD) are widely recognized to be initiated and accelerated by the loss of NPCs and the breakdown of the ECM [4]. IVDD can lead to lower back pain which, if worsened, could result in disability and deteriorate the quality of life for patients [5]. The condition involves mineralization and calcification, which reduce the IVD's nutrient supply and metabolism, thereby worsening IVDD [6-7]. Although certain perspectives have suggested that directly targeting NPCs to boost their vitality could delay IVDD [8-9], transplanted NPCs often fail to proliferate sufficiently to produce adequate cell quantities or secrete sufficient functional ECM components owing to immune responses and limited self-renewal capability [2, 5, 10]. Moreover, harvesting autologous NPCs could cause harm to the donor disc. Given these challenges, implanting NPC-based cells proves

ineffective in regenerating degenerated NP tissue. Mesenchymal stem cell (MSC)-based therapy has emerged as a new field in regenerative medicine [11-12]. MSCs, with their anti-inflammatory, regenerative, and immunomodulatory properties, are sourced from various tissues such as bone marrow, adipose tissue, the umbilical cord, and NP [1-2, 5]. Transplanted MSCs migrate to damaged IVD tissue, differentiate into chondrogenic cell types, enhance proteoglycan production, and exhibit NPC characteristics [10, 13]. Following differentiation into chondrogenic cell types, MSCs express high levels of chondrogenic markers such as type II collagen and aggrecan, key components of the ECM in the IVD [14-16]. Thus, MSC transplantation could mitigate the progression of IVDD by supplementing depleted NPCs and exerting paracrine effects on compromised or aging NPCs [17-18]. For instance, hypoxia-preconditioned MSCs maintain an NPC-like phenotype and curb IVD mineralization [19]. Furthermore, the secretion of cytokines and growth factors by MSCs is crucial for enhancing the viability of resident NPCs, upregulating NP marker gene expression, and stimulating local tissue cells [14, 17].

However, the harsh and complex microenvironment of degenerative intervertebral discs (IVDs) poses a severe challenge to the survival of transplanted MSCs, thereby limiting the effectiveness of MSC-based therapies [14-15, 20-25]. This adverse microenvironment is primarily due to excessive reactive oxygen species (ROS) and inflammation [21-22]. The combination of excess ROS and inflammation leads to oxidative damage, reduces the retention rate of engrafted MSCs, and aimpedes their osteogenic differentiation, thus diminishing the efficacy of IVDD treatment. Additionally, the pathological progression in degenerated IVDs may impair the essential functions of MSCs. Elevated ROS levels contribute to protein carbonylation, lipid peroxidation, and DNA damage in engrafted MSCs [15]. It is widely recognized that when pathological stimuli exceed their stress tolerance, MSCs undergo irreversible programmed cell death in such harsh environments [20, 23, 26-27]. Consequently, enhancing the survival rate of MSCs under oxidative stress (OS) is essential for improving the efficacy of MSC-based therapy for IVDD. The severe oxidative stress in degenerated IVDs can induce various forms of programmed cell death in transplanted MSCs, including apoptosis, pyroptosis, and necrosis [27-32]. These forms of regulated cell death are reportedly observed in MSCs under oxidative conditions [26-33]. However, studies have shown that targeted strategies have not effectively mitigated the excessive loss of engrafted MSCs [26-27, 33]. In MSC-based therapy for

liver injury repair, poor retention of MSCs in the OS environment of the liver significantly diminishes their therapeutic efficacy [27]. Notably, the addition of inhibitors of apoptosis, pyroptosis, and necrosis to MSCs under OS did not significantly delay the loss of stem cell retention. Similarly, our preliminary study on bone marrow mesenchymal stem cells (BMSCs) transplantation for repairing degenerated IVDs found that inhibiting apoptosis, pyroptosis, or necrosis did not significantly prevent BMSC death [26]. Thus, it is plausible that other forms of regulated cell death induced by ROS stress significantly contribute to the excessive loss of MSCs in degenerated IVDs. In recent years, substantial evidence has established that OS-induced ferroptosis plays a crucial role in the survival and retention of transplanted MSCs, posing a significant threat [26-27, 34-38].

Iron, a critical trace element, is indispensable for maintaining redox reactions and homeostasis in organisms [39-40]. Recent studies have shown that iron overload is an independent risk factor for human intervertebral disc degeneration (IVDD) and accelerates its pathological progression, indicating that transplanted MSCs are also exposed to this iron overload microenvironment [41-42]. An iron overload microenvironment induces oxidative stress (OS) damage to MSCs and disrupts iron homeostasis within the stem cells, affecting the balance between oxidation and antioxidant systems. Ferroptosis, characterized by iron-dependent accumulation of lipid peroxides to lethal levels, threatens the survival of transplanted MSCs and results in poor MSC retention [34, 36-37]. Our preliminary work has also confirmed that ferroptosis is responsible for the low MSC retention rate when engrafted into degenerative IVDs [26, 43]. Therefore, targeting ferroptosis in MSC-based therapy is recognized as a promising approach for IVDD, and developing inhibitors of ferroptosis in MSCs may enhance the efficacy of MSC transplantation in degenerative IVDs.

2. MSC-based therapy for IVDD

First, MSC-based therapy has shown promise in preclinical treatments for IVDD. Yuan *et al.* [44] implanted cultured autologous BMSCs into degenerative IVDs and noted improved spinal segmental stability in the goat IVD defect model. Similarly, a rat IVDD model induced by needle puncture demonstrated that intradiscal injection of MSCs effectively restored the structural integrity and tissue composition of the IVD, highlighting the potential of MSCs in treating IVDD [20]. Second, ongoing clinical trials on MSC-based therapy for IVDD have shown a moderate therapeutic effect [13, 45-53] (Table 1). Gomez-Ruiz *et al.* [13] reported on a

10-year follow-up of a prospective phase I/II clinical trial involving autologous MSC transplantation, noting improvements in radicular pain and low back pain (evaluated by the Visual Analog Scale (VAS) and the Oswestry Disability Index (ODI)). Lee *et al.* [53] evaluated the therapeutic effects of transplantation of adipose-derived stem cells (ADSCs) transplantation in patients with lumbar degenerative disc diseases, also reporting improvements in VAS pain scores, ODI scores, and radiological scores. Thus, these clinical trials support the efficacy of stem cell therapy for IVD regeneration. Current evidence suggests that stem cell transplantation therapy could be a viable option for partially restoring the biological characteristics of degenerated IVDs. However, ongoing concerns persist regarding the long-term safety and efficacy of MSC transplantation for repair treatments. Despite numerous benefits, potential long-term issues with MSC therapy include improper differentiation, immune suppression, and the risk of tumor formation [54-56]. Cultured human MSCs may undergo spontaneous transformation under *in vitro* culture conditions, which do not accurately reflect the characteristics of MSCs in the bone marrow microenvironment *in vivo* [57]. Consequently, their proliferation and differentiation capabilities may be affected, impacting the long-term efficacy of subsequent transplantation therapies. The primary concern remains that transplanted MSCs may undergo unwanted differentiation, potentially hindering anti-tumor immune responses and promoting new blood vessel formation, thereby facilitating tumor growth and metastasis [58-59]. Despite significant progress in MSC therapy over the past few decades, many challenges remain. Therefore, large-scale follow-up studies are essential to confirm the long-term efficacy and safety of stem cell therapy, including the evaluation of stem cell immunocompatibility, stability, heterogeneity, differentiation, and migratory capacity.

Nevertheless, some studies have proposed exosomes secreted by MSCs as a safer alternative to MSC-based therapy [60-61]. Stem cell-derived exosomes act as intercellular messengers and provide similar therapeutic effects to their parent MSCs, such as tissue regeneration, immunomodulation, and anti-inflammation [62-64]. To date, only a few clinical studies have reported on the safety and potential efficacy of MSC-derived exosomes (MSC-Exos), including their use in preclinical and clinical studies of IVDD [65-66]. Additionally, the rapid *in vivo* clearance of MSC-Exos and their relatively low extraction and purification efficiencies also limit their long-term therapeutic benefits [63]. Given the dominance of MSC-based therapy in current clinical trials, this review will focus on stem cell transplantation therapy and summarize the relevant literature on targeting MSC ferroptosis to optimize preclinical strategies for the effective treatment of IVDD.

3. Targeting ferroptosis for MSC-based therapy

Ferroptosis is a form of regulated cell death (RCD) distinct from apoptosis [43], triggered by the accumulation of free intracellular iron and the disruption of redox regulatory mechanisms [67-68]. It is characterized by chromatin condensation, disruption of membrane integrity, and morphologically evident by mitochondrial condensation, disappearance of mitochondrial cristae, and increased densities of the mitochondrial membrane [69-71].

