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REVIEW

Ferroptosis: New Strategies for Clinical Treatment of Rheumatoid Arthritis

Yanqiu Sun, Jian Liu, Mingyu He, Dan Huang, Yuan Wang

Department of Rheumatology and Immunology, First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, Hefei, Anhui, 230038, People's Republic of China

Correspondence: Jian Liu, Department of Rheumatology and Immunology, First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, 117 Meishan Road, Hefei, Anhui, 230038, People's Republic of China, Tel +8613955109537, Email liujianahzy@126.com

Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can lead to joint deformities, functional loss, and a significant reduction in patients' quality of life. It also imposes a considerable medical and socio-economic burden. Iron-induced cell death, or ferroptosis, is a unique form of programmed cell death characterized by dysregulated iron metabolism and the accumulation of lipid peroxides resulting from increased reactive oxygen species (ROS) and reduced activity of glutathione peroxidase 4 (GPX4). The accumulation of lipid peroxides can cause cellular damage, promotes inflammatory responses and joint destruction. This process not only plays a crucial role in the pathogenesis of RA, but also provides new therapeutic targets for its treatment. In this review, we summarize the regulatory mechanisms of ferroptosis in the pathogenesis of RA. These include its roles in regulating oxidative stress and lipid peroxidation, inhibiting the abnormal proliferation of synovial fibroblasts (FLSs), preventing cartilage erosion, restoring immune homeostasis and inflammatory responses, and other aspects. Finally, we also discuss the potential clinical applications, and future prospects of ferroptosis-based therapies for RA treatment.

Keywords: ferroptosis, rheumatoid arthritis, treatment strategy, review

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that leads to disability and premature death. It is characterized by joint swelling, pain, and stiffness, ultimately leading to joint deformities and loss of function[1] In addition, RA may also lead to systemic complications affecting multiple organs, significantly compromising the patient's physical health.[2] The prevalence of RA has been observed to range between 0.5% and 1%, with a female-to-male ratio of 3:1.[3] According to the Global Burden of Disease Study 2021, the age-standardized global prevalence of RA was 208.8 cases per 100,000 population. Projections suggest that by 2050, the number of people affected by RA worldwide will increase to 317,000.[4] These statistics underscore the urgent need for early diagnosis and the timely implementation of effective treatment strategies for RA.

At present, the exact cause of RA remains unclear, and there is no cure for the disease. Consequently, existing treatments primarily focus on controlling inflammation, alleviating symptoms, delaying disease progression, and improving the patients' quality of life.[5] Currently, disease-modifying antirheumatic drugs (DMARDs) continue to be the mainstay of RA treatment, either as monotherapy or in combination.[6,7] In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) are commonly used to manage pain and reduce inflammation.[8,9] However, frequent adverse effects and the potential for drug resistance often limit the long-term use of these therapies.[10,11] Newer treatment options, including biological and targeted synthetic DMARDs, offer promise but remain prohibitively expensive for many patients.[12] Therefore, understanding the underlying pathogenesis of RA, identifying novel therapeutic targets, and developing more effective, affordable drugs represent critical strategies for advancing the clinical management of RA.

Ferroptosis is a form of programmed cell death characterized by the accumulation of iron-dependent lipid peroxides. Simply put, ferroptosis is a form of cell death caused by the accumulation of lipid peroxides, depletion of GSH, and loss of GPX4 function.[13] In recent years, research has found that ferroptosis, as a potential therapeutic target, is widely involved in the

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progression of autoimmune diseases such as RA, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis (MS).[14] Targeting ferroptosis opens new avenues for the development of novel therapeutics for RA treatment.[15] Previous evidence has demonstrated that ferroptosis activation reduces foot swelling in collagen-induced arthritis (CIA) rats, as well as decrease arthritis scores, bone destruction, and synovitis.[16] Moreover, several anti-rheumatic drugs (including sulfasalazine) have been shown to regulate ferroptosis, indicating that the ferroptosis pathway may play a crucial role in the pathogenesis of RA and that targeting this process could offer novel therapeutic strategies.[17] Therefore, this article aims to explore the potential mechanisms of ferroptosis in the occurrence and development of RA, systematically review clinical treatment strategies involving ferroptosis in RA, and comprehensively evaluate the potential of ferroptosis as a diagnostic and therapeutic target. The schematic diagram of the mechanism is shown in Figure 1.

Regulatory Mechanism of Ferroptosis

Ferroptosis is a form of cell death driven by iron-dependent lipid peroxidation, which has garnered significant attention in recent years as a potential pathological mechanism and therapeutic target for various diseases.[18–20] The hallmark of ferroptosis at the morphological level is the significant alteration of mitochondrial structure. Studies have demonstrated that ferroptosis leads to mitochondrial swelling, reduced cristae, and rupture of the outer membrane.[21,22] These morphological changes, often referred to as the "cell swelling ffects", propagate across the cell population in a manner dependent on lipid peroxides and iron.[23] As such, dysregulated iron metabolism and lipid peroxidation, along with their regulatory systems, play an important role in the ferroptotic process.

