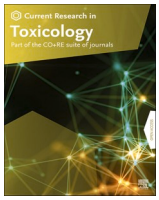
Current Research in Toxicology 7 (2024) 100181

Contents lists available at ScienceDirect

Current Research in Toxicology

journal homepage: www.journals.elsevier.com/current-research-in-toxicology



Research Paper

Ferroptosis as an emerging target in sickle cell disease

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ARTICLE INFO

Keywords:
Sickle cell disease
Iron toxicity
Ferroptosis
Oxidative stress
Lipid peroxidation
Novel targets

ABSTRACT

Sickle cell disease (SCD) is an inherited hemoglobin disorder marked by red blood cell sickling, resulting in severe anemia, painful episodes, extensive organ damage, and shortened life expectancy. In SCD, increased iron levels can trigger ferroptosis, a specific type of cell death characterized by reactive oxygen species (ROS) and lipid peroxide accumulation, leading to damage and organ impairments. The intricate interplay between iron, ferroptosis, inflammation, and oxidative stress in SCD underscores the necessity of thoroughly understanding these processes for the development of innovative therapeutic strategies. This review highlights the importance of balancing the complex interactions among various factors and exploitation of the knowledge in developing novel therapeutics for this devastating disease.

1. Introduction

Iron-mediated ferroptosis, an oxidative cell death characterized by lipid peroxide accumulation, is emerging as a pivotal factor in pathophysiology of many diseases related to iron overload, including Sickle Cell Disease (SCD). Despite advances in the field, the interplay between iron, lipid peroxides, and ferroptosis remains to be fully elucidated. This cell death pathway is inherently linked to cellular

Abbreviations: AD, Alzheimer's disease; ALI, Acute lung injury; ALOX5, Arachidonate 5-Lipoxygenase; ALOX12, Arachidonate 12-Lipoxygenase; ALOX15, Arachidonate 15-Lipoxygenase; ALS, Amyotrophic lateral sclerosis; AIFM2, Apoptosis-inducing factor mitochondria-associated 2; BACH1, BTB Domain and CNC homolog 1; BH4, Tetrahydrobiopterin; BMP, Bone morphogenetic protein; CDA, Congenital dyserythropoietic anemia; CIRI, Cardiac ischemia–reperfusion injury; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; $CO_3^{\bullet-}$, Carbonate radical; CoQ10, Coenzyme Q10; CRC, Colorectal cancer; CYB5R1, Cytochrome b5 reductase 1; DAMPs, Damage-associated molecular patterns; DFO, Deferoxamine; DFO-TDDS, Deferoxamine transdermal delivery system; ERFE, Erythroferrone; FLVCR2, FLVCR choline and putative heme transporter 2; FPP, farnesyl pyrophosphate; FSP1, ferroptosis suppressor protein 1; GC, Gastric cancer; GCH1, GTP cyclohydrolase 1; GPX4, Glutathione peroxidase 4; GSDMD, Gasdermin D; GSH, glutathione; GSSG, glutathione disulfide; HbA, Hemoglobin A; HbF, Fetal hemoglobin; $HbFe^{3+}$, Methemoglobin; HD, Huntington's disease; HbS, Hemoglobin S; $HbFe^{4+}$, Ferrylhemoglobin; HF, Heart failure; HMOX1, heme oxygenase 1; HMOX2, heme oxygenase 2; HMGB1, High mobility group box 1; HNE, 4-Hydroxy-2-nonenal; H_2O_2, Hydrogen peroxide; $HO^{\bullet}$, Hydroxyl radical; HU, Hydroxyurea; IPP, Isopentenyl-pyrophosphate; IRI, Ischemia-reperfusion injury; LIP, Labile iron pool; LIC, Liver iron concentration; L2HG, L-2-hydroxyglutarate; LPOx, Lipid peroxides; LOX, Lipoxygenase; MDA, Malondialdehyde; MRI, Magnetic resonance imaging; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; NAS, Non-alcoholic steatohepatitis; NET, Neutrophil extracellular traps; NF-κB, Nuclear factor kappa B subunit 1; NLRP3, NLR family pyrin domain containing 3; $NO^{\bullet}$, nitric oxide; $NO_2^{\bullet}$, nitrogen dioxide; NOX1, NADPH oxidase 1; NRF2, Nuclear factor erythroid 2-related factor 2; NTBI, Non-transferrin-bound iron; $O_2^{\bullet-}$, Superoxide; $ONOO^-$, Peroxynitrite; PADI4, Peptidyl arginine deiminase 4; PC, Pancreatic cancer; PD, Parkinson's disease; POR, Cytochrome P450 oxidoreductase; PUFAs, polyunsaturated fatty acids; RBCs, red blood cells; RMC, renal medullary carcinoma; ROS, reactive oxygen species; RTAs, radical-trapping antioxidants; SCA, Sickle Cell Anemia; SCD, Sickle cell disease; SLC3A2, Solute carrier family 3 member 2; SLC4A1, Solute carrier family 4 member 1; SLC7A11, Solute carrier family 7 member 11 (also known as xCT); SLC11A2, Solute carrier family 11 member 2; SLC48A1, Solute carrier family 48 member 1; SMAD1, SMAD family member 1; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; SOD1, Superoxide dismutase-1; TCA, tricarboxylic acid cycle; TF, transferrin; TFR1, Transferrin receptor 1; TXN, thioredoxin; TXNRD1, Thioredoxin reductase 1; SQUID, Superconducting quantum interference device; XO, xanthine oxidase.

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https://doi.org/10.1016/j.crtox.2024.100181
Received 30 December 2023; Received in revised form 13 June 2024; Accepted 17 June 2024
Available online 18 June 2024

metabolism and the perturbation of redox homeostasis, with implications for various hematological disorders including SCD. In SCD, recurrent blood transfusions often precipitate secondary iron overload, exacerbating oxidative stress through enhanced reactive oxygen species (ROS) and lipid peroxide generation, mechanisms central to ferroptosis induction. Moreover, the aberrant hemoglobin polymerization in SCD can lead to persistent hemolysis and episodic vaso-occlusive crises, further underscoring the toxicological significance of iron and its potential to disrupt oxidative balance. This review delineates the contribution of iron-driven ferroptosis to SCD pathology. By integrating previous findings with recent discoveries, we exploit the potential of targeting ferroptotic pathways for innovative therapeutic approaches in mitigating the burden of SCD and related hematological diseases.

2. Sickle cell disease

SCD is a significant global health concern, with approximately 100,000 cases in the United States and over 7.7 million worldwide (Kato et al., 2018). The incidence of SCD is stable in the USA but is increasing globally, particularly in regions such as sub-Saharan Africa, the Middle East, India, and the Caribbean (Thomson et al., 2023). Projections estimate over 400,000 newborns with Sickle Cell Anemia (SCA) annually by 2050 (Piel et al., 2017). SCD, an autosomal recessive blood disorder, results from a mutation (dbSNP Rs334(T)) in the β-globin gene, leading to the sickling of red blood cells (RBCs). This genetic change, causing a substitution of glutamic acid with valine, triggers the formation of rigid, elongated hemoglobin S (HbS) polymers under low oxygen conditions (Ingram, 1957).