Table 1. Clinical studies of MSC therapy for IVDD

| Location	Model	Cell type	Indication	N	Outcome
Spain [45] 2019 Feb	Autologous	BMSCs	Lumbar degenerative disc diseases	11	5-year follow-up; Improvement of low back pain and on radiograph
Sweden [46] 2019 Sep	Autologous	MSCs	Lumbar degenerative disc diseases	4	8-month or 28-month follow-up; MSCs have differentiated into chondrocyte-like cells
Spain [47] 2021 Feb	Allogenic	BMSCs	Lumbar degenerative disc diseases	12	3.5-year follow-up; Improvement of low back pain and on MRI
American [48] 2021 Feb	Allogenic	Mesenchymal precursor cells	Lumbar degenerative disc diseases	60	36-month follow-up; Improvement of low back pain
American [49] 2022 Mar	Autologous	BMSCs	Lumbar degenerative disc diseases	36	12-month follow-up; Improvement of low back pain and leg pain
China [50] 2022 Oct	Autologous	ADSCs	Lumbar degenerative disc diseases	75	24-month follow-up; The research is ongoing
Japan [51] 2023 Feb	Allogenic	BMSCs	Lumbar spinal canal stenosis	30	96-week follow-up; The research is ongoing
American [52] 2023 Mar	Allogenic	Umbilical cord stem cells	Lumbar degenerative disc diseases	33	26.88-month follow-up; Improvement of low back pain and leg pain
Spain [13] 2023 Apr	Autologous	BMSCs	Lumbar degenerative disc diseases	11	10-year follow-up; Improvement of low back pain and on radiograph
Republic of Korea [53] 2023 Nov	Autologous	ADSCs	Lumbar degenerative disc diseases	8	6-month follow-up; Improvement of low back pain and on MRI
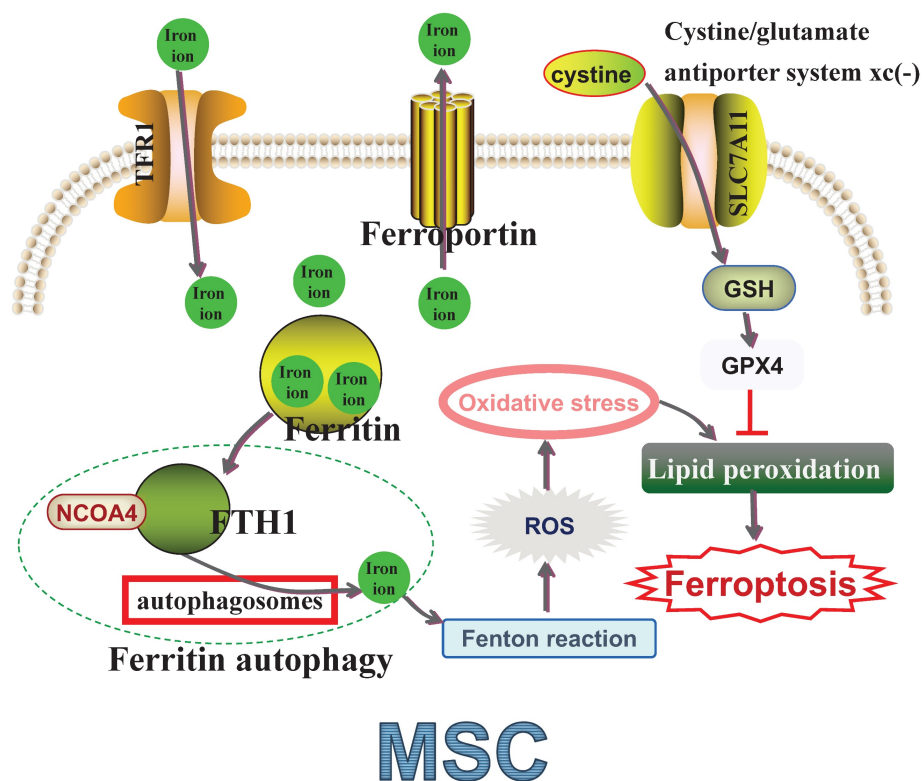
Figure 1. Molecular mechanisms of ferroptosis in MSCs. TFR1: Transferrin receptor protein 1; NCOA4: nuclear receptor coactivator 4; FTH1: ferritin heavy chain 1; ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11; GSH: Glutathione synthetase; GPX4: Glutathione peroxidase 4; MSC: Mesenchymal stem cell.

Transferrin receptor protein 1 (TFR1) is responsible for iron uptake, while ferroportin manages iron export, both essential for maintaining intracellular iron homeostasis [72-73]. Ferritin, comprising ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), also helps maintain iron homeostasis by storing iron to prevent toxicity [73-74]. Nuclear receptor coactivator 4 (NCOA4) mediates 'ferritin autophagy', where NCOA4 binds FTH1 and facilitates ferritin delivery to autophagosomes for lysosomal degradation, releasing sequestered iron [75]. This process leads to the generation of reactive oxygen species (ROS) via the iron-based Fenton reaction, and excessive ROS production, often referred to as oxidative stress (OS), accelerates lipid membrane oxidation and causes lipid bilayer membrane rupture, ultimately inducing ferroptosis [76-77]. Hence, lipid peroxidation is considered a crucial indicator of OS [78-79]. Solute carrier family 7 member 11 (SLC7A11) is vital in the cystine/glutamate antiporter system xc(-), which transports cystine intracellularly for glutathione synthetase (GSH) biosynthesis [80]. Glutathione peroxidase 4 (GPX4) uses antioxidant GSH as a cofactor to detoxify lipid peroxidation effectively and prevent ferroptosis [81-82] (Figure 1). Increasing evidence suggests that targeting ferroptosis could significantly enhance MSC-based therapies [26-27,

35-36, 83-85] (Table 2). A deeper understanding of ferroptosis mechanisms in MSCs is crucial for developing strategies to improve their functionality and survival, ultimately optimizing cell-based therapy outcomes.

3.1 Inhibiting MSC ferroptosis via the iron metabolism pathways

Ferroptosis is implicated in the OS-induced loss of transplanted MSCs under harsh degenerative conditions in intervertebral discs (IVDs), with this involvement closely regulated by intracellular iron metabolism [34-36]. Iron ions disrupt the redox balance when accumulated excessively within cells and tissues, catalyzing ROS generation and promoting ferroptosis [39-40]. In response to the initiation mechanisms of ferroptosis, researchers have developed strategies encompassing iron uptake, storage, and transport to preserve cellular iron homeostasis and prevent MSC ferroptosis. In an OS injury *in vitro* model, Jing *et al.* [37] demonstrated significant activation of the ferroptosis pathway through transcriptomic analysis and phenotypic experiments. Notably, while NCOA4 expression levels increased and ferritin levels decreased, their binding rate was found to be elevated, suggesting that NCOA4-mediated ferritin degradation contributes to iron accumulation and promotes ferroptosis.

Table 2. Targeting ferroptosis for MSC-based therapy

Authors Year	Cell type	Intervention strategy	Detection	Animal model	Results of *in vivo* experiments
Hu *et al.* [27] 2023 May	ADSCs	Pretreat MSCs with ferroptosis inhibitors and upregulate intracellular GPX4 transcription	Increase MSC survival rate	The rats' injured liver milieu	Improve MSC therapeutic efficacy in the injured liver
Huang *et al.* [83] 2023 Jul	OM-MSCs	Pretreat MSCs with antioxidant	Enhance the anti-oxidative activity of MSCs	The rats' intracerebral Hemorrhage	Show better neuroprotective effects
Xu *et al.* [26] 2023 Nov	BMSCs	Pretreat BMSCs with ferroptosis inhibitors and overexpress Prominin-2	Increase BMSC survival rate	The rats' IVD degeneration	Improve MSC therapeutic efficacy in the degenerative IVD
Xu *et al.* [84] 2024 Mar	BMSCs	Pretreat BMSCs with ferroptosis inhibitor and antioxidant	Increase BMSC survival rate	The murine type 2 diabetic osteoporosis model	Revitalize bone density, curtail ROS abundance, and amplify GPX4 presence in the distal femur
Huang *et al.* [36] 2024 May	BMSCs	Developed bone graft substitute material to load MSC	Increase BMSC survival rate	The osteoporotic bone defect rat model	Alleviate the inflammatory environment and promote bone regeneration in osteoporotic bone defect
Huang *et al.* [85] 2024 July	BMSCs	Pretreat BMSCs with antioxidant	Increase BMSC survival rate	The osteoporosis rat model	Reduce the inflammation levels and promote bone regeneration
Yuan *et al.* [35] 2024 Aug	BMSCs	Design an anti-ferroptosis 3D-printed hydrogel scaffold loaded with BMSCs	Increase BMSC survival rate	The rat model of infected bone defects	Capable of eradicating pathogens and promoting bone regeneration

Olfactory mucosa-derived mesenchymal stem cells (OM-MSCs)