Lipid Peroxidation is a Key Driver of Ferroptosis

Lipid peroxidation refers to the oxidative process in which free radicals attack the unsaturated carbon bonds of lipid molecules, triggering a cascade of oxidative reactions.[24] Research has shown that lipid peroxidation can disrupt the thickness, permeability, and overall structure of the cell membrane bilayer.[25,26] The oxidation of double bonds in lipid molecules leads to the formation of LPOs, which are further broken down into toxic byproducts such as HNE and MDA. These products can, in turn, disrupt cellular processes.[27,28] Therefore, detecting lipid peroxidation products is an effective way to evaluate the occurrence of ferroptosis. PUFAs, particularly AA and adrenaline, are common components of phospholipids and are especially susceptible to lipid peroxidation during ferroptosis. When free radicals attack PUFAs, the integrity of the plasma membrane is compromised, leading to ferroptotic death.[29,30]

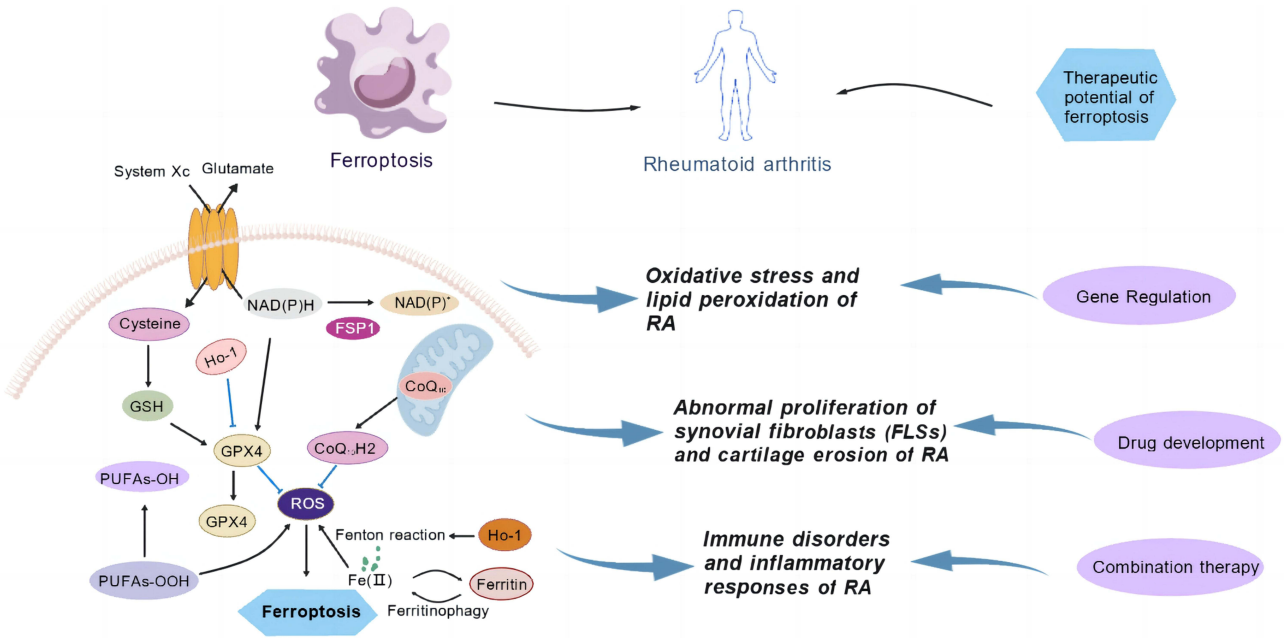

Figure 1 The pathogenesis of RA regulated by ferroptosis.

In addition, ROS, the Fenton reaction, and various enzymatic processes exacerbate lipid peroxidation. ROS are highly reactive molecules that, in small amounts, are involved in intercellular signaling. However, excessive ROS can attack PUFA in the cell membrane, triggering lipid peroxidation.[31] Iron ions (Fe^{2+}) act as catalysts in the Fenton reaction, producing additional ROS and further promoting lipid peroxidation. Mitochondria-derived ROS can also directly attack mitochondrial membrane lipids, leading to lipid peroxidation.[32] Moreover, iron-containing enzymes, such as LOXs, ALOX15, ACSL4, etc., catalyze the conversion of phosphatidylethanolamine containing PUFA to membrane lipid peroxidation (PL-PUFA), thereby amplifying lipid peroxidation.

In summary, lipid peroxidation is a core mechanism driving ferroptosis by catalyzing the oxidation of PUFA, generating lipid peroxidation products, and disrupting cell membrane integrity. Therefore, investigating the relationship between lipid peroxidation and ferroptosis not only enhances our understanding of the pathogenesis of related diseases, but also provides a critical foundation for developing new treatment strategies targeting ferroptosis.

