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GPX4 ferroptosis, rheumatoid arthritis, lipid peroxidation, biomarkers, iron metabolism, Therapeutics

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Abstract

Rheumatoid arthritis (RA) refers to a chronic autoimmune condition that is typified by chronic inflammation of the synovium, progressive destruction of the joints, and systemic comorbidities. Ferroptosis - an iron-dependent regulated cell death mediated by lipid peroxidation has been studied as an increasing body of evidence in RA pathophysiology over the past few years. Central to the ferroptosis process is the Glutathione peroxidase 4 (GPX4), which helps to balance lipid redox through the depletion of lipid hydroperoxides.GPX4 and related ferroptotic damage dysregulation could also be involved in RA-associated synovial cell death, cartilage degeneration, and inflammatory exaggeration. The synthesis of mechanistic understanding of ferroptosis, a summary of candidate biomarkers (including GPX4 expression and activity, lipid peroxidation products, iron handling proteins, and system Xc- components), and an analysis of therapeutic interventions aimed at ferroptosis (GPX4 modulators, iron chelators, lipid-peroxidation inhibitors, and combined therapeutic strategies) are summarized in this review. We address the problem of translational challenges, such as standardization of biomarkers, tissue specificity, safety of long-term anti-ferroptotic treatment, and suggest a road map towards

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clinical application of this therapeutic approach, including biomarker-assisted patient stratification, and combination therapies with existing disease-modifying antirheumatic drugs (DMARDs). This review aims to make ferroptosis and GPX4-focused biomarkers an attractive innovation in the field of RA diagnostics, prognosis, and treatment.

Keywords:

GPX4 ferroptosis, rheumatoid arthritis, lipid peroxidation, biomarkers, iron metabolism, Therapeutics

1. **Introduction**

Rheumatoid arthritis (RA) is a disease of synovial tissue, cartilage, and bone, whose development is complicated by the interactions between immune cells, resident synoviocytes, and the extracellular matrix. RA has clinical outcomes of pain[1]. stiffness and functional loss. Even though contemporary disease-modifying antirheumatic drugs (DMARDs) [2]. and biologic agents have revolutionized the results of many patients, a significant percentage fail to respond completely, relapse, or have intolerable side effects. To come up with complementary therapeutic strategies, more mechanistic knowledge of tissue-destructive mechanisms is needed. The two tissue destruction and inflammation regulation involve cell death pathways. Although apoptosis and necroptosis have received much emphasis in RA[3]. Ferroptosis has become a non-overlapping, lipid peroxidation-based cell death program with specific biochemical needs for iron-dependent, lipid hydroperoxides, and glutathione (GSH)-GPX4-centered antioxidant defences. Oxidative stress, iron homeostasis, and metabolic rewiring are the features of the synovial microenvironment in RA - circumstances that might promote ferroptotic activities and moderate the progression of the disease[4]. The role played by GPX4 is crucial since it converts phospholipid hydroperoxides into alcohols, which inhibits the occurrence of the fatal lipid peroxidation[5]. GPX4 expression and activity, as well as upstream and downstream factors (e.g., access to cysteine to make GSH, SLC7A11 activity, iron status, and lipoxygenase activity) are candidate biomarkers of ferroptotic vulnerability and ferroptosis[6].

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potential treatment approaches to ferroptosis and comment on the research barriers and future opportunities[7]