In a rat model of smoking-related osteoporosis, inhibitors of ferritinophagy or ferroptosis were shown to suppress BMSC ferroptosis, enhance cell viability, and thereby reduce BMSC dysfunction and reverse bone damage [37]. Similarly, in dental pulp stem cells, NCOA4-mediated ferritinophagy has been linked to ferroptosis, indicated by cytosolic iron overload, elevated ROS levels, and increased NCOA4 expression [86]. Knocking down NCOA4 was observed to reduce ferritin degradation. Additionally, another study targeting the iron storage pathway showed potential in inhibiting MSC ferroptosis and enhancing MSC survival rates. In an *in vitro* model of BMSC ferroptosis induced by erastin, overexpression of FTH1/FTL was found to reduce ROS levels and abrogate lipid peroxidation, markedly improving BMSC survival [87]. This finding indicates that targeting the FTH1/FTL pathway could enhance resistance to ferroptosis and improve engrafted BMSC survival. Moreover, other studies have employed pre-treatment of stem cells with deferoxamine (DFO). DFO, known as a ferroptosis inhibitor, chelates cytoplasmic iron ions, preventing their interaction with peroxides and thus inhibiting the formation of harmful radicals [88]. Hopfner *et al.* [89] found that DFO-preconditioned ADSCs significantly enhanced regenerative capabilities for wound healing in diabetes while reducing intracellular ROS levels, offering a new approach to improve diabetic ADSC functionality. Khoshlahni *et al.* [90] also reported that DFO-preconditioned BMSCs resisted OS damage in stressful environments. Through iron depletion by DFO, BMSCs showed improved survival rates under OS conditions, facilitating subsequent BMSC-based transplantation therapies. These findings underscore the importance of modulating the iron metabolism pathway in maintaining iron homeostasis and inhibiting MSC ferroptosis. We were also acutely aware of the critical role of targeting MSC ferroptosis in clinical MSC treatments.

Therefore, we hypothesized that regulating iron metabolism in MSCs influences the efficiency of stem cell transplantation in repairing degenerated IVDs. Free ferrous iron (Fe^{2+}) acts as a potent oxidative factor, generating unstable radicals via the Fenton reaction [76, 91]. Coenzyme Q10 (Co-Q10) has been reported to reduce the perferryl radical, chelate iron, and thus prevent iron overload [92-93]. Lazourgui *et al.* [92] confirmed that Co-Q10 helps regulate iron levels, improving cellular antioxidant status and alleviating oxidative stress (OS) during insulin resistance. Peng *et al.* [94] observed that intracellular iron ion levels, when overloaded, corresponded with a continuous decrease in Co-Q10, exacerbating cellular OS, further suggesting Co-Q10's efficacy as an iron chelating agent. In a rat needle puncture IVDD model, Sun *et al.* [15] administered Co-Q10 preconditioned BMSCs into degenerative IVDs, noting improved viability, restored mitochondrial structure and function, and increased production of ECM components. Thus, Co-Q10 protects against OS-induced BMSC ferroptosis, providing a protective role in cellular survival and differentiation, enhancing the efficacy of BMSC transplantation therapy, and may represent a viable treatment option for IVDD. Similarly, adding ferritin, crucial for iron homeostasis and detoxification, has shown cytoprotective effects on BMSCs and promoted their differentiation into osteoblasts, essential for bone tissue health [95-96]. The protective mechanism likely involves enhancing the iron ion storage pathway, effectively countering OS-induced BMSC ferroptosis. However, direct *in vivo* research evidence is currently lacking regarding the regulation of intracellular iron levels in stem cells and its impact on the efficiency of repairing degenerated IVDs. More importantly, future studies in both

cellular and rat IVDD models will aim to demonstrate that interventions in the iron metabolism pathway can desensitize transplanted MSCs to ferroptosis, further validating the regulation of ferroptosis by imbalanced iron homeostasis. Targeting iron-chelating drugs, iron metabolism, or redox-related proteins may offer a new strategy to enhance the efficiency of MSC-based therapy in IVDD.

3.2 Inhibiting MSC ferroptosis via the antioxidant pathways

It is widely acknowledged that oxidative stress (OS) is a primary pathogenic factor in the numerous pathophysiological processes of IVDD [8, 97-102]. Studies have shown that OS accelerates IVDD, and the OS microenvironment within degenerated discs jeopardizes the survival of transplanted MSCs [23, 97, 99]. OS is characterized by an imbalance between ROS production and scavenging [8, 98]. Iron overload, overwhelming the antioxidant defense system, initiates the classic ferroptosis pathway, closely linking ferroptosis to OS [81, 103-107]. Park *et al.* [108] reported that excessive ROS production activates OS-induced lipid peroxidation, thereby exacerbating ferroptosis-dependent cytotoxicity in human astrocytes. Sánchez-Ortega *et al.* [107] observed that excessive ROS production also induces ferroptosis in lung squamous cell carcinoma (LUSC), suggesting that targeting OS-induced LUSC ferroptosis could present a new therapeutic approach. Increasing evidence indicates that molecular pathways activated by OS intersect with those of ferroptosis in transplanted MSCs, sharing several molecular targets such as accumulation of lipid peroxidation products, and low levels of GSH and GPX4 [103, 105-106]. Persistent and excessive OS in the transplantation site triggers ferroptosis in MSCs due to elevated ROS levels, significantly reducing MSC retention after transplantation. Accordingly, targeting ferroptosis could markedly improve the effectiveness of stem cell transplantation therapy by reducing intracellular OS levels or enhancing antioxidant defenses. For example, in an erastin-treated BMSC model, the antioxidant quercetin demonstrated effective anti-ferroptosis properties through its antioxidative functions, protecting BMSCs from erastin-induced ferroptosis [109].

Tert-butyl hydroperoxide (TBHP) has been shown to induce cellular oxidative injury, and we used TBHP to simulate OS conditions in an *in vitro* model [26, 110-111]. TBHP treatment significantly increased ferroptosis indicators (Fe^{2+} aggregation, increased ROS levels, excessive lipid peroxidation) and altered levels of ferroptosis-related proteins (Long-chain-fatty-acid--CoA ligase 4 (ACSL4),

Prostaglandin G/H synthase 2 (PTGS2), GPX4, and Ferritin) [26]. Conversely, ROS scavengers and ferroptosis inhibitors (ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1), both potent lipid peroxidation inhibitors) suppressed the increase in OS-induced ferroptosis indicators and blocked the expression of ferroptosis-related proteins [26]. Therefore, previous studies and our preliminary findings collectively confirm that OS can activate ferroptosis, and suggest that employing antioxidants or activating antioxidant pathways could mitigate OS-induced MSC ferroptosis.

3.2.1 Activating KEAP1/Nrf2/GPX4 signaling pathway

As a primary defender against ferroptosis, upregulation of GPX4 levels can render MSCs resistant to ferroptosis. Hu *et al.* [27] identified ferroptosis as the cause of poor MSC retention rates shortly after exposure to an OS microenvironment or following engraftment into an injured liver setting. Strategies to suppress MSC ferroptosis include pretreating MSCs with Fer-1 and Lip-1 and enhancing intracellular GPX4 transcription [27]. These approaches have effectively increased MSC retention under ROS stress and improved the liver-protective outcomes post-implantation. Conversely, BMSCs influenced by neuroblastoma displayed increased sensitivity to ferroptosis, due to GPX4 downregulation [112]. Similarly, pretreatment of BMSCs with poliumoside, which boosts intracellular GPX4 expression levels, effectively countered OS-induced BMSC ferroptosis, as indicated by reduced mitochondrial ROS and malondialdehyde (MDA) levels, and increased GPX4 protein levels [84]. In contrast, disrupting GPX4 expression through lentiviral transfection diminished the anti-ferroptosis effects.

The nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor located in the mammalian nucleus, regulates the stress-induced activation of cytoprotective genes, including GPX4 [106, 113-114]. Bhat *et al.* [115] mechanistically demonstrated that enhancing Nrf2 transcriptional activity could prevent lipid peroxidation and reduce suppression of GPX4 expression during ferroptosis. Furthermore, activating the Nrf2-dependent GPX4 antioxidant pathway in doxorubicin-stimulated H9c2 cardiomyocytes markedly alleviated ferroptosis and mitochondrial damage [113]. In addition, Nrf2 nuclear translocation is negatively regulated by Kelch-like ECH-associated protein 1 (KEAP1), and the KEAP1/Nrf2 complex can modulate intracellular OS levels [107, 116]. In cardiomyocytes, reducing KEAP1 levels promoted the nuclear translocation of Nrf2 and transcription of SLC7A11 and GPX4, thus offering

protection against doxorubicin-induced ferroptosis [113]. Koppula *et al.* [117] also confirmed that KEAP1transcriptionally regulates Nrf2 levels, and the KEAP1/Nrf2 pathway regulates ferroptosis via a GPX4-independent mechanism. In an erastin-induced BMSC ferroptosis *in vitro* model, the import of excess iron via TFR1 and minimal export by ferroportin, alongside a dysregulated KEAP1/Nrf2/GPX4 axis and low SLC7A11 levels, collectively exacerbated BMSC ferroptosis [118]. Deactivating the KEAP1/Nrf2/GPX4 pathway reduced BMSC ferroptosis, as indicated by decreased KEAP1 protein levels and increased Nrf2 and GPX4 protein levels. The cystathionine γ-lyase (CSE)/hydrogen sulfide (H_2S) pathway is vital for redox homeostasis, including ROS scavenging, antioxidant activation, and cellular protection against OS [119-120]. The CSE/H_2S pathway is crucial in modulating ferroptosis [121-122]. Regulation of this pathway in MSCs has been shown to protect against ferroptosis, improving low retention and engraftment rates post-MSC delivery. Notably, enhancing the CSE/H_2S pathway induced Keap1 S-sulfhydration, activating Nrf2 and inhibiting ferroptosis, as evidenced by reduced iron levels and ROS production, and increased GPX4 protein levels [122]. Thus, the CSE/H_2S pathway exerts anti-ferroptosis effects by mediating the KEAP1/Nrf2/GPX4 in MSCs, ultimately enhancing MSC survival post-delivery into mice [122].