The complex pathophysiology of SCD includes chronic inflammation, oxidative stress, and vaso-occlusion, leading to diverse clinical outcomes. Symptoms include painful crises, progressive organ damage (e.g., osteonecrosis, nephropathy, pulmonary disease, retinopathy), heightened risk of complications such as pulmonary hypertension, renal dysfunction, and stroke. Genetic factors like fetal hemoglobin (HbF) gene expression and α-thalassemia presence influence these clinical variations (Gladwin et al., 2004; Conran and Embury, 2021). Curiously, however, SCD might offer protection against HIV-1 infection by activating a complex protein network in response to hemolysis, hypoxia and interferon signaling (Nekhai and Kumari, 2022). Recent studies have also illuminated the detrimental role of iron overload and ferroptosis in SCD progression, impacting vital organs such as the heart, skin, kidneys, liver, lungs, and brain, as well as the coagulation system. This highlights the necessity of exploring these pathways for possible therapeutic interventions (Rodrigues et al., 2018; Hebbel et al., 2020; Menon et al., 2022; Salama et al., 2022; Hopp et al., 2023; Vokshi et al., 2023).

3. Iron homeostasis

Approximately 80 % of the body's iron is found in erythrocyte hemoglobin, with the remainder stored in macrophages, hepatocytes, or in other heme groups and iron-sulfur clusters. Iron is crucial for many biological functions, including oxygen transport and enzyme catalysis. Its ability to alternate between ferric (Fe^{3+}) and ferrous (Fe^{2+}) states, while essential, also generates ROS, potentially leading to cell damage and ferroptosis. The labile iron pool (LIP), mainly composed of Fe^{2}, is particularly active in redox reactions and can induce cell death through the Haber–Weiss and Fenton reactions (see below) necessitating strict regulation of its levels (Dutt et al., 2022).

On a daily bases, the human body produces roughly 200 billion RBCs, requiring substantial amounts of hemoglobin (about 6 g) and iron (about 20 mg). This necessitates a delicate balance between iron supply for erythropoiesis and iron processing by tissue macrophages, hepatocytes, and duodenal epithelial cells to maintain iron homeostasis. Macrophages, especially those in the spleen, bone marrow, and liver, are instrumental in recycling a significant portion of the body's iron for RBC production. This recycling, along with dietary iron absorption, caters to the body's iron needs, with hepatic iron reserves acting as an additional buffer (Theurl et al., 2016).

Regulation of iron absorption is crucial due to the absence of a regulated iron excretion pathway, with the body losing about 1–2 mg of iron daily through gastrointestinal shedding (Hsu et al., 2022). Erythroid cells demand significant iron quantities, primarily sourced through transferrin (TF)-mediated transport. Iron absorbed by duodenal enterocytes binds to plasma transferrin for its transport, minimizing free radical production. This process involves strict regulation of transferrin saturation to prevent iron overload. Iron enters developing RBCs via the transferrin receptor 1 (TFR1) through clathrin-dependent endocytosis and is released within endosomes, transported into the cytoplasm by divalent metal transporter SLC11A2 (Solute carrier family 11 member 2), illustrating the complexity and precision of cellular iron management (Dutt et al., 2022).

Iron is primarily stored in hepatocytes and macrophages as ferritin and, to a lesser extent, as hemosiderin in splenic macrophages. However, iron overload, a risk factor for conditions like liver damage and neurodegeneration, arises when transferrin saturation leads to non-transferrin-bound iron (NTBI) in serum (Silva and Rangel, 2022). Consequently, excessive intracellular iron, derived from ferritin degradation (ferritinophagy) and its returning to the cytosolic labile iron pool (LIP), can exceed storage capacities. This escalation significantly increases the risk of oxidative stress, ferroptosis, and toxicity, highlighting the delicate balance required in iron metabolism (Liu et al., 2022a; Kontoghiorghes, 2023).

Macrophages are central to iron metabolism, managing iron release and uptake in various forms, including transferrin-bound, heme-bound, and hemoglobin-associated iron. They are instrumental in extravascular hemolysis, primarily occurring in the spleen, and to a lesser extent in the liver and bone marrow, through a process called erythrophagocytosis. This involves engulfing aged or damaged RBCs to prevent the release of inflammatory agents (Sesti-Costa et al., 2023). During erythrophagocytosis, Solute Carrier Family 48 member 1 (SLC48A1) facilitates translocation of heme across membrane into the cytosol to be catabolized by heme oxygenases, producing biliverdin, carbon monoxide, and labile iron. Notably, HMOX1, an inducible isozyme, is upregulated by hemoglobin/heme and serves as a protective feedback mechanism against cellular stress, whereas HMOX2 is constitutively expressed. The resultant iron is then stored in ferritin, bound to poly (rC)-binding proteins, or exported from the cell, underscoring the complexity of iron regulation within macrophages (Galy et al., 2023).

Iron export from macrophages is meticulously regulated by ferroportin-1, whose activity is controlled by hepcidin, the primary systemic iron regulator produced by liver hepatocytes. Hepcidin manages iron flow, impacting ferroportin's activity and thus influencing systemic iron homeostasis (Nemeth et al., 2004). Its synthesis in the liver is regulated by intracellular iron levels and oxygen availability, involving the nuclear factor erythroid 2-related factor 2 (NRF2)/sMAF/IREs pathway (Galy et al., 2023). NRF2 activation modulates hepcidin synthesis through bone morphogenetic protein (BMP) 2/6 and the SMAD1/5/8 signaling pathway. The proper functioning of this regulatory system is crucial for preventing iron overload conditions like hereditary hemochromatosis or iron-restricted anemia in chronic inflammation, accentuating the importance of this regulatory mechanism in managing iron-related disorders (Li et al., 2023a).

4. Iron in SCD

In SCD, the occurrence of iron overload, though infrequent, can occur due to chronic transfusion regimens or increased intestinal iron absorption caused by reduced hepcidin levels. Hepcidin reduction may occur as a result of erythroid hyperplasia in the bone marrow. While non-transfused SCD patients usually do not exhibit iron overload, mouse models of SCD have demonstrated spontaneous development of iron accumulation, secondary to chronic hemolysis. Hemolysis increases the

body's iron demand for erythropoiesis, leading to enhanced intestinal iron absorption and subsequent accumulation of iron (Das and Shah, 2023).

In SCD, altered RBC morphology and fragility lead to increased hemolysis and cell turnover, which manifests as decreased hemoglobin, hematocrit, and RBC count (Paulson et al., 2020). Despite elevated bone marrow activity indicated by high reticulocyte counts, standard RBC indices like mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) are not reliable indicators of iron homeostasis due to their variability. This variability is influenced by disease severity, complications, chronic inflammation, and treatments with medications such as hydroxyurea (Kato et al., 2017).

Iron balance in SCD is complex, with challenges arising from disease pathology and blood transfusions. Non-transfused patients rarely have storage iron levels exceeding 2000 mg, similar to healthy individuals, but iron deficiency anemia still affects about 9 % of SCD patients (Koduri, 2003). Conversely, 25–35 % of SCD patients may develop iron overload due to frequent transfusions (Darbari et al., 2006; Porter and Garbowski, 2013; Shah et al., 2022). Intravascular hemolysis causes the release of RBC contents into the bloodstream, elevating labile iron levels. This increase can lead to urinary iron losses, potentially resulting in iron deficiency, with iron loss primarily occurring through urinary and biliary excretion. Elevated urinary iron is common in SCD patients, especially during hemolytic crises, where iron levels are similar to those obtained via transfusions (Porter and Garbowski, 2013; Patel et al.,2023). Non-transfused patients often have abnormally low hepcidin levels, leading to increased iron absorption which can be exacerbated by suppressed ferroportin activity (Girelli and Busti, 2020; Mangaonkar et al., 2020). The intricate iron homeostasis in SCD is further complicated by the presence of substantial iron deposits in tissues that do not contribute to erythropoiesis and may not be reflected in serum ferritin levels (Koduri, 2003; Castro and Kato, 2015). This complexity requires extra attention in maintaining iron homeostasis in SCD.