2. Ferroptosis: mechanisms and biological significance

DFerroptosis is a controlled type of cell death that is characterized by iron-dependent lipid peroxidation and is morphologically unlike apoptosis or necrosis[8]. Its biochemical characteristics are the accumulation of peroxidized polyunsaturated fatty acids (PUFAs) in membrane phospholipids, loss of lipid peroxide detoxification, and radical generation with the help of iron [9]. Iron metabolism and its role. Iron promotes Fenton chemistry and enzymatic oxidation of lipids by lipoxygenases as an iron catalyst in the production of reactive oxygen species (ROS) [10]. Stored ferritin exported ferroportin, and ferritinophagy (ferroptosis), LIP size, and hence susceptibility to ferroptosis[11]. Lipid peroxidation cascade. The initial stage of lipid peroxidation involves the abstraction of a hydrogen atom of the PUFAs in the membrane phospholipids to create the lipid radicals[12]. which react with oxygen to produce lipid peroxyl radicals and hydroperoxides. Increasing the pool of peroxidizable substrates are enzymes such as ACSL4 and lipoxygenases (LOXs)[13]. which catalyze the incorporation and oxidation of PUFA, respectively[14]. The unlimited generation of lipid hydroperoxides deteriorates the integrity of the membranes and causes ferroptotic death(15). The GPX4-GSH axis is the main cellular defense against lipid peroxidation, having GSH as a cofactor to reduce lipid hydroperoxides to non-reactive lipid alcohols [16]. Synthesis of GSH is determined by the presence of cysteine, which is not only imported through the system Xc- antiporter (SLC7A11/SLC3A2) in exchange for glutamate but also in exchange for galactose. Any of the points of disruption, including reduced cystine import, defective GSH biosynthesis, and lower GPX4 expression/activity, bring cells to ferroptosis. Parallel protecting systems[17]. Other than GPX4, ferroptosis may be inhibited by FSP1 (ferroptosis suppressor protein. which replenishes coenzyme Q10 (CoQ10) and suppresses lipid peroxidation, and by the action of pathways that prevent LIP accumulation or the availability of lipid substrates. The antioxidant responses mediated by NRF2 regulate most of these axes in terms of regulating the expression of the GSH synthesis enzymes, the iron-handling proteins, and the

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detoxifying enzymes[18].

Table1. delineates the principal molecular constituents underpinning ferroptosis, a distinctive iron-dependent regulated cell death modality characterized by unchecked lipid peroxidation.

Component	Function	Role in Ferroptosis	Relevance to RA	Reference
Iron (Fe^{2+})	Redox reactions	Lipid peroxidation initiation	Synovial iron overload	[19]
GPX4	Reduces lipid hydroperoxides	Prevents ferroptosis cell death	Reduced expression/activity	[20]
Glutathione (GSH)	Antioxidant cofactor	Supports GPX4 function	Depleted during inflammation	[21]
SLC7A11	Cystine transport	Maintains GSH synthesis	Dysregulated in RA	[22]

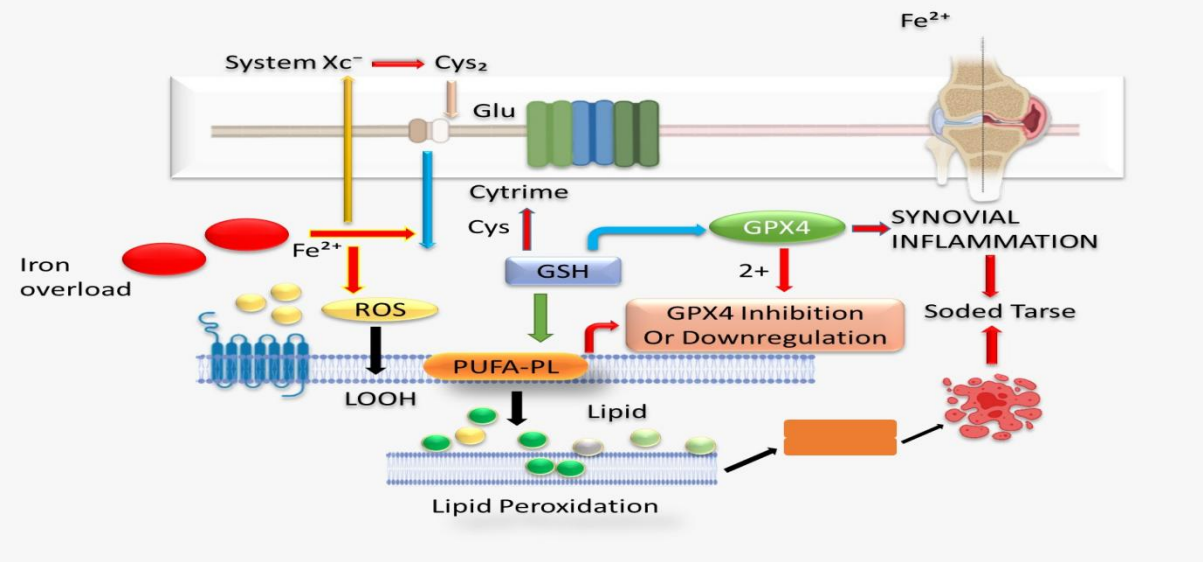

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Figure 1 illustrates the molecular pathway of ferroptosis in rheumatoid arthritis, depicting iron overload and ROS accumulation that deplete GSH via system Xc^−/cysteine inhibition, leading to GPX4 downregulation, PUFA-PL peroxidation, lipid peroxidation, and exacerbated synovial inflammation, positioning GPX4 as a promising therapeutic targetting