Targeting ferroptosis has proven effective in enhancing the therapeutic efficacy of endogenous MSCs for treating IVDD. Increasing GPX4 expression in NP-derived MSCs (NPSCs) inhibited NPSC ferroptosis and promoted their proliferation, revealing significant therapeutic potential for endogenous MSCs in IVDD treatment [123]. Additionally, activating Nrf2 in ADSCs effectively alleviated stem cell dysfunction and the cell death rate in degenerative IVDs and stimulated ADSC differentiation into an NPC-like phenotype [124]. This suggests that targeting ferroptosis could enhance ADSC transplantation therapy for IVDD and is promising for improving stem cell transplantation efficacy. Although direct evidence is lacking for modulating the KEAP1/Nrf2/GPX4 pathway to inhibit MSC ferroptosis in treating IVDD, existing evidence supports enhancing the KEAP1/Nrf2/GPX4 axis in MSCs for use in preclinical and clinical trials of MSC-based therapies for IVDD.

3.2.2 Preconditioning of MSCs with antioxidants

In addition to targeting antioxidant pathways within MSCs, recent studies have utilized direct pre-treatment with antioxidants to protect MSCs from ferroptosis. Quercetin was shown to inhibit erastin-induced BMSC ferroptosis through antioxidant pathways, potentially converting into its metabolite quercetin diels-alder anti-dimer (QDAD) during this process [109]. Both quercetin and QDAD exhibit strong antioxidant and anti-ferroptosis properties. Ebselen, an antioxidant with glutathione peroxidase-like activity, was found to prevent BMSC ferroptosis and reduce its inhibitory effect on osteogenic differentiation of BMSCs [125]. Curcumin, known for its potent antioxidant properties, enhanced the antioxidant capacity of MSCs, as indicated by increased survival rates [83]. Curcumin preconditioning also reduced MSC death in the hostile brain microenvironment and improved MSC therapeutic efficacy for treating intracerebral hemorrhage. Curcumin-preconditioned MSCs exhibited neuroprotective effects in an intracerebral hemorrhage model, characterized by reduced cellular injury and lower ROS levels in neuronal cells [83]. Geraniin showed ferroptosis-inhibitory effects in BMSCs induced by erastin, involving inhibition of lipid peroxidation, iron chelation, and antioxidant actions [126]. Picein, possessing antioxidant properties, ameliorated erastin-induced oxidative stress and enhanced the proliferation and migration of BMSCs [85]. The protective mechanism of Picein involves activating the Nrf2/Heme oxygenase 1 (HO-1)/GPX4 pathway. HO-1, regulated by Nrf2 and associated with antioxidant proteins, helps counter oxidative stress by facilitating Nrf2 nuclear translocation to bind the antioxidant response element of the HMOX1 gene [127-131]. Activation of the Nrf2/HO-1 pathway increases GPX4 levels to counter OS [132-133], highlighting the importance of the Nrf2/HO-1/GPX4 axis in countering BMSC ferroptosis. This class of antioxidants similarly exerts ferroptosis-inhibiting effects by activating intracellular antioxidant pathways. However, Yuan *et al.* [35] presented a contrasting view, noting an upregulation of HO-1 in macrophages that increased intracellular Fe 2+ and promoted ferroptosis, indicating that the anti-ferroptosis effects of Picein in BMSCs require further exploration.

Growing evidence has shown that antioxidant preconditioning effectively enhances MSC proliferation, migration, and yields better therapeutic outcomes for repairing degenerated intervertebral discs (IVDs). Icariin, a flavonoid with anti-ferroptotic activity, mitigates oxidative stress damage and promotes BMSC osteogenesis [134]. Icariin treatment has been shown to improve the therapeutic efficacy of stem cell transplantation for repairing degenerated IVDs by alleviating pathological trends of IVDD and increasing collagen II and aggrecan levels in IVD tissues [134]. Neochlorogenic acids, possessing

antioxidant and anti-ferroptosis properties, potentially act through the Nrf2/HO-1 pathway [135]. These acids have been shown to reduce hydrogen peroxide (H_2O_2)-induced ROS production in BMSCs, thereby inhibiting ferroptosis. *In vivo*, BMSCs preconditioned with neochlorogenic acids exhibited enhanced protective effects for IVDD compared to other model groups, attributed to improved BMSC stability during the repair process [135]. Similarly, co-encapsulating BMSCs with salvianolic acid B, a potent antioxidant, in 1% hyaluronic acid methacrylate hydrogel significantly reduced cell death rates compared to the BMSCs + hydrogel group [136]. It was observed that salvianolic acid B efficiently reduced ferroptotic damage caused by H_2O_2 to BMSCs and increased cell survival percentages *in vitro*. In a rat model, pretreatment of BMSCs with salvianolic acid B delayed disc degeneration progression compared to stem cell therapy alone, as evidenced by histological and immunohistochemical analyses [136]. Thus, encapsulating BMSCs with salvianolic acid B presents potential research value for regenerative disc tissue repair. In summary, these findings collectively support the use of MSC transplantation with antioxidants as a viable approach for advancing MSC-based tissue engineering for IVDD repair, potentially through ferroptosis inhibition. This also offers a new perspective on suppressing MSC ferroptosis to increase the retention of grafted MSCs and enhance the efficiency of stem cell transplantation repair.

3.3 Inhibiting MSC ferroptosis by targeting specific molecular and pathway

3.3.1 HIF-1α

Hypoxia-inducible factor 1-alpha (HIF-1α) was identified as a key ferroptosis gene by analyzing differentially expressed genes from OS-induced BMSCs compared to controls, based on the Gene Expression Omnibus databases and a ferroptosis dataset [137-138]. The pivotal role of HIF-1α in regulating ferroptosis was further validated in an animal model, suggesting that targeting HIF-1α to suppress MSC ferroptosis might be a novel approach for treating IVDD [137]. Previous studies have shown that a hypoxic microenvironment stabilizes cellular HIF-1α and enhances ferroptosis resistance in a HIF-1α-dependent manner, likely through increased HIF-1α expression and its interaction with hypoxia-inducible factor 1 beta to form the HIF-1 complex [139-140]. Activation of the HIF-1/hypoxic response elements (HRE) signaling pathway then promotes the binding of HRE to the solute carrier

family 2, facilitated glucose transporter member 12 (SLC2A12) promoter, elevating SLC2A12 expression, modulating glutathione metabolism, and conferring resistance to ferroptosis [140]. Transplanting ADSCs into degenerative IVDs demonstrates the therapeutic potential of MSC-based therapy for IVDD, although the physiological hypoxic state and OS contribute to low retention of transplanted ADSCs [141-142]. Hypoxia-preconditioned ADSCs have shown increased cell proliferation and migration capabilities and promoted differentiation into NPC-like cells via HIF-1α, whereas inhibiting HIF-1α produced the opposite effect [143]. He *et al.* [144] observed significant decreases in HIF-1α levels and NPSC counts in degenerative rat and human IVDs. Similarly, hypoxia-preconditioned NPSCs demonstrated enhanced resistance to cell death by activating HIF-1α, involving HMOX1 and solute carrier family 2, facilitated glucose transporter member 1 [144]. Overexpressing HIF-1α in NPSCs also resulted in higher survival rates post-transplantation into degenerative discs *in vivo* [144]. These findings collectively support the anti-ferroptosis effect of HIF-1α under the severe hypoxic and OS conditions typical of degenerative discs, suggesting HIF-1α's crucial role in enhancing the therapeutic efficacy of MSCs for IVDD treatment. However, other research presents a contrary view, indicating that inhibition of HIF-1α enhanced the anti-ferroptosis effects of Fer-1 in chondrocytes [145], and downregulation of HIF-1α reduced ferroptosis and improved gastric and minor intestinal mucosal injury in an animal model [138, 146]. Therefore, the approach of targeting HIF-1α to suppress MSC ferroptosis remains controversial, and extensive foundational research on MSC-based therapy for IVDD is essential to elucidate this strategy.