An Imbalance of the Antioxidant Defense System is a Key Trigger for Ferroptosis

The generation and accumulation of LPO are central to the process of ferroptosis, and these events are tightly regulated by the cellular antioxidant defense system. Key pathways involved in this regulation include the classic GSH/GPX4 pathway, the FSP1/CoQ10A pathway, the NADPH oxidase system, and the GCH1 system. These pathways help prevent ferroptosis by clearing lipid peroxides or maintaining antioxidant balance. When the intracellular antioxidant system is damaged, lipid peroxides accumulate, leading to membrane rupture and cell death.

GSH, a tripeptide composed of glutamic acid, cysteine, and glycine, is an important antioxidant and free radical scavenger in cells. It helps protect against lipid peroxidation and other forms of oxidative stress by maintaining intracellular redox balance.[33] During ferroptosis, lipid peroxidation leads to the oxidation of membrane lipids such as phosphatidylethanolamine (PE), forming reactive lipid peroxides (ROOH). These peroxides further catalyze additional lipid peroxidation reactions, thereby establishing a vicious cycle.[34,35] GPX4, a GSH-dependent antioxidant enzyme, can reduce lipid peroxides to non-toxic lipid alcohols, thereby inhibiting lipid peroxidation and preventing ferroptosis.[36] However, when intracellular GSH levels decrease, GPX4 activity is compromised, leading to the accumulation of lipid peroxides and ultimately triggering ferroptosis.[37] Research has shown that depletion of GSH not only directly inhibits GPX4, but also indirectly activates the Fenton reaction, releasing Fe^{2+} and promoting ROS generation, further exacerbating cell damage.[38]

Nuclear respiratory factor 2 (NRF2) is a transcription factor widely involved in cellular antioxidant responses, redox balance, and iron homeostasis. In response to oxidative stress, Nrf2 upregulates the expression of genes related to GSH synthesis (such as GCLC, GSH synthase, etc)., enhancing cellular antioxidant capacity, reducing the accumulation of lipid peroxides, and maintaining intracellular redox balance. These actions ultimately inhibit the occurrence of ferroptosis.[39] In addition, Nrf2 has been shown to directly regulate GPX4 expression, further preventing the accumulation of lipid peroxides and protecting cells from ferroptosis.[40]

Ferroptosis suppressor protein 1 (FSP1) is an NADPH-dependent ubiquinone oxidoreductase that reduces Coenzyme Q10 (CoQ10) to its active form, dihydroubiquinone (CoQH2), thereby clearing ROS and free radicals in cells and inhibiting ferroptosis.[41–43] Research has shown that FSP1 can effectively prevent ferroptosis in GPX4-knockout cells, indicating that the FSP1/CoQ10A pathway is an independent regulatory system that operates parallel to the GPX4 pathway, without relying on the function of GPX4.[44] NADPH oxidase (NOX) is a key enzyme that oxidizes NADPH to generate ROS through the ubiquitin-proteasome system, which contributes to lipid peroxidation and cell membrane damage, ultimately leading to ferroptosis.[45,46] However, recent studies have shown that NADPH oxidase may have a dual role in ferroptosis regulation. The FSP1 protein inhibits ROS production by oxidizing NADPH, thereby reducing lipid peroxidation and ferroptosis.[42] Conversely, inhibiting NADPH oxidase (for example, by targeting NOX4 or NOX2 inhibitors) has been shown to reduce ROS generation and alleviate ferroptosis.

Tetrahydrobiopterin (BH4) is a potent antioxidant that can capture LPO and prevent lipid peroxidation. GCH1 (guanosine triphosphate cyclase 1) is the rate-limiting enzyme in the synthesis of BH4. It catalyzes the coenzyme synthesis of aromatic amino acid hydroxylase, thereby promoting the generation of BH4.[47] In addition, GCH1 indirectly supports cellular energy metabolism and antioxidant defense by promoting the synthesis of CoQ10. Notably, the GCH1 system has also been identified as an independent ferroptosis inhibition pathway, functioning independently of GPX4.

Overexpression of GCH1 can significantly enhance cell resistance to ferroptosis inducers, even in the absence or impairment of GPX4 function. This suggests that even if GPX4 activity is impaired, GCH1 can still protect cells from ferroptosis through other mechanisms, such as the antioxidant effect of BH4 and lipid metabolism regulation.[48,49]

Overall, the imbalance of the antioxidant defense system is a key factor driving ferroptosis. When the antioxidant system fails to effectively remove lipid peroxides, their accumulation can lead to cell membrane damage, mitochondrial dysfunction, and, ultimately, cell death. Therefore, restoring the balance of the antioxidant defense system is a crucial step in protecting cells from iron-induced cell death.