3.Therapeutic Strategies targeting GPX4 –regulated ferrosptosis in rheumatoid arthritis (RA)

The GPX4 is a protein that has a selenocysteine residue at the active site that gives it a powerful peroxidase activity[23]. It is the only glutathione peroxidase that selectively oxidizes complex lipid hydroperoxides that are part of membranes. GPX4 is found in cytosolic, mitochondrial, and nuclear forms, and each of them may have a unique ferroptosis sensitivity to different subcellular compartments[24]. GPX4 expression and activity are regulated. The level of GPX4 is regulated transcriptionally, translationally, and post-translational[25]. Selenium has an impact on melanoprotein biosynthesis, whereas oxidative stress and transcription factors (e.g., NRF2) influence the expression of the GPX4 The stability of the GPX4 protein can be altered by post-translational modifications and the proteasomal pathways of degradation[26]. The functional competency of GSH is also indirectly affected by GSH availability, which makes the functional competency of GPX4 depend on the metabolic state of cells. There are implications of the lack of GPX4 The decreased or suppressed activity of GPX4 results in the rapid development of lipid peroxide and ferroptosis[27]. Genetic ablation or drug-inducedinhibition of GPX4 leads to a reversible death of cells, that were demonstrated in experimental models, and which can also be prevented by lipid peroxidation inhibitors or iron chelate. Dysregulated GPX4 in inflammatory tissues, including RA synovium, may favour cnidocyte death and release of the DAMPs (damage-associated molecular patterns), which may raise local inflammation[28].The immune and stromal cells contain GPX4 The functions of GPX4 are not restricted to parenchymal cells. The sensitivity of immune cells to ferroptosis is not uniform, which affects the processes of inflammatory signaling[29]. In particular, depending on the loss of GPX4, some T-cell subsets and macrophage

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phenotypes can vary in their response to the loss or benefit, changing the cytokine milieu and phagocytic activities[30]. Homeostatic regulation of GPX4 could be applied to fibroblast-like cnidocytes (FLS) and infiltrating immune cells in the synovium.

Table 2. delineates therapeutic strategies targeting GPX4-regulated ferroptosis in rheumatoid arthritis, enumerating regulatory factors, their modulatory effects on GPX4, underlying mechanisms, and consequential impacts on disease pathology from impaired defenses to joint damage.

Regulatory Factor	**Effect on GPX4**	**Mechanism**	**Impact in RA**	**Reference**
Selenium	Activation	Selenoprotein synthesis	Impaired antioxidant defense	[31]
GSH availability	Stabilization	Cofactor binding	Oxidative stress susceptibility	[32]
TNF-α / IL-6	Down regulation	Transcriptional suppression	Enhanced ferroptosis	[33]
Iron overload	Functional inhibition	Excess lipid ROS	Joint tissue damage	[34]
NRF2 pathway	Up regulation	Antioxidant gene activation	Protective response	[35]