Iron homeostasis in SCD is impacted by both increased natural RBC breakdown and altered iron metabolism. In SCD, the rate of iron recycling by macrophages is higher due to enhanced RBC destruction (Theurl et al., 2016). Following the lysis of old erythrocytes, macrophages release iron, some of which is retained, while the rest is exported to plasma. Notably, macrophages in SCD adopt a unique anti-inflammatory phenotype in response to hemolytic RBCs, distinct from classic M1/M2 polarization (Pfefferlé et al., 2020), characterized by M1-like markers and enhanced heme iron uptake (Sesti-Costa et al., 2023). It is to be noted that M1 designation refers to inhibition of cell proliferation leading to tissue damage, while M2 refers to promotion of cell proliferation and tissue repair (Mills, 2012; Yunna et al., 2020).

Iron overload in SCD is not only a consequence of chronic transfusions but can also arise from disturbances in iron metabolism, similar to other inflammatory diseases with increase demand in erythropoiesis. This condition leads to an imbalance in hepcidin production relative to iron load. During acute systemic immune activation, increased IL6 and IL-1b levels, and elevated hepcidin levels hinder iron export and reduce intestinal iron absorption, contributing to erythrophagocytosis and anemia (Weiss et al., 2019). On the other hand, chronic inflammation suppresses hepcidin as a compensatory response to reduced RBC count and tissue hypoxia, resulting in iron overload, a scenario reminiscent of stable SCD cases with low hepcidin levels (Kearney et al., 2007; Elbostany et al., 2023).

In SCD, erythroferrone (ERFE) plays a crucial role by inhibiting hepcidin synthesis and enhancing iron availability for erythropoiesis (Karafin et al., 2015; Coffey et al., 2022). ERFE inhibits hepcidin synthesis by strongly binding to bone morphogenetic protein 6 (BMP6) via its N-terminal domain, creating a ligand trap and disrupting the BMP/SMAD signaling pathway (Wang et al., 2020; Mast et al., 2023). Chronic overproduction of ERFE in mouse models caused systemic iron overload, increased plasma iron concentrations and hepatic tissue iron stores (Coffey et al., 2022). Recent findings indicate ERFE's levels in SCD patients corresponds to the bone marrow's response to anemia, and might serve as a therapeutic target, particularly for those with iron overload (Girelli and Busti, 2020; Mangaonkar et al., 2020).

Transfusional iron overload may also lead to iron deposition in other tissues such as heart, liver and pancreas causing cellular toxicity and organ damage (van Beers et al., 2015; Wood, 2017). Therefore, identifying reliable and noninvasive biomarkers for iron overload is crucial. While serum ferritin estimation is commonly used to assess body iron stores, its reliability can be compromised by inflammation or tissue damage (Porter and Garbowski, 2013; Shah et al., 2022). Liver iron concentration (LIC), which closely correlates with total body iron, can be measured through liver biopsy or noninvasive methods like biomagnetometry or superconducting quantum interference device (SQUID) (Kontoghiorghes, 2023), which can be also applied to spleen (Bruzzese et al., 2023). However, these methods, while effective in quantifying hepatic iron overload, do not evaluate liver inflammation or fibrosis (Wood, 2023). Magnetic Resonance Imaging (MRI) on the other hand, offers a non-invasive approach to assess the three-dimensional distribution of excess iron in the body.

The assessment of cardiac iron overload is controversial, primarily due to the risks associated with myocardial biopsy. Malondialdehyde (MDA), a byproduct of lipid peroxidation, has been suggested as a sensitive marker for assessing oxidative stress and iron overload in transfusion-dependent SCD patients (Elbostany et al., 2023), offering a less invasive and potentially more accurate monitoring method. Regular monitoring of ferritin levels and MRI assessments are recommended for SCD patients, with adjustments to chelation therapy being made based on the initial severity of the iron overload, thus aiding in the management of sustained iron burden (Shah et al., 2022; Patel et al., 2023).

5. Ferroptosis

Ferroptosis, a distinct form of non-apoptotic cell death marked by iron-driven peroxidation of polyunsaturated fatty acids (PUFAs) in cell membranes, was first identified by Stockwell and colleagues (Dixon et al., 2012; Stockwell, 2022). It involves an iron-dependent sequence that causes degradation of cellular membranes and oxidative damage to crucial cell components (Su et al., 2019).

The ferroptosis process is intimately linked to cellular metabolism and the disruption of redox balance due to the synthesis and activation of PUFAs and culminating in lipid peroxidation. It is triggered by various agents, including pharmacological compounds, natural substances, and intrinsic proteins, through mechanisms such as trapping free radicals in lipid membranes and enhancing iron levels (Scarpellini et al., 2023).

Characterized by specific morphological and biochemical shifts, particularly within mitochondria, ferroptosis manifests as mitochondrial shrinkage, reduced cristae, and ruptured outer membranes. These changes lead to decrease membrane potential and increase permeability. However, mitochondrial involvement in ferroptosis is considered indirect and secondary, whereas lipid peroxidation, initiated at various cellular locations via different pathways is considered the primary factor in ferroptosis (Chen et al., 2021a; Pope and Dixon, 2023). This process escalates rapidly, resulting in ion fluxes and culminating in plasma membrane permeabilization (Hirata et al., 2023). The accumulation of lipid peroxides and their by-products, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), induces cellular changes including rounding, swelling, and rupture. These occur alongside chromatin condensation within a still-intact nucleus, signifying ferroptosis's concluding phase.

From a biochemical point of view, ferroptosis is defined by three main characteristics: accumulation of iron, increased lipid peroxidation, and an impaired system for scavenging lipid peroxides. Membrane lipids are susceptible to peroxidation both under normal and stress conditions, a process that can be spontaneous or driven by enzymes such as NADPH

oxidase 1 (NOX1), cytochrome P450 reductase (POR), NADH-cytochrome b5 reductase (CYB5R1), and lipoxygenases (Stockwell et al., 2017). This peroxidation process selectively affects polyunsaturated fatty acids (PUFAs) like arachidonic acid (AA, 20:4), which are particularly prone to oxidation due to their bisallylic hydrogens. In contrast, fatty acids with a single bisallylic group, such as linoleic acid, are less susceptible (Möller et al., 2022). Other membrane components like sphingolipids and cholesterol are also vulnerable to peroxidation, leading to various derivatives including lipid hydroperoxides, alcohols, and aldehydes, formed through both enzymatic and non-enzymatic pathways.

Lipid peroxidation in cell membranes starts when reactive oxygen species (ROS) remove a hydrogen atom from a PUFA, creating a carbon-centered radical. This radical undergoes molecular rearrangement for stabilization, leading to further hydrogen extraction from neighboring lipids, thereby propagating a chain reaction of lipid hydroperoxide formation. Concurrently, these lipid peroxides react with ferrous iron (Fe^{2+}), forming peroxyl radicals that perpetuate the lipid peroxidation process by stripping hydrogen atoms from more acyl chains in the lipid membrane, exacerbating the damage (Forcina and Dixon, 2019; Ursini and Maiorino, 2020).