Bidirectional Regulation of Iron Metabolism in Ferroptosis

Imbalances in iron metabolism are key factors that contribute to the onset of ferroptosis. Both excessive and insufficient intracellular iron levels can induce oxidative stress and lipid peroxidation, triggering ferroptosis. Iron is an essential trace element in the human body, serving as an important cofactor in mitochondrial electron transport and matrix metalloproteinases (MMPs).[50] Excessive intracellular iron can lead to the formation of an unstable iron pool, often referred to as the "lipoxygenase active iron pool". This pool is highly prone to oxidation, converting Fe^{3+} to Fe^{2+} and generating hydroxyl radicals through the Fenton reaction. These reactive species can damage the integrity of the cell membrane, disrupt cellular function, and ultimately lead to cell death.[51]

Conversely, iron deficiency triggers a series of compensatory mechanisms. The level of transferrin receptor (TTR) increases in response to reduced intracellular iron, which then binds to the CNOT4 complex and degrades target mRNAs. This inhibits the expression of iron transporters (such as SLC7A14 and SLC39A14), thereby reducing iron uptake. This iron scarcity also impairs the activity of the key antioxidant enzyme GPX4, promoting lipid peroxidation accumulation.[52,53] In addition, iron deficiency can induce mitochondrial dysfunction, decreasing the efficiency of the mitochondrial electron transport chain. This results in increased ROS generation, inhibition of antioxidant enzyme activity, and a significant exacerbation of oxidative stress. These effects ultimately contribute to cellular damage and cell death.[54]

The bidirectional regulation of iron metabolism thus plays a central role in ferroptosis. By precisely regulating the absorption, storage, utilization, and excretion of iron, intracellular iron homeostasis can be effectively maintained, thereby preventing lipid peroxidation and preserving cellular function. This understanding not only provides new insights into the mechanisms of cell death, but also highlights potential therapeutic targets for diseases associated with ferroptosis.

The Mechanism of Ferroptosis in RA

In recent years, advancements in bioinformatics technology and deeper investigations into the pathogenesis of RA have revealed that ferroptosis plays an important role in the occurrence and development of RA.[55–57] A large-scale bioinformatics analysis identified 34 potential ferroptosis-related genes in RA, further validating their regulatory roles in the disease.[58] Moreover, increasing evidence suggests that ferroptosis contributes to the pathogenesis of RA by regulating oxidative stress, lipid peroxidation, abnormal proliferation, and cartilage erosion of synovial fibroblasts (FLSs), as well as immune dysregulation and inflammatory responses. These findings indicate that ferroptosis may represent a novel therapeutic target for RA.

Oxidative Stress and Lipid Peroxidation in the RA

The accumulation of lipid peroxide is the core mechanism of ferroptosis, causing cellular damage that promotes inflammatory responses and joint destruction. Jiao Wu's analysis of synovial tissue from RA patients revealed that FLSs showed iron accumulation and increased lipid peroxides. Additionally, the level of iron in the synovial fluid of patients with high disease activity was significantly higher than that of patients with moderate disease activity.[59] Specifically, active RA patients showed significantly lower levels of GSH, GPX4, Nrf2, and Keap1 compared to healthy individuals and those with RA in remission. Further observations of human FLSs using transmission electron microscopy revealed that ferroptosis inducer (erastin) increased the density and quantity of mitochondrial membranes and reduced the expression of GPX4. In contrast, the ferroptosis inhibitor (Ferrostatin-1, Fer-1) inhibited mitochondrial growth and upregulated the expression of GPX4.[16]

Abnormal Proliferation of RA-FLSs and its Relationship with Cartilage Erosion and Ferroptosis

In RA, FLSs are key pathological cells involved in disease progression. Studies have found that iron levels in synovial tissue and fluid are elevated in RA patients, and ferroptosis is increased in chondrocytes.[60] Therefore, ferroptosis is believed to play a crucial role in maintaining the balance between synovial cell proliferation and death. Wang et al investigated the role of ferroptosis in inflammatory hypoxic RA joints using lipopolysaccharide (LPS)-induced RA-FLS. Their results highlighted that NCOA4-mediated ferritin autophagy protected RA-FLSs from LPS-induced ferroptosis, suggesting that modulating this pathway could offer therapeutic benefits.[61] Pelissier et al found that BACH1, a ferroptosis-related target, is downregulated in RA-FLSs. This downregulation impairs FLS adhesion and fluidity, disrupts the formation of thick actin fibers, and prevents the polarization of pseudopodia, all of which are essential for the destructive behavior of RA-FLSs.[62] A bioactive peptide derived from the galectin-1 domain, Galectin-1 Derived Peptide 3 (G1dP3), has been reported to exhibit anti-inflammatory and anti-proliferative properties in RA-FLSs. In an RA model induced by TNF-α stimulation of MH7A cells, G1dP3 induced ferroptosis in MH7A cells by promoting the accumulation of lipid peroxides and iron deposition. Moreover, G1dP3 increased the expression of p53, thereby inhibiting the transcription of SLC7A11, indicating that G1dP3 promotes RA-FLS ferroptosis through a p53/SLC7A11 axis-dependent mechanism.[63]