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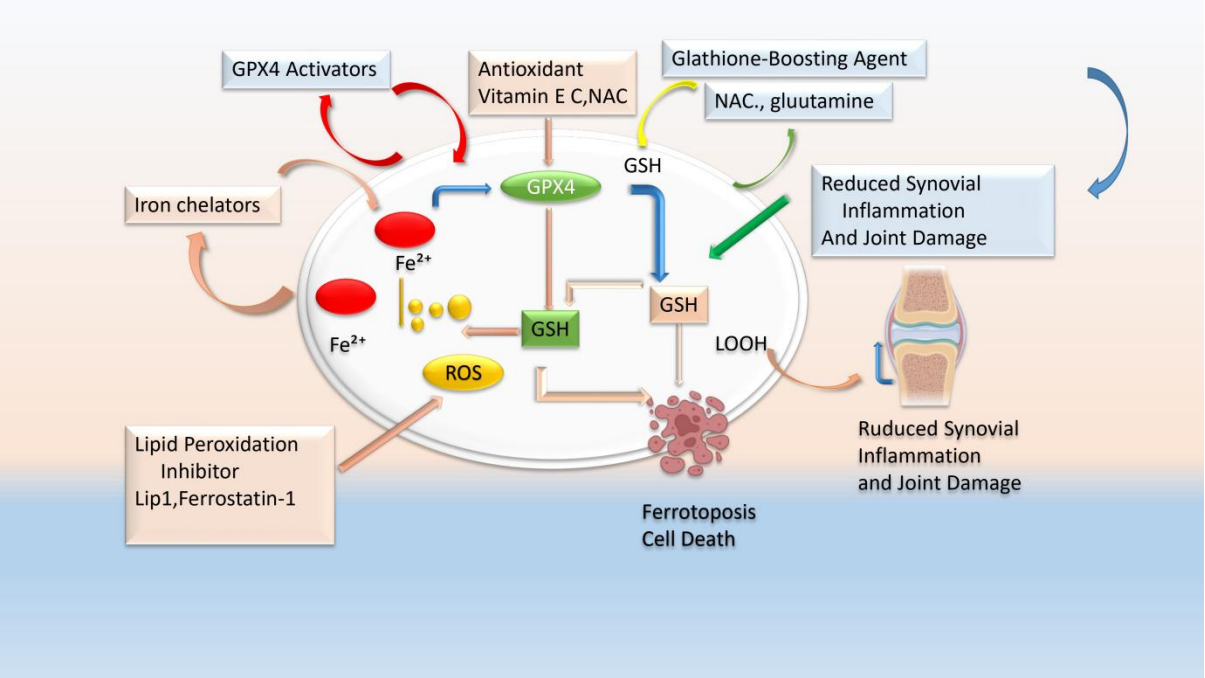

Figure 2. This figure explains how GPX4 helps protect joint cells in rheumatoid arthritis by reducing iron-related oxidative damage. Treatments like antioxidants, iron chelators, and glutathione boosters may help decrease inflammation and joint injury.

4. Evidence for Ferroptosis in rheumatoid arthritis

Microenvironment of the synovium and oxidative stress.RA synovium is featured by increased ROS generation, mitochondrial dysfunction, and oxidative damage indicators. Hypoxia, stimulated immune responses, and infiltrating neutrophils are some of the conditions that promote a pro-oxidative environment that supports lipid peroxidation[36]. These settings lead to the biological plausibility of ferroptosis events. Disordered iron management in RA joints[37]. Clinical data show that in a proportion of patients with RA, there are disturbed systemic and local iron parameters: elevated ferritin, intermittent serum iron, and iron deposition in synovial tissues. Macrophages loaded with iron and changes in the dynamics of ferritin may increase the size of the labile iron pool leading to the oxidation of lipid The lipid peroxidation is indicated by the following molecular markers

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Increased concentrations of lipid peroxidation end-products, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) have been detected in RA serum and synovium They signify continued lipid peroxidation but are not ferroptotic[38]. When used together with iron profiles and GPX4 profiles, they point to a ferroptotic signature. Cellular models and animal investigations. In vitro studies of FLS and chondrocytes indicate that disruptions that lower the levels of GPX4 or cystine expose cells to lipid peroxidation and cell death, which can be reversed in many cases using ferroptosis inhibitors. In vivo studies of inflammatory arthritis have revealed that iron control or antioxidant system control can modify the disease severity and tissue damage, and thus ferroptotic mechanisms are functional. The inflammation crosses with crosstalk. Ferroptosis will be capable of generating pro-inflammatory mediators and DAMPs, which nourish innate immune activation[39]. On the other hand, the action of inflammatory cytokines (e.g., TNF-α, IL-1β) may modify that of antioxidant genes and iron handling in a feedback loop with inflammation and ferroptosis, reinforcing one another[40]. The two-way interaction of ferroptosis as an outcome and cause of synovial pathology is a consequence of this two-way interaction[41].

Table 3. Enumerates ferroptosis-related biomarkers in rheumatoid arthritis, specifying their sample sources, biological roles in lipid peroxidation or iron/antioxidant homeostasis, and clinical utility as indicators of disease progression, activity, severity, inflammation, or therapy response.