The mechanism of ferroptosis indicates its critical role in the development of a broad spectrum of diseases, encompassing neurodegenerative, cardiovascular, metabolic, autoimmune, and hematologic disorders (Carvalho et al., 2024; and see below). Its involvement in ischemia/reperfusion injury and its capacity to suppress tumor growth by inhibiting cell proliferation makes it a promising target for new therapeutic strategies (Jiang et al., 2021). Advancing our understanding of ferroptosis's molecular mechanisms and regulator pathways opens up new avenues for therapeutic interventions across diverse medical conditions, including hemoglobinopathies such as SCD (Scarpellini et al., 2023).

5.1. Ferroptosis regulators

5.1.1. Glutathione peroxidase 4 (GPX4) pathway

Lipid peroxidation is regulated by the selenoenzyme glutathione peroxidase 4 (GPX4), which transforms lipid hydroperoxides in phospholipid acyl chains into lipid alcohols, concurrently oxidizing reduced GSH to glutathione disulfide (GSSG) (Forcina and Dixon, 2019; Pope and Dixon, 2023). Central to preventing ferroptosis, the GPX system, particularly GPX4, operates in synergy with GSH and the Xc^- system, maintaining cellular antioxidant defenses. Furthermore, the Xc^- system, a glutamate-cystine antiporter, functions by transporting cystine into the cell and exporting glutamate at a 1:1 ratio. This system, which belongs to the heterodimeric amino acid transport family, is extensively distributed across cell membranes. The Xc^- system consists of two subunits: the light chain SLC7A11, which facilitates amino acid exchange, and the heavy chain SLC3A2, serving as a chaperone, both connected by a disulfide bridge (Xie et al., 2016,2023). Consequently, pharmacological inhibition of GPX4 (e.g., by RSL3, FIN56) or depletion of GSH (e.g., by erastin) triggers rampant lipid peroxidation, leading to the accumulation of reactive lipid aldehydes, disruption of the cell membrane, and ferroptotic cell death (Kwon et al., 2015).

GPX4, present in various cellular compartments including the nucleus, cytosol, and mitochondria, is integral to the cellular defense against oxidative stress. Its activity is tightly linked to cysteine availability for GSH synthesis (Xie et al., 2023). Among the GPX family, GPX4 is uniquely capable of neutralizing hydroperoxides, thus safeguarding cells from oxidative damage and preserving redox equilibrium. Moreover, the critical role of the Xc^- system in supplying cystine for GSH production underscores its importance in bolstering GPX4's antioxidant capacity. This, coupled with selenocysteine's presence in GPX4, significantly enhances the enzyme's efficiency in warding off peroxidation. (Pei et al., 2023). Note, cysteine is a nonpolar amino acid containing a thiol (-SH) functional group, whereas cystine refers to a dimeric amino acid composed of cysteine molecules connected by a disulfide (-S-S-) bond.

Despite GPX4's capacity to mitigate lipid hydroperoxides and reduce the toxicity of H_2O_2, ferroptosis can arise from under expression or inhibition of GPX4 by specific agents, disturbing redox homeostasis. This highlights the complex interplay between biological ROS and membrane phospholipids, which can culminate in toxic lipid hydroperoxide accumulation, membrane damage, and cell death (Seibt et al., 2019). Remarkably. the pathway involving the Xc^- system and GPX4 not only emphasizes the enzyme's antioxidant function but also illustrates the delicate balance maintained within cells to prevent oxidative stress-induced ferroptosis, offering insights into potential therapeutic strategies to modulate this intricate process.

5.1.2. Ferroptosis suppressor protein 1/CoQ10 pathway

Research into ferroptosis has unveiled the ferroptosis suppressor protein 1 (FSP1)/CoQ10 pathway as an essential regulator of this cell death modality (Bersuker et al., 2019). Significantly, FSP1, a member of the NAD(P)H:quinone oxidoreductase (NDH-2) family, encoded by the gene AIFM2, utilizes NAD(P)H to produce ubiquinone, also known as coenzyme Q10. While ubiquinone is known for its role in the mitochondrial respiratory chain, its reduced form, ubiquinol, has been of growing interest due to its ability to trap lipid peroxyl radicals and mitigate lipid peroxidation (Doll et al., 2019). FSP1 does not only recycle CoQ10 (ubiquinone) using NAD(P)H, but is also involved in the conversion of vitamin K and α-tocopheryl radicals back to their reduced forms, thus playing a key role in prevention of lipid peroxidation (Conrad et al., 2018; Kuang et al., 2020). Importantly, the FSP1/CoQ10 pathway provides insights into how non-mitochondrial components contribute to cellular antioxidative defenses. The localization of FSP1 to the plasma membrane, where it interacts with CoQ10, situates this pathway at a critical juncture between the cell's internal and external environments, allowing it to efficiently counteract lipid peroxyl radicals generated at the membrane level (Santoro, 2020).

In scenarios where GPX4 levels are insufficient to prevent ferroptosis, FSP1 emerges as a capable regulator of this process, even in the absence of GPX4 activity. This has been shown in cells lacking GPX4 and in cells treated with 4-chlorobenzoic acid, an inhibitor of CoQ10 biosynthesis (Bersuker et al., 2019). Additionally, the GTP cyclohydrolase 1 (GCH1) pathway, along with its product tetrahydrobiopterin (BH4), supports the formation of reduced CoQ10, thereby influencing lipid peroxidation (Kraft et al., 2020). Similar to FSP1/CoQ10, this pathway operates independently of GSH, presenting as an alternative mechanism to inhibit ferroptosis and maintain cellular integrity (Douglas et al., 2015; Larbalestier et al., 2022). Moreover, the dihydroorotate dehydrogenase (DHODH) pathway enhances the CoQ10 pathway and by working in synergy with GPX4, transforms ubiquinone into ubiquinol, hence maintaining a pivotal role in preventing ferroptosis at the mitochondrial inner membrane. This action offers a targeted strategy for cancer therapy through induction of ferroptosis, highlighting DHODH's crucial contribution to ferroptosis defense alongside GPX4 and FSP1 (Mao et al., 2021). Hence, the redundancy and complementarity among these pathways suggest that cells can deploy multiple defenses against ferroptosis, depending on the specific context and stimulus.

5.1.3. The mevalonate pathway

The mevalonate pathway plays a crucial role in regulating ferroptosis by producing biomolecules such as squalene, coenzyme Q10 (CoQ10), farnesyl pyrophosphate (FPP), and isopentenyl pyrophosphate (IPP). These compounds are essential for the synthesis of selenium (Se)-enriched proteins. Selenium, a key trace element found in antioxidant enzymes like GPXs and thioredoxin reductase 1 (TXNRD1), is essential for maintaining cellular redox balance under oxidative stress (Ursini and Maiorino, 2020). Changes in this pathway can impact the synthesis of selenoproteins, including GPX4, which is pivotal in preventing

ferroptosis. Recent studies highlight the significance of other selenoproteins, such as TXNRD1, selenoprotein K, and thioredoxin (TXN), in the regulation of ferroptosis (Zheng et al., 2021).