Articular cartilage plays a crucial role in the structural and functional integrity of joints. In RA, cartilage degeneration and damage can lead to the loss of joint function, a process that is closely linked to the regulation of ferroptosis.[15] It has been reported that downregulation of GPX4 in chondrocytes enhances their sensitivity to oxidative stress, ultimately leading to the degradation of ECM.[64] One of the characteristic features of RA is the outbreak of inflammation. The large release of the inflammatory factor IL-1β can disrupt iron metabolism and promote lipid peroxidation by increasing the expression of NCOA4 and reducing the expression of FTH, thereby inducing ferritin autophagy. In addition, IL-1β suppresses the expression of key antioxidant proteins, such as SLC7A11 and GPX4, which contributes to ferroptosis in chondrocytes.[65] Tang et al found that inhibition of ASIC1a with the specific inhibitor PcTx-1 was found to reduce acid-induced ferroptosis and improve histopathological features in the ankle joints of CIA mice.[66]

In summary, joint cavity hypoxia induces the production of mitochondrial ROS, promotes the abnormal proliferation of RA-FLSs. This process further enhances the proliferation and secretion of inflammatory cytokines by RA-FLSs.

RA Immune Disorder and Inflammatory Response are Closely Related to Ferroptosis

Recent studies have confirmed that activation of inflammatory pathways such as NF - κB, STING pathway, and retinoic acid signaling can regulate cell ferroptosis sensitivity.[67–69] Cai et al utilized machine learning algorithms and immune infiltration analysis to show that RA is characterized by extensive immune cell infiltration, such as B cells, T cells, and macrophages. Sustained immune activation is likely a key factor driving the progression of ferroptosis in RA.[70] Single-cell RNA sequencing of proliferative synovial cells in RA patients showed that ferroptosis-related pathways are enriched in M2 macrophages. Interestingly, in the synovial environment, M2 macrophages are more susceptible to ferroptosis than M1 macrophages.[71] In addition, iron overload in RA lesions induces ferroptosis in anti-inflammatory macrophages by promoting P62-dependent autophagic degradation of GPX4.[72]

Ferroptosis interacts in complex ways with gut microbiota and systemic inflammation. Ma et al used 16S rDNA sequencing and metabolomics analysis of fecal samples from CIA mice to demonstrate that the ferroptosis agonist erastin disrupted the microbiota, leading to metabolic abnormalities in these mice.[73] Similarly, Zhu et al found that ferroptosis exacerbates RA-related inflammation and joint damage in the CIA mouse model by upregulating the expression of PAD4, which subsequently alters the gut microbiota composition and related metabolite profiles.[74]

In summary, ferroptosis contributes to the immune dysregulation in RA by regulating the function of immune cells, such as macrophages, T cells, and B cells. Moreover, ferroptosis may also influence the immune microenvironment of RA through its effects on the gut microbiota. Therefore, targeted therapies aimed at regulating cell ferroptosis, gut microbiota, and systemic inflammation may offer a novel direction for the development of new RA treatments. Table 1 summarizes the regulatory role of ferroptosis in the pathogenesis of RA.

Table 1 The Mechanism of Ferroptosis in RA

Model/ Organization	Targets	Expression	Biological Function	Ref
Active RA patients	GSH, GPX4, Nrf2, and Keap1	Down	Increase the activity of RA disease	[16,59]
RA-FLS	NCOA4	Up	Mediating ferritin autophagy and driving iron death in inflammatory RA-FLS	[61]
RA-FLS	BACH1	Down	Inhibit the destructive behavior of RA-FLS	[62]
MH7A	G1dP3	Up	Promotes RA-FLS ferroptosis through a p53/SLC7A11 axis	[63]
CHs	GPX4	Down	Activate MAPK/NF - κ B pathway to promote ECM degradation	[64]
CHs	IL-1β	Up	Inhibiting the expression of LC7A11 and GPX4 induces ferroptosis in CHs	[65]
CHs	ASIC1a	Up	In response to extracellular acidification, induce iron death in chondrocytes	[66]
RA-FLS	M2 macrophages	Up	Iron overload in RA lesions induces ferroptosis in anti-inflammatory macrophages by promoting autophagic degradation of GPX4	[69–72]
CIA mouse	PAD4	Up	Ferroptosis exacerbates RA-related inflammation and joint damage by upregulating the expression of PAD4 and regulating gut microbiota	[74]

Note: "-"representing missing relevant data.
Abbreviations: RA, rheumatoid arthritis; FLS, fibroblast-like cells; CIA, Collagen-induced arthritis; CHs, chondrocytes; GSH, Glutathione; GPX4, glutathione peroxidase 4; Nrf2, Nuclearrespiratoty factor 2; Keap1, Kelch-like ECH-associated protein 1; NCOA4, Nuclear Receptor Coactivator 4; BACH1, BTB domain and CNC homolog 1; G1dP3, Ferroptosis-inducing peptide; GPX4, Glutathione Peroxidase 4; IL-1β, Interleukin-1 Beta; ASIC1a, Acid-sensing Ion Channel 1a; PAD4, Protein Arginine Deiminase 4.