3.3.2 SIRT1

NAD-dependent histone deacetylase sirtuin-1 (SIRT1) is a nicotinamide adenine dinucleotide-dependent enzyme that regulates critical metabolic proteins during oxidative stress (OS) [147-148]. The SIRT1/Nrf2 signaling pathway provides anti-OS effects and can prevent ferroptosis, restoring redox balance. Sanz-Alcázar *et al.* [149] reported that frataxin deficiency in dorsal root ganglion neurons disrupts iron homeostasis, reduces SIRT1 expression, diminishes Nrf2 activation, and impairs the cellular response to OS, ultimately leading to ferroptosis. Conversely, increased SIRT1 levels activate the liver kinase B1 homolog/5′-AMP-activated protein kinase pathway, which in turn activates Nrf2, playing a vital role in the antioxidant response [149]. Activation of the Sirt1/Nrf2/GPX4 pathway also protects BMSCs

from erastin-induced ferroptosis and enhances cell viability, thereby improving the effectiveness of BMSC-based therapy [36]. Interestingly, in fundamental research on MSC-based therapy for IVDD, activating SIRT1 reduced ROS accumulation, decreased expression of senescence-related proteins, and increased the proliferation ability of NPSCs [150]. SIRT1 activation also confirmed the efficacy of NPSCs in alleviating IVDD in a puncture-induced IVDD rat model based on *in vivo* assessments [150]. However, inhibiting SIRT1 partially reversed the therapeutic effects of NPSCs on degenerated IVDs [150-151]. Further research showed that overexpressing SIRT1 in MSCs effectively mitigated IVDD, as evidenced by the recovery of IVD height and volume and increased mRNA and protein levels of type II collagen and aggrecan, which inhibit the NF-kappaB p65 inflammatory pathway [152]. Additionally, activating the SIRT1/PPAR-γ co-activator 1α pathway, closely associated with mitochondrial function and antioxidant activities [147, 153], alleviated OS-induced mitochondrial dysfunctions, including reduced mitochondrial ROS production, increased mitochondrial membrane potentials, and enhanced survival rates of transplanted NPSCs, thus enhancing the therapeutic potential of MSCs for IVDD [154]. Overexpression of SIRT1 could mitigate some limitations in MSC survival and adaptation under the severe conditions of disc degeneration, potentially due to SIRT1-mediated anti-ferroptosis effects in MSCs. Collectively, these findings indicate that targeting SIRT1 holds promise for treating IVDD by improving the therapeutic efficacy of MSC-based therapy.

3.3.3 PI3K/AKT pathway

ROS accumulation in degenerative IVDs can trigger ferroptosis in MSCs and reduce the survival rate of engrafted MSCs. Suppressing MSC ferroptosis could potentially enhance their survival in the oxidative stress (OS) microenvironment of degenerative IVDs. Further mechanistic studies have shown that the phosphatidylinositol 3-kinase (PI3K)/threonine-protein kinase (AKT) signaling pathway can modulate ferroptosis, offering a novel approach for stem cell therapy in treating IVDD [155-156]. The PI3K/AKT signaling cascades are activated by hormones, growth factors, and other extracellular stimuli to regulate essential cellular functions such as cell proliferation, regulated cell death (RCD), and cell survival [157-159]. For example, activation of the PI3K/AKT pathway provides neuroprotection by phosphorylating Nrf2, which then enhances FTH1 transcription to store excess iron ions and prevent iron toxicity from excessive Fe^{2+}

accumulation [160]. Furthermore, activation of the PI3K/AKT pathway has been shown to increase optic atrophy 1 expression, a member of the mitochondrial fusion protein family, promoting mitochondrial fusion and preventing mitochondrial structural and functional abnormalities, ultimately reducing ferroptosis [155, 161-162]. The PI3K/AKT pathway, associated with resistance mechanisms and cell survival, can be activated to desensitize cells to ferroptosis, offering an alternative approach to stem cell therapy for IVDD. In an OS microenvironment *in vitro* model of BMSCs, the PI3K/AKT signaling pathway was found to be involved in OS-induced BMSC ferroptosis [163]. The upregulation of PI3K and AKT phosphorylation increased anti-oxidative gene expression and reduced intracellular ROS levels, thereby inhibiting BMSC ferroptosis and enhancing cell viability [163]. Interestingly, activation of the PI3K/AKT signaling pathway also improved the antioxidant defense of BMSCs under the OS microenvironment and enhanced their osteogenic differentiation capacity, as demonstrated by increased mRNA transcripts of osteogenic markers [164]. Activating the PI3K/AKT pathway has improved anti-OS processes in MSCs by suppressing ferroptosis, providing a theoretical foundation for enhancing stem cell-based therapy for treating IVDD by increasing the survival of transplanted MSCs in the OS microenvironment.

NPSCs can differentiate into NPCs and exert paracrine effects that maintain the quantity and quality of IVD cells, thus enhancing stem cell-based therapy for intervertebral disc regeneration [144, 165]. Activation of the PI3K/AKT pathway promotes NPSC proliferation and adaptation to the niche of degenerated IVDs, advancing the endogenous repair process [166-167]. In an *in vitro* oxidative stress (OS) microenvironment simulated by H2O2, activation of the PI3K/AKT pathway alleviated mitochondrial dysfunction, including changes in mitochondrial ultrastructure and mitochondrial ROS production, thereby reducing ROS levels and increasing NPSC viability [166]. Conversely, pretreatment of NPSCs with a PI3K inhibitor diminished these protective effects and exacerbated NPSC ferroptosis. In rat models of mechanical loading stress-induced IVDD, excessive mechanical loading inactivated the PI3K/AKT pathway in human NPSCs, resulting in intracellular ROS accumulation, mitochondrial dysfunction, and decreased cell viability [168]. This validated the role of the PI3K/AKT signaling pathway in regulating and inhibiting ferroptosis. Activation of the PI3K/AKT pathway reversed these effects and efficiently suppressed ferroptosis in NPSCs. Significantly, activation of the PI3K/AKT pathway

alleviated cell death in human NPSCs *in vivo* models and substantially mitigated IVDD [168]. The structure of the IVD was restored, the amount of extracellular matrix (ECM) increased, and cell numbers were augmented. Furthermore, in a rat IVDD model induced by needle puncture, activation of the PI3K/AKT pathway reduced ROS generation and maintained mitochondrial homeostasis in NPSCs, while inhibitors of this pathway attenuated these protective effects [165]. The PI3K/AKT pathway alleviated excessive cell death of NPSCs induced by OS in the microenvironment of degenerative IVDs, as evidenced by X-ray, magnetic resonance imaging (MRI), and histological analyses [165]. Thus, the PI3K/AKT signaling pathway emerges as a promising candidate for treating IVDD by increasing the survival rate of NPSCs. Therefore, suppressing MSC ferroptosis via the PI3K/AKT pathway could be adopted for IVDD treatment, establishing a specific therapeutic strategy to preserve MSC viability and potentially enhance IVD regeneration.

3.3.4 GDFs

Growth differentiation factors (GDFs) modulate cellular processes such as proliferation, differentiation, and cell death [169-170]. Previous research has indicated that GDFs may mediate oxidative stress (OS) responses and be involved in ferroptosis [171-172]. For example, in a mouse model of sepsis-induced cardiomyopathy, GDF-15 provided protection to cardiomyocytes by inhibiting OS and suppressing ferroptosis, thereby reducing myocardial injury [173]. Further research showed that GDF-15 promotes the transcription of GPX4, reducing lipid peroxidation in cardiomyocytes. In another model, GDF-15 knockout in ferroptosis induced by erastin led to decreased intracellular glutathione (GSH) levels and accelerated ferroptosis progression [174]. This study also demonstrated that GDF-15 enhances the expression of SLC7A11, explaining its role in increasing intracellular GSH and GPX4 levels. In a sepsis model induced by cecal ligation and puncture in mice, overexpression of GDF-11 inhibited ferroptosis by upregulating SIRT1, thereby reducing lung tissue damage and inflammation, and preserving alveolar barrier integrity, thus presenting a promising molecular target for acute lung injury treatment [175]. These findings underscore the role of GDFs in maintaining redox balance and regulating ferroptosis in BMSCs.