Simultaneously, membrane lipids are shielded from oxidation by the combined effects of α-tocopherol and ascorbate. α-Tocopherol interrupts the lipid peroxidation chain reaction by forming a tocopheroxyl radical with lipid intermediates. This radical is then converted back to α-tocopherol by ascorbate, generating dehydroascorbate in the process. Dehydroascorbate is restored to ascorbate by glutaredoxin (Grx) and GSH, concluding the cycle with glutathione peroxidase and GSH reducing lipid hydroperoxides to alcohols, thus preventing the generation of damaging alkoxyl radicals. This mechanism, alongside pathways such as FSP1/CoQ10/Se and GSH-GPX4, collectively plays a role in reducing phospholipid peroxidation and ferroptosis, thereby bolstering the cell's defenses against oxidative stress (Xie et al., 2016; Fang et al., 2023).

The regulation of the mevalonate pathway itself presents another layer of complexity in the context of ferroptosis. Enzymes such as HMG-CoA reductase, which catalyzes the rate-limiting step of the pathway, are subject to regulation by feedback mechanisms and pharmacological inhibitors like statins. Statins, widely used to lower cholesterol levels, can inadvertently affect the synthesis of selenoproteins and CoQ10, thereby influencing the cell's susceptibility to ferroptosis under certain conditions (Moosmann and Behl, 2004; Caso et al., 2007). This potential side effect highlights the need for a comprehensive understanding of the mevalonate pathway's regulation and its implications for ferroptosis and cell health.

5.2. Ferroptosis in human diseases

Recent advances in the study of ferroptosis have revealed its significant impact on numerous human diseases, illustrating a complex duality in its physiological function. Ferroptosis's critical role in maintaining long-term viral immunity as well as and its vital contribution to hematopoiesis have been well documented (Wortmann et al., 2013; Altamura et al., 2020; Hu et al., 2021; Yamane et al., 2022).

Importantly, the fundamental mechanisms of ferroptosis have become crucial in cancer immunotherapy. This strategy aims to activate immune cells to fight cancer, rather than directly targeting tumors. Most notably, T lymphocytes, especially CD8+ T cells, by releasing cytokines that suppress the expression of certain solute carriers, promote lipid peroxidation and induce ferroptosis during cancer immunotherapy (Wang et al., 2019; Lei et al., 2022).

In the context of aging, ferroptosis may be associated with clearing away damaged cells, but there's a delicate balance to be struck to prevent the loss of healthy cells (Jenkins et al., 2020). Achieving this balance is essential in preventing many diseases, particularly those due to the disruption of the GPX4 enzyme (Patanè et al., 2023). Such disruption leaves a wide range of cells and tissues —including neurons, photoreceptors, kidney tubular cells, hepatocytes, endothelial cells, hematopoietic cells, and T cells — susceptible to ferroptosis.

In cancer, where specific types characterized by iron accumulation, ferroptosis emerges as a potent tumor suppressor, notably against RAS mutant cancers (Stockwell, 2022). In this context, ferroptosis can also boost the effectiveness of conventional chemotherapy agents such as temozolomide and cisplatin, presenting a novel approach for tackling drug-resistant and/or aggressive cancers (Stockwell et al., 2017). Ferroptosis has also been linked to improved outcomes in radiotherapy, highlighting its potential in inducing cancer cell death through mechanisms distinct from apoptosis (Chen et al., 2021b; Lei et al., 2022). Roles of ferroptosis, however, extend well beyond cancer and ischemic injuries, affecting neurodegenerative, cardiovascular, renal, pulmonary,

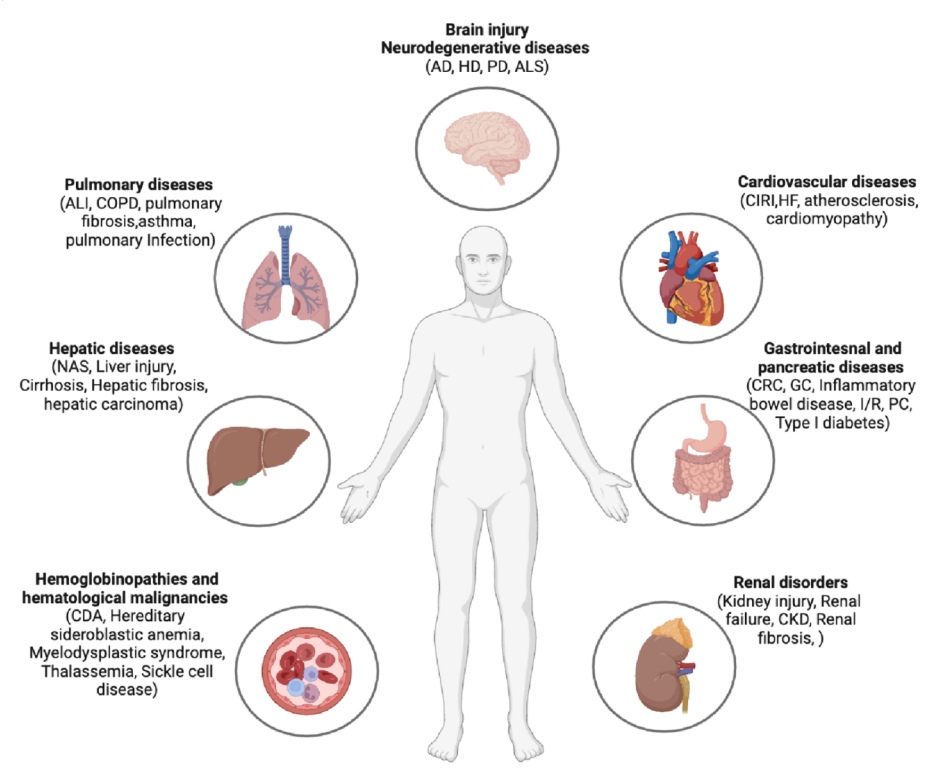

Fig. 1. Ferroptosis plays a role in a range of diseases impacting multiple systems, highlighting its extensive pathophysiological implications. Ferroptosis initiates disorders across various physiological systems, including the nervous, digestive, respiratory, circulatory, urinary, and immune systems. AD, Alzheimer's disease; ALI, Acute lung injury; ALS, Amyotrophic lateral sclerosis; CDA, Congenital dyserythropoietic anemia; CIRI, Cardiac ischemia–reperfusion injury; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; CRC, Colorectal cancer; GC, Gastric cancer; HD, Huntington's disease; HF, Heart failure; I/R, intestinal ischemia–reperfusion injury; NAS, Non-alcoholic steatohepatitis; PC, Pancreatic cancer; PD, Parkinson's disease;

hepatic, endocrine, metabolic, iron-overload, orthopedic, and autoimmune diseases, underscoring its widespread impact on human health (Fig. 1) (Wang et al., 2019; Jiang et al., 2021). Across these diseases, ferroptosis-targeting treatments, including iron chelators and inhibitors of lipid peroxidation, show promise in reducing symptoms and slowing disease progression (Wang et al., 2023a). The essential role of lipid peroxides in immunity and inflammation, central to these diseases, highlights the need to determine whether the primary pathophysiological mechanisms in these conditions are governed by modulation of inflammation, ferroptosis, or an interplay of both (Jiang et al., 2021; Wang et al., 2023a).

The significance of iron-dependent accumulation of lipid peroxides and its association with numerous hemoglobinopathies and anemias characterized by disrupted iron homeostasis and ferroptosis is gaining recognition (Stockwell et al., 2017; Wang et al., 2017; Fang et al., 2023). This association is evident in inherited anemias and ineffective erythropoiesis such as beta thalassemia (Lin et al., 2024), congenital dyserythropoietic anemia, hereditary sideroblastic anemia, and anemia in acquired conditions such as myelodysplastic syndrome (Cazzola, 2022).