Although the role of ferroptosis in RA is becoming increasingly clear, its specific mechanism still needs further research. For example, the sensitivity of different cell types to ferroptosis varies greatly, and how to precisely regulate ferroptosis in specific cells remains a challenge. In addition, there is crosstalk between ferroptosis and other cell death modes such as apoptosis and necrosis, and how to avoid adverse side effects needs to be further explored. Finally, the expression regulation mechanism of ferroptosis related genes and proteins is not fully understood, which limits their development as therapeutic targets.

Overall, ferroptosis, as a novel form of cell death, demonstrates a novel target for the diagnosis and treatment of RA through its different regulatory effects, demonstrating broad application prospects in the treatment of RA. Therefore, many scholars, based on emerging bioinformatics analysis methods and sequencing technologies, have delved into the potential biomarkers of ferroptosis in RA (Table 2), developed clinical drugs targeting ferroptosis in RA, and combined

Table 2 Potential Biomarkers of Ferroptosis in RA

Cells/Animals	Key Genes / Potential Biomarkers	Expression	Biological Function	Ref
RA-FLS	SLC2A3	Down	Induce ferroptosis in RA-FLS	[75]
C57BL/6 mice were immunized with bovine type II collagen	SLC2A3	Down	Reduced inflammation levels and ferroptosis through the inactivation of mitochondrial damage by Tiam1 in model of RA	[76]
Bone marrow mesenchymal stromal cells were then cocultured with bone marrow-derived macrophages/ CIA mice	EZH2	–	Targeting EZH2 attenuates the ferroptosis-mediated osteoblast-osteoclast imbalance in RA	[77]
AA rats/ CHs model	TRPM7	Up	TRPM7 attenuated articular cartilage damage and chondrocyte ferroptosis via the PKCα-NOX4 axis	[78]
RA-FLS	CTSB	Up	Inhibit iron death and increase the migratory capacity of RA-FLS	[79]
RA-FLS	Semaphorin 5A	Up	Suppressing ferroptosis through the PI3K/AKT/ mTOR signaling pathway	[80]

Note: "-"representing missing relevant data.
Abbreviations: RA, rheumatoid arthritis; FLS, fibroblast-like cells; SLC2A3, solute carrier family 2 member 3; CIA, Collagen-induced arthritis; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; TRPM7, transient receptor potential melastatin 7; AA, adjuvant arthritis; CHs, chondrocytes; CTSB, cathepsin B.

traditional Chinese medicine diagnosis and treatment strategies to explore the therapeutic potential of ferroptosis in RA from multiple perspectives.

Therapeutic Potential of Ferroptosis in RA

Gene Regulation: Potential Biomarkers and Targeted Therapy

Targeted therapy and precision intervention have emerged as promising approaches in the treatment of RA. By regulating ferroptosis-related genes, precise intervention in ferroptosis can be achieved. Recent research primarily focuses on screening and validating RA ferroptosis-related genes using bioinformatics analysis, leading to the identification of numerous potential biomarkers for ferroptosis in RA. In a bioinformatics study, Xiang et al used RSL3 (a ferroptosis inducer) to treat RA-FLS and found that RSL3 could downregulate SLC2A3 expression, thereby inducing ferroptosis in RA-FLS.[75] In addition, Lin et al confirmed through animal experiments that, in the RA model, SLC2A3 reduces inflammation and ferroptosis by preventing mitochondrial damage through Tiam1.[76]

Ferroptosis not only affects synovial tissue, but also promotes osteoclast activity and inhibits osteoblast differentiation, further leading to bone destruction and joint dysfunction. Piao et al found that overexpression of EZH2 promoted ferroptosis in RA osteoblasts, leading to increased levels of MDA, Fe^{2+}, ROS, and PTGS2, while simultaneously reducing the SLC7A11. The silencing EZH2 can reverse these changes, improving osteoblast ferroptosis. These findings suggest that targeting EZH2 can alleviate the osteoblast-osteoclast imbalance mediated by ferroptosis in RA, positioning it as a potential therapeutic target.[77] In addition, a comprehensive experimental study using AA rats, human RA patients, and chondrocyte models treated with the ferroptosis inducer erastin demonstrated that TRPM7 might induce chondrocyte ferroptosis through an increase in intracellular Ca^{2+}. Blocking TRPM7 was shown to alleviate joint cartilage damage and inhibit chondrocyte ferroptosis in AA rats.[78]