Biomarker	**Sample Source**	**Biological Role**	**Clinical Significance**	**Reference**
GPX4	Synovial tissue, serum	Lipid peroxide detoxification	Disease progression marker	[42]
Malondialdehyde (MDA)	Serum, synovial fluid	Lipid peroxidation	Disease activity index	[43]
4-HNE	Plasma, tissue	Oxidative damage	Severity assessment	[44]
Ferritin	Serum	Iron storage	Inflammatory status	[45]
SLC7A11	Synovial tissue	GSH homeostasis	Therapy response prediction	[46]

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5. Ferroptosis biomarkers in RA Applications and candidates

The optimal biomarker of ferroptosis in RA would include markers of the biochemical environment (iron, lipid peroxide) and the condition of protective mechanisms (GPX4 expression/activity, GSH, SLC7A11) and the outcome (cell death, tissue damage)(47). The markers of the candidate and their possible clinical applications are presented below: GPX4 (expression and activity). Rationale. Majorly involved in ferroptotic susceptibility(48). Statistically lowering the level of lipid peroxide detoxification, reduction of the expression or activity is an indicator of ferroptotic vulnerability Sample type Synovial biopsy tissue (immunohistochemistry, western blot), synovial fluid cell, peripheral blood mononuclear cells (PBMCs) as a systemic signalUtility Diagnostic (evidence of ferroptotic predisposition in tissue), prognostic (association with aggressive joint damage), and predictive (response to anti ferroptotic therapy[49]. Hospital-acquired infection Lipid peroxidation products (MDA, 4-HNE, oxidized phospholipids)[50]. Rationale: Direct products of lipid oxidation and proxies of ferroptosis. Types of samples: Synovial fluid, tissue extract, serum/ plasma. Utility: The oxidative burden and therapeutic response monitoring; it is more specific when used together with iron and GPX4 levels. Metabolism of iron (ferritin, saturation of transferrin, labile plasma iron) of serum[51]. uptake of cystine to manufacture GSH; the lowering of its functionality predisposes to ferroptosis. The rationale is that iron availability controls ferroptosis, ferritin indicates storage, and an inflammatory condition. Utility stratifies the patients depending on the risk of ferroptosis, direct iron-targeting therapies (e.g., chelation). System Xc- Components (SLC7A11 expression)[52]. Rationale: Regulates the Types of samples: Tissue or cellular mRNA/protein assays. Utility: Forecasts the reaction to the intervention involving the GPX4 or cysteine supplementation.The antioxidant markers (GSH, NRF2 targets, NADPH, etc.).Reason: This is a reflection of the total redox buffering capacity. Utility is used to assess metabolic contamination to ferroptotic vulnerability or treatment effect.

PUFA metabolism (ACSL4, LOXs) enzymes. Rational. Identify the composition of fatty acids of membranes and the tendency to peroxidation. Utility. Determine patients with a membrane lipid

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profile that predisposes them to ferroptosis and can be treated with lipid-modulatory therapy. Index of ferroptotic cell death.Rationale: Single markers are not specific; a composite index (which includes GPX4, lipid peroxides, LIP, SLC7A11) could be more loyal to ferroptotic activity.Usability.Diagnostic, prognostic, and stratification instruments of clinical trials. Technical and clinical issues: Specificity. Ferroptosis does not have specific oxidative markers. Many of the oxidative markers are also found in other situations, which must be confirmed at the multi-analyte level and tissue level[53]. Accessibility to samples. Synovial biopsy has the best fidelity and is invasive; synovial fluid and peripheral blood are more convenient and less specific. Standardization.Assay harmonization, e.g., validated ELISAs, mass-spec lipidomics, set protocols to measure labile iron, etc. Not only is it critical to reproducibility and clinical translation, but it also implies capatibility across different harmonized assays

Table 4 outlines therapeutic strategies targeting ferroptosis in rheumatoid arthritis, detailing molecular targets, example agents, and rationales for protecting synovial cells, reducing oxidative damage, blocking cell death, restoring redox balance, and enabling cytoprotection.