In β-thalassemia, the condition manifests through ineffective erythropoiesis leading to the premature destruction of erythroid precursor cells and a decreased lifespan of mature erythrocytes, inducing hemolytic anemia. This situation is exacerbated by increased iron release from reticuloendothelial cells and enhanced intestinal iron absorption, leading to iron overload and subsequent ferroptosis (Manolova et al., 2019; Kontoghiorghes, 2023). While ferroptosis has recently been recognized as a key contributor to anemia in thalassemia (Lin et al., 2024), its role in the hemoglobinopathy SCD is still emerging (Stockwell, 2022).

6. Ferroptosis and SCD

Although research into the impact of ferroptosis on the pathogenesis of SCD is still in the early stages, emerging evidence suggests that iron-dependent cell death plays an essential role in exacerbating the clinical outcomes of SCD. One of the first connections between SCD and ferroptosis was established through the observation that renal medullary carcinoma (RMC), an aggressive form of cancer, disproportionately impacts young adults and adolescents with SCD hemoglobinopathy (Msaouel et al., 2018). This connection is largely attributed to the unique pathophysiological conditions in SCD, particularly the release of iron from lysed sickled RBCs, which supports ferroptosis in renal medullary cells (Friedmann Angeli et al., 2014; Belavgeni et al., 2020). The extreme hypoxic and hypertonic environment of the renal medulla, exacerbated by regional ischemia from RBC sickle micro-occlusions, triggers DNA repair mechanisms leading to deletions and translocations in the SMARCB1 gene (Jia et al., 2019; Tourigny et al., 2022). These genetic alterations increase oncogenic activity and confer ferroptosis resistance to pre-tumor cells, aiding their survival under conditions of hypoxia and hypertonicity (Soeung et al., 2023).

Recent genomic, metabolic, and single-cell RNA sequencing studies reveal that RMC cells in SCD patients with SMARCB1 mutations demonstrate significant resistance to ferroptosis and proteotoxic stress, a survival mechanism linked to MYC-induced proliferation and activation of NFE2L2-related ferroptosis defense pathways. These factors collectively enhance oncogenic resistance to both ferroptosis and proteotoxic stress in RMC cells. Furthermore, the survival of ferroptosis-resistant RMC in SCD patients is notably influenced by the abundance of extracellular labile iron, a byproduct of hemolysis, which acts as a selective pressure in an oncogenic environment facilitated by mutagenic events (Vokshi et al., 2023). Paradoxically, the inherent basal rate of ferroptosis in SCD may confer resistance to conditions typically susceptible to cancer, such as chronic leg ulcers, although the exact mechanisms behind this remain to be fully elucidated (Feng et al., 2022; Dick et al., 2023).

7. Ferroptosis and oxidative stress in SCD

In individuals with SCD, reactive oxygen species (ROS) emerge from various sources, leading to an accumulation of lipid peroxides (LPOx) that adds to the disease's complexity (Fig. 2). Significantly, ferroptosis exacerbate oxidative stress in SCD, leading to increased cellular damage (Fig. 2).

RBCs, while primarily responsible for oxygen transport, inadvertently generate superoxide radicals through the autoxidation of hemoglobin. This autoxidation results in superoxide ($O_2^{\bullet -}$) and methemoglobin ($HbFe^{+3}$), necessitating the control of oxidative damage. The occurrence of ferroptosis in RBC, due to heightened iron and lipid peroxidation, could amplify this damage (Kozlova et al., 2023).

Interestingly, RBCs are equipped with robust antioxidant systems designed to neutralize ROS such as $O_2^{\bullet -}$, hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$). These systems effectively prevent the formation of more harmful oxidants like the hydroxyl radical ($HO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), and carbonate radical ($CO_3^{\bullet -}$). However, ferroptosis poses a challenge by promoting the formation of these harmful oxidants, which compromises hemoglobin functionality and RBC integrity (Fujii et al., 2021).

The antioxidant defense system in RBCs is comprehensive, encompassing low molecular weight molecules like reduced GSH, ascorbate, urate, and α-tocopherol, as well as enzymes such as peroxiredoxin-2 (Prx2), superoxide dismutase-1 (SOD-1), and catalase. This system relies on NADPH from glucose-6-phosphate and the pentose phosphate pathway, crucial for maintaining redox balance (Möller et al., 2022). Ferroptosis disrupts this delicate balance by overwhelming the antioxidant capacity of RBCs (Chen et al., 2022; Orrico et al., 2023).

Within RBCs, Prx2 serves as the primary defense against hydrogen peroxide, while catalase acts as a secondary line of defense when Prx2 is depleted. GPx1 plays a minor role due to its lower abundance, in contrast to GPx4, which is critical for protecting lipid membranes from oxidative damage induced by ferroptosis (Chen et al., 2022; Orrico et al., 2023). The combined action of these antioxidants, including α-tocopherol, GPH, and ascorbate, helps mitigate lipid peroxidation and maintain membrane integrity (Möller et al., 2022). Therefore, the balance between ROS generation and antioxidant mechanisms determines the impact of oxidative stress in SCD, with ferroptosis significantly influencing this equilibrium.

7.1. Hemoglobin s (HbS) autoxidation

Hemoglobin S (HbS) autoxidizes faster than Hemoglobin A (HbA) (Jana et al., 2018), leading to faster generation of superoxide ($O_2^{\bullet -}$) and other oxidation products like methemoglobin ($HbFe^{+3}$) and ferrylhemoglobin ($HbFe^{+4}$). This process is accelerated in partially deoxygenated conditions, which also promote HbS instability and polymerization. In sickle RBCs, the SOD-1enzyme converts superoxide into H_2O_2 and oxygen. Elevated iron levels catalyze the conversion of H_2O_2 into $HO^{\bullet}$ through Fenton ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + HO^{\bullet} + OH^-$) and Haber–Weiss ($O_2^- + H_2O_2 \rightarrow HO^{\bullet} + OH^- + O_2$) reactions, causing membrane damage. Ferroptosis further aggravates this process by enhancing lipid peroxidation. The elevated levels of hemoglobin oxidation intermediates lead to the formation of lipid hydroperoxides (Kassa et al., 2015; Wilson and Reeder, 2022), which interact with RBC membrane proteins (i.e., Band 3 of Solute Carrier Family 4 Member 1, SLC4A1) and trigger membrane alterations (Voskou et al., 2015; Jana et al., 2018). These changes induce band 3 clustering and its dissociation from the membrane/cytoskeleton complex, undermining the RBC membrane's integrity and potentially initiating microparticle formation (Orrico et al., 2023). As a result, these modifications render the RBCs more fragile, enhance hemolysis and microparticle production, and amplify oxidative damage to the vascular system (Möller et al., 2022). In the context of SCD, ferroptosis significantly heightens the oxidative stress and cell death burden, further complicating the disease's impact on patients.