GDF-5, part of the transforming growth factor-beta superfamily, enhances chondrogenic differentiation [176-177]. In an oxidative stress environment simulating IVDD, adding GDF-5 reduced OS-induced cell death in NPSCs and promoted their chondroid differentiation. This effect is possibly mediated by the RhoA/Rho-associated protein kinase (ROCK) signaling pathway [176]. In models of myocardial injury and subarachnoid hemorrhage in mice and rats, modulation of the RhoA/ROCK pathway has been shown to influence cardiomyocyte and neuronal ferroptosis, respectively [178-179]. This suggests that GDF-5 may enhance MSC survival by suppressing ferroptosis through the RhoA/ROCK pathway, indicating potential for gene-targeted NPSCs. Additionally, in a rat tail IVDD model, GDF-5-preconditioned BMSCs significantly improved NP regeneration and outperformed the sole BMSC treatment [180]. Okoro *et al.* also reported that GDF-5 enhanced differentiation of BMSCs into NP-like cells, supporting the NPC phenotype [181]. A series of experiments suggests that GDF-5 not only inhibits ferroptosis in engrafted MSCs but also effectively induces their differentiation into NP-like cells both *in vivo* and *in vitro*, offering a feasible approach for NP regeneration and IVDD repair. In summary, targeting MSC ferroptosis using GDF-5 as a gene target has shown great potential and warrants further validation in additional *in vivo* IVDD animal models.

3.3.5 Activating Prominin-2 exerts anti-ferroptosis effects

As a 100-kDa glycoprotein, Prominin-2 comprises five transmembrane domains and two glycosylated extracellular loops [182-183]. It is a member of cholesterol-binding proteins and is associated with plasma membrane protrusions [184]. PROM2 (encoding the prominin 2) mRNA is expressed in various normal human tissues [185]. Recently, Prominin-2 has been recognized as a ferroptosis inhibitor that can transport ferritin out of the cell, thereby reducing intracellular iron ion accumulation and preventing ferroptosis [182, 186-188]. Adamiec-Organisciok *et al.* [187] confirmed that PROM2 is a ferro-resistance marker, as evidenced by increased PROM2 mRNA levels in resistant cell lines, and decreased levels in sensitive cell lines. Paris *et al.* [186] discovered that overexpression of Prominin-2 is associated with ferroptosis resistance by reducing cytoplasmic Fe^{2+} accumulation, thus reducing lipid peroxidation and ferroptosis. Brown *et al.* [189] reported that Prominin-2 opposes ferroptotic cell death. They found that 4-hydroxynonenal, a lipid peroxidation by-product and a known ferroptosis biomarker, activates heat shock factor protein 1 (HSF1), which induces Prominin-2 expression through HSF1-dependent transcription of PROM2. Additionally, activating transcription factor 1 enhances ferroptosis resistance by upregulating

N6-adenosine-methyltransferase subunit transcription, thereby stabilizing PROM2 mRNA [184]. Increased Prominin-2 reduces erastin-induced ferroptosis and improves cell viability and proliferation rate [184]. These findings demonstrate that Prominin-2-activated iron export contributes to ferroptosis resistance and has significant implications for enhancing MSC-based therapy for IVDD.

Based on this research, we proposed that targeting the mechanism inducing Prominin-2 expression could expand the options to enhance MSC ferroptosis resistance. Activating Prominin-2 expression could be a viable approach for improving the therapeutic efficiency of MSC-based therapies for IVDD. Our preliminary work supports that ferroptosis is a major factor in the early, rapid, and extensive depletion of BMSCs under *in vitro* ROS stress, consistent with the aforementioned findings [26]. Additionally, we transfected BMSCs with an overexpression lentivirus to generate Prominin-2-overexpressed BMSCs. We also confirmed that activating Prominin-2 expression significantly mitigates the loss of BMSCs during the initial stage after implantation into degenerative IVDs. Enhanced BMSC retention slows the depletion of engrafted BMSCs and effectively boosts their therapeutic efficacy in the harsh environment of degenerative IVDs. Although our previous findings are impactful for MSC-based therapy, targeted Prominin-2 activators are not yet available.

In MSC-based therapy for IVDD, targeting Prominin-2-mediated ferroptosis defense offers a potential intervention. Our future work will delve into the involvement and underlying mechanisms of Prominin-2 in ferroptosis and reveal its additional roles. For instance, our preliminary work discovered that Prominin-2 not only transports iron ions beyond the cell but also physically interacts with BTB and CNC homolog 1 (BACH1) and facilitates its degradation [26]. BACH1, a transcription factor, represses multiple antioxidant genes (including Nrf2) and thus disrupts cellular redox homeostasis [190-192]. Increasing evidence indicates that BACH1 enhances ferroptosis by inhibiting the transcription of various OS-induced protective genes [193-195]. Regarding its mechanism, Prominin-2 exerts a dual role in OS-induced ferroptosis through the iron metabolism pathway and the Prominin-2/BACH1 antioxidant pathway (Figure 2). Investigating the upstream and downstream nodes of this pathway could clarify the function of Prominin-2 and provide new insights for Prominin-2-activating drug discovery. Moreover, evidence has shown that hydrogels could boost MSC survival after engraftment in the adverse OS microenvironment [196-197]. In this context, we also plan to explore the potential of Prominin-2 activator-delivering hydrogels to enhance MSC resistance to OS. Activating Prominin-2 could prevent ferroptotic cell death of transplanted MSCs and improve the therapeutic effect of MSCs for IVDD. In summary, a deeper exploration of the anti-ferroptosis mechanism based on Prominin-2 is highly promising.
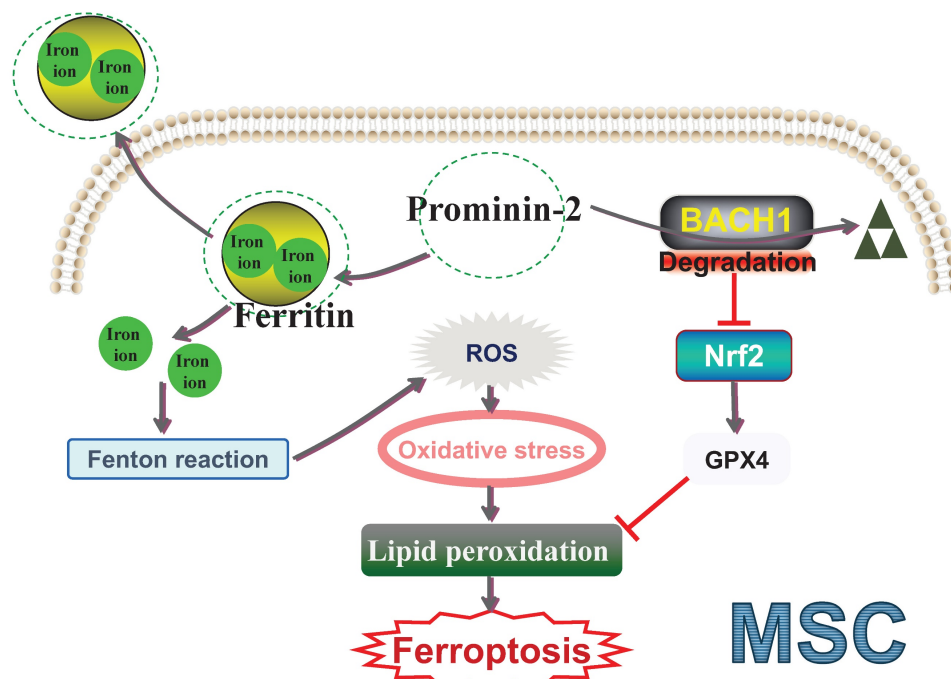

Figure 2. Prominin-2 exhibits dual anti-ferroptosis effects effects MSC ferroptosis. ROS: Reactive oxygen species; BACH1: BTB and CNC homolog 1; Nrf2: Nuclear factor erythroid 2-related factor 2; GPX4: Glutathione peroxidase 4; MSC: Mesenchymal stem cell.

3.4 Hydrogel-encapsulated stem cells exert anti-ferroptosis effects

Given the harsh OS microenvironment in degenerative IVDs sensitizes MSCs to ferroptosis, targeting transplanted MSC ferroptosis is essential for enhancing the clinical efficacy of cell transplantation therapy for IVDD. This includes modulating the ferroptosis signaling pathway in stem cells or enhancing the intracellular antioxidant defense system. It is important to note that injecting gene-modified or antioxidant preconditioned MSCs might cause a sudden increase in intradiscal pressure, contributing to the leakage of engrafted MSCs. Considering the challenge of injecting MSCs into degenerative IVDs, an optimal candidate carrier could be designed to address this challenge. Composite hydrogels exhibit good biocompatibility, are injectable for minimally invasive administration, and maintain stable mechanical strength after injection to prevent MSC leakage [198-200]. More importantly, hydrogel encapsulation creates a defensive shield for the transplanted MSCs and protects them from ferroptotic damage, thus reducing ferroptosis in stem cells [33, 35, 201]. *In vivo* research on aged bone regeneration showed that the fabricated injectable hydrogel was highly sensitive to ROS and effectively scavenged intracellular ROS of BMSCs in the OS microenvironment [199]. This demonstrated that composite hydrogels efficiently modulate the antioxidant function of BMSCs to defend against ferroptosis and improve the host microenvironment, thereby enhancing BMSCs' self-renewal ability and osteogenic capacity. Additionally, composite hydrogels could also be utilized for sustained drug release, including ferroptosis inhibitors and antioxidants [35, 202-203]. The sustained drug release from the hydrogel has a persistent and strong anti-ferroptosis effect on MSCs. In a rat-infected bone defect model, ferroptosis was identified as the primary cause of BMSC death under the infected bone microenvironment. Based on this, Yuan *et al.* [35] designed a hydrogel composite scaffold with ROS-responsive and anti-ferroptosis properties, featuring long-term Fer-1 release to deliver BMSCs for repairing infected bone defects. Targeting ferroptosis mitigated OS damage to BMSCs and protected their cell viability, thus preserving osteogenic differentiation potential and facilitating osteogenic regeneration. Results from micro-CT, X-ray, and histological evaluations indicated that the hydrogel composite scaffold-loaded BMSCs targeted ferroptosis to better promote bone regeneration than the pure hydrogel group and are a promising therapeutic approach for repairing infected bone

defects. As a result, composite hydrogels for MSC encapsulation provide a direct protective barrier and continuously inhibit ferroptosis through the OS pathway within the stem cells. Alternatively, it can achieve sustained and controlled release of ferroptosis inhibitors, thus achieving continuous suppression of ferroptosis.