Targeting potential biomarkers of ferroptosis in RA macrophages represents a strategy for the treatment of RA. Cathepsin B (CTSB), a gene associated with ferroptosis, is highly expressed in RA patients and can promote the release of M2 macrophages, neutrophils, and T-cell follicular helper cells. The use of the CTSB inhibitor CA-074Me can reduce the proliferation and migration of RA-FLSs and induce ferroptosis in these cells.[79] Macrophages in RA synovial fluid secrete large amounts of Semaphorin 5A, which enhances GPX4 expression, thereby inhibiting ferroptosis in RA-FLSs. Morphologically, Semaphorin 5A can mitigate the mitochondrial reductions, and increase cristae rupture induced by ferroptosis inducer RSL3 in FLSs.[80]

With the development of bioinformatics and sequencing technology, based on the prediction and screening of known ferroptosis key proteins, new ferroptosis related compounds can be quickly discovered, providing direction and targets for drug development. Although a large number of potential biomarkers for ferroptosis in RA have been identified in relevant studies, relying solely on bioinformatics analysis method and basic experimental validation is insufficient to fully elucidate the underlying mechanisms through which these genes regulate ferroptosis. In addition, research in bioinformatics still needs to be validated through in vivo and in vitro experiments. Therefore, the next step should be to accelerate experimental validation of ferroptosis related targets in RA, and further validate the function of biomarkers through clinical patients.

Drug Development: Clinical Application of Targeted Ferroptosis Drugs in RA

Ferroptosis inhibitors (such as etanercept, TNF inhibitors, etc). have shown promise in effectively alleviating inflammation, reducing cartilage and bone damage, and improving joint function in RA patients. These drugs protect joint tissues from further damage by inhibiting lipid peroxidation and reducing ROS generation. Research has indicated that TNF promotes cysteine uptake via the NF-κB signaling, which helps protect FLS from lipid peroxidation and ferroptosis-induced damage.[81] In the CIA model, low-dose imidazole ketone erastin (IKE), in combination with the TNF antagonist etanercept, induces ferroptosis in FLSs and alleviates the progression of arthritis. This suggests that the combination of TNF inhibitors and ferroptosis inducers may offer a promising therapeutic approach for RA.[59] In addition, the ferroptosis inhibitor Lip-1 has been shown to act in the pre-symptomatic stage of the CIA model, while overexpression of GPX4 in macrophages protects M2 macrophages from ferroptosis.[71]

Certain anti-RA drugs have been found to regulate ferroptosis in RA. Auranofin (AUR), an anti-rheumatic drug approved for RA treatment due to its anti-inflammatory properties, has been shown to upregulate ferritin expression both in vitro and in vivo through the NF-κB signaling pathway. Notably, high-dose AUR induces ferroptosis by inhibiting the thioredoxin system.[82] A clinical observational study comparing the effects of COX inhibitors on oxidative stress markers in RA showed that diclofenac, meloxicam, and celecoxib exhibit varying degrees of antioxidant activity. This study highlighted the mechanism by which NSAIDs improve RA independently of COX inhibition, namely through the regulation of oxidative stress.[83] Additionally, another clinical study also identified the risk associated with long-term use of NSAIDs.[84]

Nanomaterials have garnered significant attention due to their ability to precisely target specific cells for therapeutic effects. Yang et al developed an injectable bioadhesive hydrogel containing M1 macrophage-targeting nanodrug capsules, which was used to inhibit synovitis and chondrocyte ferroptosis in RA.[85] Ruan et al used macrophages as carriers to deliver Fe_3O_4 nanoparticles and sulfasalazine (SSZ), thereby damaging the proliferating synovium. Simultaneously, the iron released by Fe_3O_4 nanoparticles synergistically interacted with SSZ, producing a synergistic ferroptosis effect.[86]

In summary, drugs targeting ferroptosis providing new therapeutic approaches for RA patients by regulating immune-inflammatory responses, protecting cellular function, and delaying cartilage destruction. However, some ferroptosis inducers suffer from low bioavailability, poor water solubility, and poor targeting ability, which limits their clinical translation. In addition, ferroptosis involves multiple metabolic pathways and regulatory networks, and there is a lack of accurate and reliable biomarkers for ferroptosis. This increases the requirements for drug selectivity and specificity in the research and development process. Future research needs to further optimize drug design, improve drug selectivity and specificity, and develop reliable biomarkers to guide clinical applications.

Combination Therapy: Diagnostic and Therapeutic Strategies of Traditional Chinese Medicine (TCM)