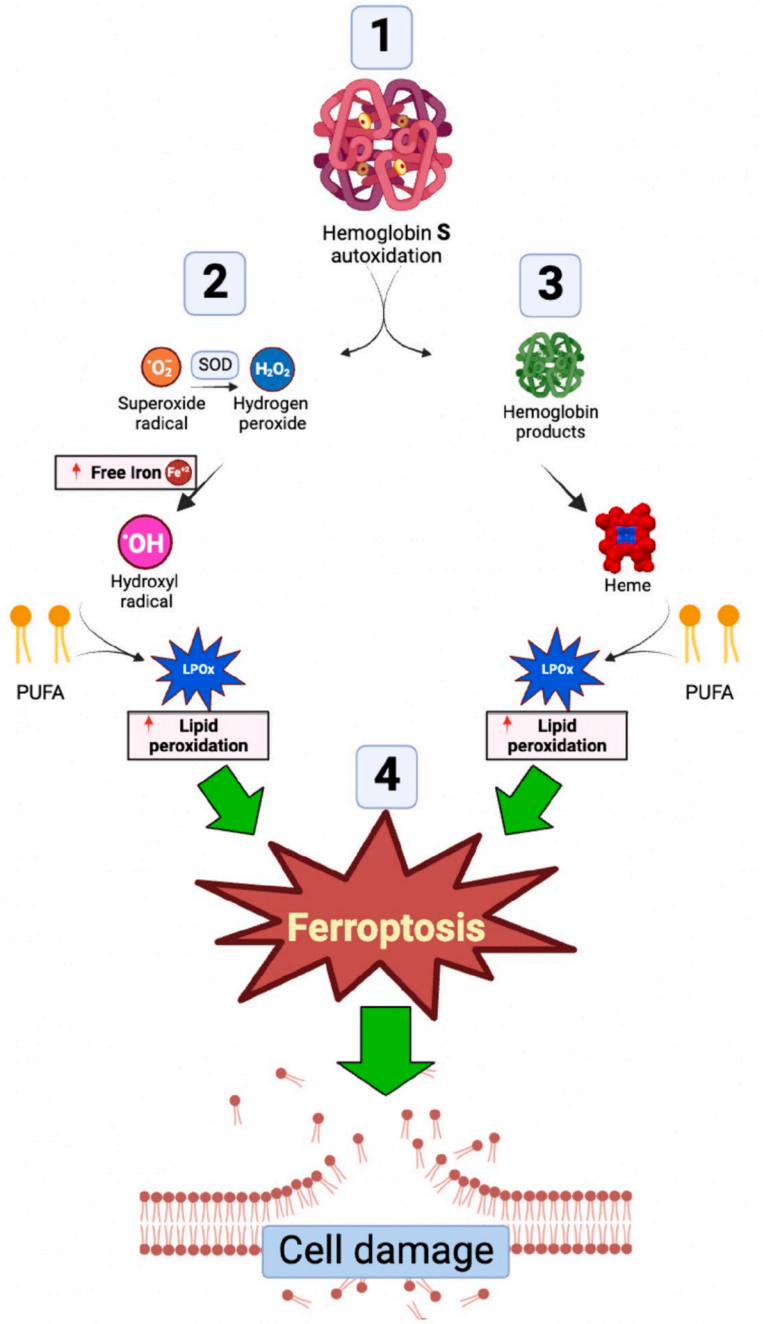

Fig. 2. Ferroptosis and Lipid Peroxidation Induced by Hemoglobin S Autoxidation in Sickle Cell Disease. (1) Hemoglobin S (HbS) in sickle cell disease (SCD) is subject to autoxidation due to frequent oxygenation and deoxygenation cycles that promote polymerization. This autoxidation yields hydrogen peroxide (H_2O_2), methemoglobin (MetHb), free heme, and iron, all of which are implicated in the oxidative stress characteristic of red blood cells (RBCs) in SCD. (2) The presence of ferrous iron (Fe^{2+}) enables H_2O_2 to produce hydroxyl radicals (HO•) via Fenton /Haber–Weiss reaction, which are highly reactive and can induce lipid peroxidation by attacking PUFAs. This lipid peroxidation, a hallmark of ferroptosis, leads to the production of lipid peroxides, disrupting cellular function and triggering iron-dependent cell death. (3) Additionally, hemoglobin oxidized products and free heme contribute to this oxidative process by further attacking PUFAs. They also exhibit an affinity for the cytoplasmic domain of band 3 proteins on the RBC membrane, inducing oxidation and clustering. These processes impair the proteasome system and result in the accumulation of protein aggregates and lipid peroxidation by-products, exacerbating ferroptotic pathways. (4) Ultimately, this leads to a compromise in membrane integrity and permeability, causing hemolysis and subsequent release of RBC contents into circulation, which manifest as SCD symptoms and further potentiate ferroptotic cell death. LPOxs: lipid peroxides; PUFA: polyunsaturated fatty acids; RBC: red blood cell; SOD: superoxide dismutase.

7.2. Reduced antioxidant protection

SCD is marked by an increased pro-oxidant status in both tissues and RBCs, leading to weakened antioxidant defenses. This decline is demonstrated by decreased levels of antioxidants such as vitamins A and E, reduced GSH, ascorbic acid, selenium, zinc, and reduced activity of enzymes like superoxide dismutase and catalase (Antwi-Boasiako et al., 2019,2020; Dosunmu-Ogunbi et al., 2019; Nemati et al., 2019; Delesderrier et al., 2020). Additionally, the recycling of peroxiredoxin-2 (Prx-2), a key antioxidant protein, is significantly slower in sickle RBC, compromising its effectiveness against oxidative stress (Oh et al., 2022).

Consequently, the weakened antioxidant defenses in SCD pave the way for the production of hydroxyl radicals, triggering lipid

peroxidation in PUFAs. This leads to a cascade of reactions that escalate lipid peroxidation in cell membranes, culminating in cell death (Kozlova et al., 2018; van Dam and Dansen, 2020; Kozlova et al., 2023). The lipid peroxidation induced by reduced antioxidants compromises the integrity of the RBC membranes, resulting in altered cell morphology and function, with the eventual consequence of intense hemolytic events in SCD (Vona et al., 2021; Aninagyei et al., 2022;).

Interestingly, this process bears similarities to the formation of lipid pores seen in necroptosis and pyroptosis, suggesting a potential parallel (Kayagaki et al., 2015). Hence, ferroptosis in SCD emerges as a pivotal mechanism that exacerbates lipid peroxidation and cell death, further weakening the already impaired antioxidant defenses. This highlights the crucial role of ferroptosis in aggravating the oxidative stress landscape in SCD, underscoring the need for targeted therapeutic strategies to bolster antioxidant capacity and mitigate lipid peroxidation.

7.3. Increased mitochondrial retention

In SCD, there is a notable increase in mitochondrial retention within both reticulocytes and mature RBCs, which is closely associated with diminished activity of the selenoprotein GPX4, essential for regulating ferroptosis (Ouled-Haddou et al., 2020; Esperti et al., 2023). This abnormal mitochondrial retention contributes to elevated oxidative stress (Jagadeeswaran et al., 2017; Gallivan et al., 2023) and alters oxygen consumption, thereby exacerbating the polymerization of hemoglobin S (HbS), compromising the integrity of the cell membrane, and promoting hemolysis. The exact relationship between mitochondrial metabolism and the increased fragility of sickle RBC membranes due to lipid peroxidation is complex and not fully elucidated. Recently, a mitochondrial-dependent form of non-canonical ferroptosis induced by labile iron was described (Li et al., 2023b). This ferroptosis may involve the generation of specific lipid peroxidation precursors, possibly linked to intermediates of the tricarboxylic acid (TCA) cycle. These intermediatory metabolites which are involved in lipogenesis, can increase mitochondrial permeability resulting in Ca^{2+} influx and worsen lipid peroxidation-induced cell death (Gao et al., 2019). This, combined with the observed reduction in antioxidant defense in SCD (Morris et al., 2008), as well as decreased GPX4 activity in hemolytic and non-nucleated RBCs underscore the significant role of ROS in cellular damage and death (Ouled-Haddou et al., 2020; Stolwijk et al., 2021).