Strategy	**Molecular Target**	**Example Agents**	**Therapeutic Rationale**	**Reference**
GPX4 activation	Lipid peroxides	Selenium, GPX4 stabilizers	Protect synovial cells	[54]
Iron chelation	Free iron pool	Deferoxamine	Reduce oxidative damage	[55]
Ferroptosis inhibitors	Lipid radicals	Ferrostatin-1	Block cell death	[56]
Antioxidant therapy	ROS	N-acetylcysteine	Restore redox balance	[57]
NRF2 activation	Antioxidant genes	Sulforaphane	Cytoprotection	[58]

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6. Ferroptosis as a therapeutic target in RA

These two conceptual approaches are prevention and induction of ferroptosis in resident joint cells, preventing pathological mechanisms of ferroptosis and pathogenic immune or stromal cells, maintaining inflammation, respectively[59]. The goal of RA is primarily protective, i.e. avoid the excessive ferroptotic tissue damage, but selective induction may apply to some pathogenic cell populations.GPx4 agonists and stabilizers.GPX4 expression or activity should be increased in order to improve lipid hydroperoxide detoxification. Strategies. Small molecules, which increase transcription of GPX4, selenium supplementation to enhance production of selenoproteins (with caution), or agents that promote the enhancement of the stability of GPX4. Considerations: Long-term upregulation can cause changes in the immune cell functionality; it can be necessary to orderly dose and target the tissues.Iron chelationIdea. Lower the amount of labile iron in the pool to provide restriction on Fenton chemistry and lipid peroxidation Agents. Deferoxamine, deferiprone, or new nano chelator systems, which attack the synovium[60]. Evidence and considerations: Chelators have the potential to decrease oxidative damage, but have the risk of causing systemic iron overload and anemia. Local delivery of the chelator to the joint could decrease systemic toxicity[61]. Radical-trapping antioxidants (radical-trapping inhibitors, RTAs) inhibit lipid peroxidation in lipid peroxides by acting as trappers of a radical, thereby preventing overproduction of lipid peroxy radicals and the ensuing development of lipid peroxy radicals (LOO)[62]. Mechanism: Ferrostatin-1 and liproxstatin-1, and other RTAs are molecules that bind lipid radicals and inhibit damage to membranes.Indication: To help in the protection of cartilage and synovocytes during flares in the form of adjuvant treatment.Challenges: Bioavailability, Tissue penetration, and long-term safety should be assessed. Regulation of Xc- / cystine metabolism in the system.Idea: Improve the intake of cystine or increase the synthesis of GSH to provide the GPX4 cofactor.Intervention. N-acetylcysteine (NAC) or cysteine prodrugs, which are SLC7A11 modulators.Risks. Systemic impacts on the immune system; moreover, in a few cancer cases, the elevated density of cysteine could be harmful. Targeting lipid metabolism. Idea: Decrease the addition of PUFAs into the membrane or prevent the enzyme ACSL4/LOX to decrease peroxidizable substrates.Strategies: Nutritional adjustment of fatty acid content,

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lipoxygenase/ACSL4 inhibitors, or lipid pathway pharmacologic reprogramming in synovial cells. Natural products and reformulated drugs.Available as a candidacy: Polyphenols (quercetin, resveratrol), curcumin, and other antioxidants with anti-lipid peroxidation effects.Rationale: Easily accessible, and not necessarily dangerous; possible to use in conjunction with DMARD. Limitations: Changeable potency and bioavailability; require a stringent clinical trial.Combinations with the available treatment of RA.Rationale.Ferroptosis modulators may be used together with DMARDs, anti-TNF, anti-IL-6, or JAK inhibitors with additive/synergistic effects, e.g., tissue damage could be minimized, and inflammation could be managed. Note: Trial design is biomarker-guided to ensure that there is a greater likelihood of showing benefit in targeted subpopulations. Safety and monitoring. Any anti-ferroptotic approach cannot be unbalanced to potential risks, including disrupting immune cell turnover, immune host defense, metabolic imbalances, and iron homeostasis[63]. In trials, it will be necessary to monitor biomarkers (GPX4, LIP, lipid peroxides) to evaluate on-target effects and safety[64]. Clinical and recent (overview and translational status) research. Note: In this narrative review, I provide a summary of trends that are found in preclinical and translational studies. To obtain accurate study-level data, it may be suggested to use a targeted literature search and add references.