As a therapeutic system with thousands of years of clinical experience, TCM plays an important role in the clinical management of RA, owing to its proven efficacy, minimal side effects, and low cost. In recent years, the exploration of TCM's mechanisms in treating RA has gained momentum. Researchers have found that the active ingredients of TCM, compound preparation, acupuncture, and moxibustion therapies can exert therapeutic effects on RA by regulating ferroptosis. Osmundacetone (Osu), a phenolic compound derived from Elsholtzia, has shown promising effects in RA treatment. Osu can reduce ROS levels, downregulate GPX4 expression, and increase lipid peroxidation, reduce membrane fluidity, and promote osteoclast fusion, effectively alleviating swelling and bone destruction associated with arthritis.[87] Another polyphenolic compound, Amentoflavone (AMF), derived from Selaginella tamariscina, suppresses the proliferation of RA-FLS by inhibiting PIN1-induced ferroptosis.[88] Asiatic acid (AA), derived from Centella asiatica, induces ferroptosis in RA-FLS through the Nrf2/HMOX1 pathway.[89] Anemoside B4, a bioactive component of triterpenoid saponins from Bai Tou Weng, has demonstrated anti-inflammatory and analgesic effects. Research has found that Anemoside B4 can alleviate RA pain by reducing Drp1-mediated mitochondrial dysfunction, and inhibiting neuroinflammation.[90] Icariin (ICA), a promising therapeutic agent for synovitis, has been shown to inhibit ferroptosis in synovial cells by activating the Xc-/GPX4 axis, thereby reducing cell death.[91] In addition, wasp venom (WV) from Vespa magnifica induces ferroptosis in MH7A cells by regulating the GPX4-mediated ferroptosis pathway.[92] Quercetin and emodin have also been identified to effectively control joint inflammation in rats by inhibiting the ferroptosis signaling pathway.[93,94]

In TCM theory, the rational combination of drugs can enhance their synergistic effects, thereby achieving optimal therapeutic outcomes. Based on this principle, TCM compound preparations, formulated according to the principle of "Jun-Chen Zuo-Shi" compatibility, have received widespread attention for their multi-pathway and multi-target therapeutic approaches. For instance, the TCM compound JinWu JianGu capsule (JWJGC) has been shown to reduce ROS and inflammation levels in CIA rats, and its mechanism is related to regulating the SLC7A11/GPX4/GSH signaling pathway to target M1 macrophages, alleviate ferroptosis, and inhibit inflammatory response.[95] Sun et al demonstrated through clinical data mining, cell experiments, and animal experiments that Xinfeng Capsules (XFC) activate the Nrf2/HO-1 pathway, exerting inhibitory effects on RA inflammation and oxidative stress.[96] Wang et al explored the mechanism of the TCM compound Jingfang Granules (JFG) in treating RA from the perspective of the "gut joint" axis. According to their findings,

JFG can activate AMPK by regulating the gut microbiota, which improves fatty acid metabolism disorders.[97] Furthermore, TCM compound preparations have shown significant therapeutic effects in the treatment of RA-associated interstitial lung disease (RA-ILD). For example, the classic TCM formula Simiao Wan (SMW) has been linked to the ferroptosis pathway in the prevention of RA-ILD.[98]

As non-invasive treatments with minimal side effects, acupuncture and moxibustion have demonstrated significant efficacy in alleviating joint pain in RA. However, the specific mechanisms underlying their effects remain unclear. Studies have shown that acupuncture and moxibustion can modulate ferroptosis through multiple targets and pathways. Huo et al found that acupuncture treatment could regulate the levels of propionic acid and butyric acid in rat feces, which in turn affects the expression of GSH. This modulation inhibits ferroptosis in synovial tissue and reduces the inflammatory response in RA.[99] Similarly, moxibustion can reduce the expression level of p53 and serum ROS content in synovial tissue, while increasing the mRNA and protein expression levels of SLC7A11 and GPX4, along with the serum GSH content. These effects contribute to alleviating synovial injury.[100,101]

Overall, traditional herbal medicine, compound therapy, acupuncture, and moxibustion have a long history in the treatment of RA, characterized by holistic regulation, multi-target therapy, and high safety. Given its various biological benefits targeting ferroptosis in RA, it is expected to become a new treatment for RA. However, the mechanism of action of traditional Chinese medicine treatment is complex, lacking standardization and quantitative research, and the efficacy varies from person to person. Further clinical verification is still needed. In the future, modern science and technology can be used to deeply study its mechanism of action, optimize the formula, and improve the efficacy and safety.

Summary and Prospect

Ferroptosis plays an important role in the pathogenesis of RA. By regulating oxidative stress, lipid peroxidation, abnormal proliferation and cartilage erosion of FLSs, immune dysregulation, inflammatory responses, and other pathways, ferroptosis is involved in multiple pathological processes of RA. This provides new therapeutic targets for the treatment of RA. The development of ferroptosis-targeting drugs, along with the integration of TCM diagnostic and therapeutic strategies, plays a key role in regulating ferroptosis and improving the clinical management of RA. Future research should focus on exploring the specific mechanism of ferroptosis in RA, with particular attention to the intervention effects of existing drugs and diagnostic/therapeutic methods targeting ferroptosis-related pathways. Furthermore, exploring more effective ferroptosis-targeting drugs or combination therapies is essential to improving clinical symptoms for RA patients.

Data Sharing Statement

There are no data and no material associated with this manuscript.

Ethics Approval and Consent to Participate

There is no human subject, and this is a review, so there is no need for ethical approval and consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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