Increasing numbers of *in vivo* studies on IVDD show that composite hydrogels carrying MSCs are promising for enhancing the effectiveness of stem cell-based therapy [14, 20, 66, 204]. These hydrogels have shown anti-ferroptosis effects on engrafted MSCs, thus promoting IVD regeneration. In rat models of IVDD, ADSCs or ADSC-laden hydrogels were transplanted into degenerative IVDs [124]. Four weeks post-implantation, the retention of ADSCs in the composite hydrogels was higher, and the proportion of the NP area was also larger than in other groups. Notably, there was a significant increase in cell proliferation rate and a decrease in intracellular MDA levels in the ADSC-laden hydrogel group, indicating that hydrogel-encapsulated ADSCs effectively resisted ferroptotic damage under OS conditions. More importantly, these hydrogels showed a more substantial effect in delaying IVDD, preserving IVD tissue integrity, and boosting NP-like ECM production [124]. In another study using a rat IVDD model, MSCs were encapsulated by alginate and gelatin microgel, and the biocompatible hydrogel loaded with MSCs was delivered into degenerative IVDs [20]. It is noteworthy that damage to mitochondrial cristae was reduced under transmission electron microscopy in the hydrogel-encapsulated group, demonstrating that ferroptosis contributed to engrafted MSC death under OS conditions. Hydrogel encapsulation protected MSCs in the harsh disc microenvironment, prolonged MSC retention, and preserved their migration, proliferation, and differentiation properties, ultimately resulting in more effective reduction of disc degeneration compared to treatment with MSCs alone [20]. Based on this defense against MSC ferroptosis after transplantation, Wang *et al.* designed a manganese oxide (MnOx) nanohydrogel to deliver BMSCs to repair IVDD [125]. MnOx has strong antioxidant enzyme activities and can continuously eliminate ROS in degenerative IVDs and improve the OS microenvironment [205-206]. This injectable composite nanohydrogel enables MnOx to be more resistant to degradation, allowing it to maintain effective concentrations in the lesion area for extended periods. Importantly, MnOx nanohydrogel reduced ferroptotic damage to BMSCs, as evidenced by increased cell proliferation, enhanced BMSC metabolic activity, and lowered intracellular ROS

levels [207]. Due to its superior anti-ferroptosis effects, the BMSCs released by hydrogels maintain high stemness and low senescence under OS conditions, and also remodel NPCs' ECM. *In vivo*, injection of BMSC-loaded MnOx nanohydrogel showed the highest therapeutic efficacy, as assessed by gross evaluation, X-ray and MRI examinations, and histological staining [207]. In conclusion, the biocompatible MSC hydrogel suppressed ferroptosis activation and improved MSC survival after intradiscal transplantation. Targeting the ferroptosis signaling pathway, combined with hydrogel encapsulation, shows great potential and could be an effective strategy to enhance the effectiveness of MSC-based therapy for treating IVDD diseases.

4. Research prospects

Existing evidence suggests that cell therapy is a feasible method for partially restoring the biological characteristics of degenerated IVDs. MSCs, noted for being non-tumorigenic and easily accessible, are commonly used as cell therapy source cells. Reports indicate that intradiscal engraftment of MSCs can boost the accumulation of proteoglycans and collagen, leading to improved radiological results and pain alleviation. However, the effectiveness of unmodified MSCs is largely limited. The ineffective therapeutic outcomes of MSC therapy are attributed to the OS microenvironment within the degenerated IVDs, which is characterized by ischemic and hypoxic stress that disrupts the balance between the synthesis and degradation of the ECM. It is increasingly clear that simply implanting stem cells *in vivo* is insufficient to maximize their healing capabilities. Therefore, protecting the engrafted MSCs and maintaining their physiological functions is critical to enhancing the efficacy of MSC-based therapy for IVDD. Moreover, inhibiting transplanted MSC cell death to promote MSC retention is essential. The harsh OS microenvironment could trigger apoptosis, necrosis, and pyroptosis in MSCs [27-32]. However, studies have shown that inhibiting apoptosis, necrosis, and pyroptosis could only partially restore the vitality of transplanted MSCs [26-27, 33]. It seems that other RCD pathways might also contribute to transplanted MSC death. The process leading to ferroptosis activation involves a complex disruption of cellular iron balance, resulting in elevated cytosolic metal ion levels that cause OS and irreversible damage to cell structures and biomolecules. Notably, the harsh OS microenvironment within degenerated IVDs compromises the balance between oxidative and antioxidative systems in MSCs, making them prone to ferroptosis. Therefore, ferroptosis-associated cell death could further reduce the therapeutic effects of MSC therapy. Conversely, protecting MSCs from ferroptosis could enhance the efficacy of MSC treatment. Increasing evidence suggests that targeting ferroptosis for stem cell transplantation therapy effectively enhances their retention within degenerated IVDs. By manipulating stem cells to intervene in ferroptosis, researchers and clinicians could further boost MSC survival rate and provide a significant advantage during the initial stages of *in vivo* placement, where MSCs face numerous challenges. Hence, suppressing transplanted MSC ferroptosis and enhancing their preservation under the harsh microenvironment of the discs are crucial for optimizing MSC-based transplantation therapy. This review focused on current ferroptosis-related strategies for enhancing *in vivo* cell survival and subsequent tissue regeneration by manipulating stem cells or their surrounding environment.

The MSCs to the host microenvironment is critical for successful stem cell-based transplantation therapies. Strategies for preconditioning, including genetic modification, drug preconditioning, and hydrogel encapsulation, have been developed to enhance the adaptation and functionality of MSCs in pathological contexts. Recent advances in targeted ferroptosis treatments have proved beneficial in both *in vitro* and *in vivo* models of IVDD, employing stem cell transplantation. Moreover, these treatments are associated with reduced ROS accumulation and the activation of antioxidant pathways. Preconditioning MSCs through iron metabolic pathways can effectively inhibit ferroptosis by reducing intracellular ROS levels. The application of antioxidants during preconditioning significantly enhances the adaptability of engrafted MSCs to the harsh conditions of the IVD. This improvement may be due to the activation of the Nrf2/GPX4 signaling pathway. Non-canonical molecules, such as HIF-1α, SIRT1, PI3K/AKT, GDFs, and Prominin-2, modulate the ferroptosis process by influencing the balance between oxidation and antioxidation within MSCs. Therefore, reducing intracellular iron content and enhancing antioxidant defenses are key mechanisms for improving the adaptability of preconditioned MSCs to stressful environments. Developing MSC preconditioning strategies based on these aspects could enhance the survival rate of transplanted MSCs within the degenerated IVDs, better utilizing their intrinsic properties for repair (Figure 3). In our review of preliminary clinical studies on stem cell transplantation for the repair of degenerated IVDs, various tissue-derived stem cells were considered. MSCs can be obtained from various tissues, such as bone marrow, umbilical cord, adipose tissue, each exhibiting distinct phenotypic and functional features
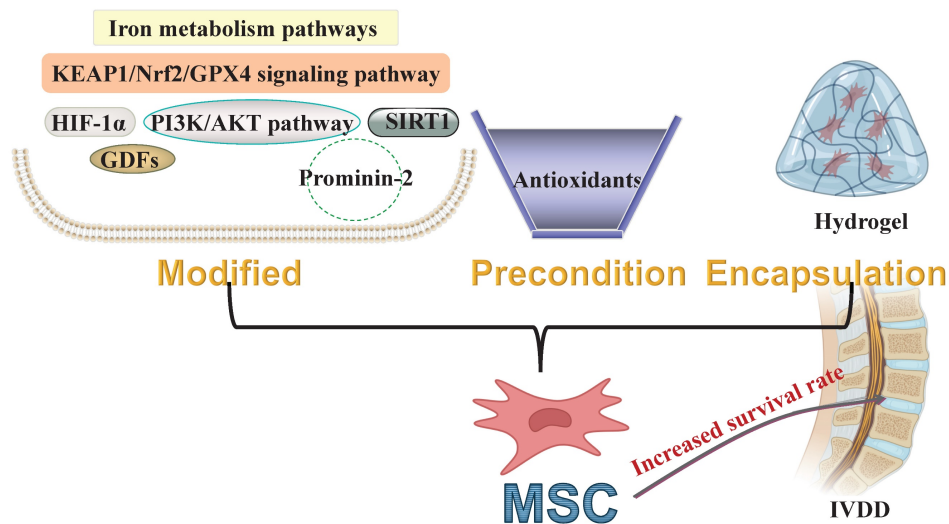
Figure 3. Developing preconditioning strategies for MSCs to increase the survival rate of transplanted MSCs within the degenerated IVDs. KEAP1: Kelch-like ECH-associated protein 1; Nrf2: Nuclear factor erythroid 2-related factor 2; GPX4: Glutathione peroxidase 4; HIF-1α: Hypoxia-inducible factor 1-alpha; PI3K: Phosphatidylinositol 3-kinase; AKT: Threonine-protein kinase; SIRT1: NAD-dependent histone deacetylase sirtuin-1; GDFs: Growth differentiation factors; MSC: Mesenchymal stem cell; IVDD: Intervertebral disc degeneration.