7. Clinical evidence and recent research (overview & translational status)

Preclinical models. Inflammatory arthritis animal models that are subjected to iron chelators or antioxidants have less joint swelling and lower tissue destruction indicators. In vitro simulations of FLS and chondrocytes that have been altered to decrease the amount of GPX4 or cysteine show enhanced lipid peroxidation and cell death - usually reversible with the use of ferroptosis inhibitors. Human tissue studies. Synovial tissue and fluid studies of RA patients demonstrate increased oxidative stress markers and protein changes in iron handling in most cohorts, with some studies also demonstrating a reduction in antioxidant enzyme activity. It has been inconsistently reported that GPX4 expression is down-regulated in harmed or inflamed tissues in small cohorts; these need to be standardized and larger. Stratification using the biomarkers [50]. There is some preliminary susceptibility to translate these findings that suggests patients with greater levels of

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lipid peroxidation markers and distorted iron profiles may be associated with more aggressive disease phenotypes or worse structural results. There needs to be prospective validation. Clinical trialling and therapeutic development. Up to date (summary), there are preclinical stages of direct GPX4 modulators(68). Other areas of exploratory clinical application of iron chelation and antioxidant interventions have been reported, though randomized trials have been limited with a specific focus on ferroptosis as a therapeutic intervention in RA. Early-phase trials (biomarker**.** driven) with a test of ferroptosis-modulating strategies exert their safety and efficacy in RA are an opportunity.Difficulties, weaknesses, and prospective directions [52].

Table 5. summarizes key ferroptosis studies in RA from 2020–2025, categorizing study types, models/systems, principal findings, and clinical implications from target validation to biomarker and therapeutic potential.

Study Type	**Model/System**	**Key Findings**	**Implication**	**References**
In-vitro	RA synovial fibroblasts	GPX4 suppression induces ferroptosis	Target validation	[52]
Animal model	Collagen-induced arthritis	Iron chelation reduces joint damage	Therapeutic potential	[53]
Clinical	RA patient serum	Elevated lipid peroxidation markers	Biomarker utility	[54]
Translational	Human synovium	Reduced GPX4 expression	Severity correlation	[55]

8. Challenges, gaps, and future directions

Standardization of biomarkers. Standardization is necessary for biomarkers used to detect or serve as predictors of disease. Standardized assays and agreement on the markers that constitute the activity of ferroptosis in RA are urgently required.It is recommended to perform comparative studies that will compare combinations of markers of GPX4, lipid peroxides, LIP, and system Xc-

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in tissue and blood compartments. Tissue specificity/systematic measure. The synovial biopsies are invasive and have high specificity. It would be helpful to develop validated surrogate blood markers that can indicate synovial ferroptosis so that they can be widely used in the clinic Safety and unintended consequence. Regulation of ferroptosis can affect immune subsets in varied ways that can compromise host protection or affect immune regulation. It requires long-term data regarding safety, risk of carcinogenesis, and metabolic effects. Patient stratification and personalized medicine. All of the RA patients will respond equally. Biomarker panels had the potential to define subpopulations with ferroptosis-based pathology and would be the most likely to respond to a specific intervention. Delivery and targeting plans. Intra-articular (local) systems of delivering chelators or RTAs can be most effective in the protection of the joint, as well as in reducing the systemic exposure. The targeting and prodrug strategies of nanoparticles should be considered. Combinatorial trial design. The clinical trials of the future should incorporate ferroptosis markers as inclusion criteria and endpoints, as well as test combinations with immunomodulatory agents to assess additive improvements on symptoms and structural progression.

10. Conclusion

Ferroptosis and its master regulator GPX4 are a very promising, mechanistically based axis of RA pathophysiology.Candidate biomarkers include GPX4 expression and activity, lipid peroxidation products, iron parameters, and system Xc- components, which offer a pattern of diagnosing ferroptotic activity, stratification of patients, and response to treatment. The involvement of therapeutic approaches that maintain the activity of GPX4, reduce the labile iron, or eliminate lipid radicals is promising in their ability to prevent the damage of tissues in the joints associated with ferroptosis. The standardized biomarkers, strict preclinical to clinical pathways, and well-planned trials with an appropriate balance between efficacy and safety will be the keys to success in translation. Through these endeavors, the focus on ferroptosis would be beneficial to use along with the current anti-inflammatory treatment options and aid in filling the gap in RA management.

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