[208]. Although these stem cells from different sources have shown some repair effectiveness, comparing the results of various studies is challenging. One possible reason for this issue is the inherent and extensive heterogeneity among these stem cells [54]. This variation in tissue sources may also contribute to inconsistencies in the outcomes of future clinical applications. As MSC-based therapies progress through multiple clinical trials, it is crucial to implement strategies to minimize product heterogeneity. Therefore, a standardized evaluation of the specific functions of MSCs is necessary in the future (for example, defining the optimal tissue source), moving towards more consistent and effective MSC-based therapy for IVDD [209]. Moreover, there is currently a lack of studies that reproducibly and reliably confirm the potential of targeted MSC ferroptosis in early simulated clinical settings. Although targeted ferroptosis strategies have improved the regenerative effects of these stem cells from different sources in transplantation repair of degenerated IVDs, their preclinical and early clinical efficacy may be inconsistent and often requires verification in later trials. The susceptibility of these stem cells from different sources to ferroptosis varies in the OS environment of degenerated IVDs, leading to different retention rates after transplantation. Therefore, evaluating the efficacy of targeted MSC ferroptosis more effectively and reliably is essential. Approaches to address these differences may include carefully selecting tissue sources, donors, and specific MSC subpopulations, as well as standardized cultivation conditions and potency evaluations [209-210]. This is also a key focus area of our future research.

This review outlines the potential applications of targeting MSC ferroptosis through iron metabolism and antioxidant pathways, critical molecules involved in ferroptosis, and MSC encapsulation with hydrogels. The delivery of preconditioned or genetically modified MSCs, combined with composite hydrogels, creates a three-dimensional protective environment that more effectively inhibits ferroptosis. It is particularly important to develop strategies that fully leverage the anti-ferroptosis effects of Prominin-2 in MSCs through dual-pathway inactivation of ferroptosis. Based on our previous research, activating Prominin-2 maintains intracellular iron ion homeostasis and may also repress BACH1 expression to regulate antioxidant pathway in MSCs. However, excessive and prolonged OS prevents Prominin-2 from effectively suppressing BACH1 expression in MSCs due to the cellular response to transcription factor BACH1 [190-191]. The BACH1 inhibitor hemin can effectively degrade BACH1, offering potential for regulating antioxidant metabolism within stem cells [211-212]. We envision combining these three strategies to target MSCs effectively, enhancing targeted ferroptosis effects. We plan to design a hydrogel composite scaffold that provides a cellular protective barrier and allows for sustained delivery of the BACH1 inhibitor hemin. This is expected to enable gene-modified MSCs to acquire barrier protection directly in the transplantation OS microenvironment and continuously inhibit intracellular BACH1 expression, thereby more effectively suppressing ferroptosis in MSCs through both oxidative and antioxidative pathways. A growing body of evidence

confirms that MSCs preconditioned by targeting ferroptosis show potential for IVD regeneration in preclinical models, where engrafted MSCs increased disc height, upregulated ECM production, and elevated the expression of NP marker genes. In summary, targeted ferroptosis preconditioning is promising for promoting MSC adaptation to OS microenvironments, and introducing ferroptosis-targeting drugs can help MSCs survive in these environments and enhance their repair efficiency for IVDD.

5. Conclusion

Supported by preclinical and clinical studies, MSC-based cell therapy has emerged as a promising option for IVDD diseases and is gradually entering clinical practice. However, the low retention of MSCs in the harsh microenvironment is a major reason for their loss and suboptimal therapeutic outcomes after transplantation into degenerative IVDs. The OS microenvironment triggers a surge in intracellular ROS, destabilizing the balance between oxidation and antioxidation. This imbalance is a key pathway for ferroptosis and has been linked to the loss of MSC retention. Clinical translation strategies that target ferroptosis in MSCs could improve retention, prolong survival, and boost therapeutic outcomes. Our review emphasized the potential benefits of targeting ferroptosis inhibition in MSCs for treating IVDD diseases, drawing on a comprehensive assessment of basic research and early clinical translation. We also provided a comprehensive overview of pertinent basic research and early clinical translational studies. We believe that targeting ferroptosis in MSCs could offer new perspectives for the future treatment of IVDD diseases. However, there is currently a lack of clinical translational research focusing on targeting ferroptosis in MSCs to enhance the efficiency of degenerated IVD repair. In future research, we need to further confirm *in vivo* the impact of targeting ferroptosis on MSC retention rate and the efficiency of repairing degenerated IVDs. Additionally, there is an urgent need for specific biomarkers that are common to both MSCs and ferroptosis to accurately predict the efficiency of MSC ferroptosis inhibition. Moreover, the data from primary research still needs to meet the standards required for clinical application. Therefore, more effective strategies for inhibiting MSC ferroptosis need to be developed. Nevertheless, targeting MSC ferroptosis holds promise for novel therapies for IVDD diseases.

Abbreviations

ADSCs: Adipose-derived stem cells
BMSCs: Bone marrow mesenchymal stem cells
BACH1: BTB and CNC homolog 1
Co-Q10: Coenzyme Q10
CSE: Cystathionine γ-lyase
DFO: Deferoxamine
ECM: Extracellular matrix
FTH1: Ferritin heavy chain 1
Fer-1: Ferrostatin-1
Fe^{2+}: Ferrous iron
FTH1: Ferritin heavy chain 1
FTL: Ferritin light chain
GPX4: Glutathione peroxidase 4
GSH: Glutathione synthetase
GDFs: Growth differentiation factors
HSF1: Heat shock factor protein 1
HO-1: Heme oxygenase 1
H_2O_2: Hydrogen peroxide
H_2S: Hydrogen sulfide
HIF-1α: Hypoxia-inducible factor 1-alpha
HRE: Hypoxic response elements
IVD: Intervertebral disc
IVDD: Intervertebral disc degeneration
KEAP1: Kelch-like ECH-associated protein 1
Lip-1: Liproxstatin-1
ACSL4: Long-chain-fatty-acid--CoA ligase 4
LUSC: Lung squamous cell carcinoma
MRI: Magnetic resonance imaging
MnOx: Manganese oxide
MSC: Mesenchymal stem cell
MSC-Exos: Mesenchymal stem cell-derived exosomes
SIRT1: NAD-dependent histone deacetylase sirtuin-1
Nrf2: Nuclear factor erythroid 2-related factor 2
NCOA4: Nuclear receptor coactivator 4
NP: Nucleus pulposus
NPCs: Nucleus pulposus cells
NPSCs: Nucleus pulposus-derived mesenchymal stem cells
ODI: Oswestry Disability Index
OS: Oxidative stress
PI3K: Phosphatidylinositol 3-kinase
PROM2: encoding the prominin 2
PTGS2: Prostaglandin G/H synthase 2
QDAD: Quercetin diels-alder anti-dimer
ROS: Reactive oxygen species
RCD: Regulated cell death
ROCK: Rho-associated protein kinase
SLC2A12: Solute carrier family 2, facilitated glucose transporter member 12
SLC7A11: Solute carrier family 7 member 11
TBHP: Tert-butyl hydroperoxide
AKT: Threonine-protein kinase
TFR1: Transferrin receptor protein 1
VAS: Visual Analog Scale

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Author contributions

Yuzhu XU and Xiaotao WU designed the manuscript.

Yuzhu XU and Xiaotao WU wrote the manuscript.

Yuzhu XU, Xuanfei XU, Renjie CHAI and Xiaotao WU provided opinions.

Yuzhu XU, Xuanfei XU, Renjie CHAI and Xiaotao WU were involved in the discussion.

All authors have read and approved the final manuscript.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethical approval

This review does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests

The authors have declared that no competing interest exists.

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