In sum, RBCs in SCD are exceptionally vulnerable to oxidative damage due to compromised antioxidant defenses and abnormal mitochondrial retention, which escalates ferroptosis. This disturbance not only upsets the redox equilibrium but also undermines the integrity and

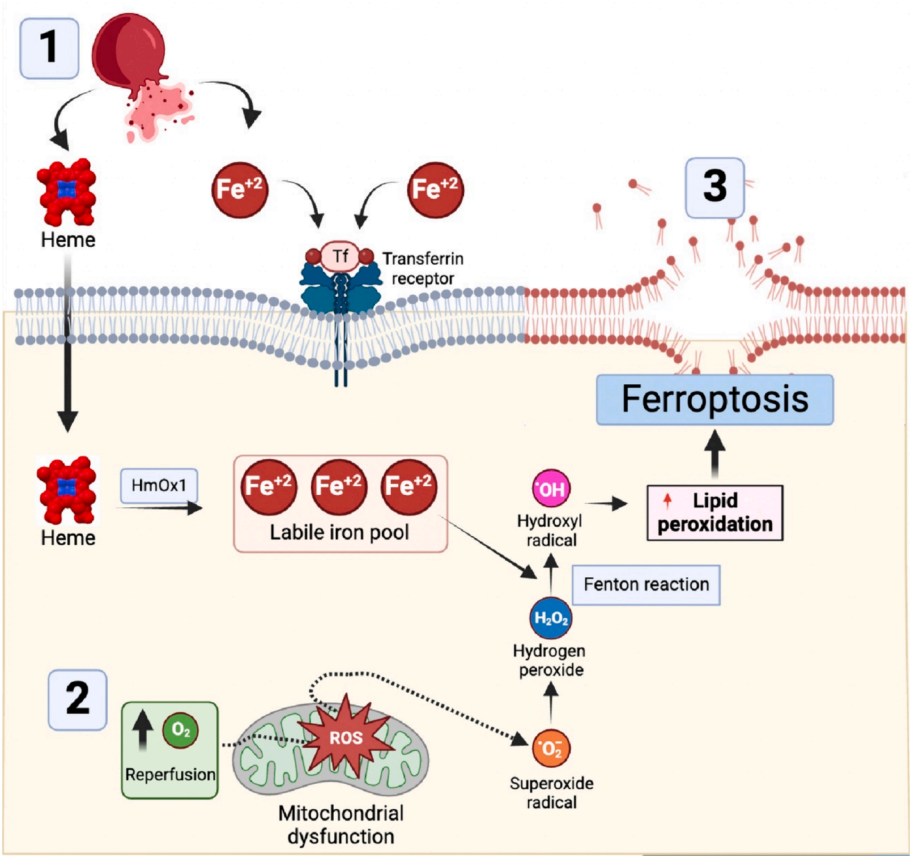

Fig. 3. Proposed mechanism of Ferroptosis mediated cell death during hemolysis and ischemia–reperfusion injury in Sickle Cell Disease (SCD). Ferroptosis in SCD results from iron-induced accumulation of lipid peroxides and increased ROS levels. (1) In SCD, excessive hemolysis saturates hemopexin's capacity, leading to heme uptake (ex., SLC48A1, FLVCR2, and aged RBC endocytosis), and upregulating HMOX1. The resultant HMOX1 catabolism liberates iron, increasing the labile iron pool, and precipitating lipid peroxidation via Fenton /Haber–Weiss reactions. Transfer of Fe^{2+} into cells can be mediated by transferrin receptor or divalent metal transporter 1 (SLC11A2) (2) Ischemia-Reperfusion and Oxidative Burst: Ischemic conditions force mitochondria into anaerobic metabolism, reducing ATP production and causing tissue acidosis. Upon reperfusion, the rapid reintroduction of oxygen generates an oxidative burst predominantly from the mitochondrial respiratory chain and NADPH oxidase 1, leading to lipid peroxidation and an increase in intracellular iron levels, which further drive lipid oxidation through the Fenton reaction. The activity of uncoupled nitric oxide synthase, cytochrome P450, and lipoxygenase within the endothelium also boost the formation of highly reactive hydroxyl radicals. (3) Ferroptosis Induction: The hydroxyl radicals thus formed exacerbate lipid peroxidation, significantly impairing cellular membranes. The intracellular iron acts as a catalyst in this process, aggravating the lipid peroxidation and culminating in ferroptosis, a distinctive iron-dependent form of cell death characterized by compromised membrane integrity, which is particularly detrimental in the context of SCD and ischemia–reperfusion injury. HMOX1: Heme oxygenase 1; LPOxs: Lipid peroxides; ROS: Reactive oxygen species; Tf: Transferrin.

functionality of cell membranes, leading to increased hemolysis and exacerbating the clinical challenges associated with SCD.

8. Ferroptosis – Vaso-occlusion and hemolysis in SCD

Hemolysis in SCD is triggered by the fragility of sickle RBCs and the polymerization of hemoglobin, releasing free hemoglobin, heme, and iron. This release leads to an overload of heme and iron (Reiter et al., 2002). Intravascular hemolysis, accounting for about one-third of SCD-related hemolysis, along with extravascular hemolysis in organs like the spleen and liver (Kato et al., 2017), initiates the production of uncoupled nitric oxide ($NO^{\bullet}$) and ROS formation via Fenton and Haber–Weiss reactions. Consequently, this process exacerbates inflammation and overwhelms antioxidant defense mechanisms, contributing to lipid peroxide accumulation and increasing oxidative stress and cell death (Fig. 3) (Fibach and Rachmilewitz, 2008; Nagababu et al., 2008; Rifkind et al., 2015; Voskou et al., 2015; Fujii et al., 2021; Gbotosho et al., 2021; Vinchi et al., 2021).

Ferroptosis plays a crucial role in exacerbating these conditions by promoting platelet activation and death through lipid peroxidation. This mechanism, dependent on divalent iron, further amplifies platelet aggregation, thromboxane formation, and fibrinogen binding. Thus, ferroptosis not only contributes to cellular damage but also plays a critical role in blood clotting processes, potentially affecting vascular complications in SCD (NaveenKumar et al., 2018, 2019; Conran and De Paula, 2020).

Additionally, oxidative modifications in sickle RBCs, caused by oxidants like nitric oxide ($NO^{\bullet}$) and $ONOO^{-}$ released during hemolysis, lead to further complications including vaso-occlusion, renal damage, and continued hemolysis (Nader et al., 2020; Jutant et al., 2021; Wang and Zennadi, 2021; Aboderin et al., 2023).

Ischemia-reperfusion injury (IRI) in SCD, marked by tissue damage after the restoration of blood flow to ischemic tissues, exacerbates this scenario, leading to further cellular death and oxidative stress (Ansari and Gavins, 2019; Hebbel et al., 2020; Khaibullina et al., 2021) (Fig. 3). During reperfusion, a burst of ROS from the mitochondrial respiratory chain and NOX1 aggravates IRI (Hebbel et al., 2020).The conversion of xanthine dehydrogenase to xanthine oxidase (XO) generates superoxide and hydroxyl radicals, contributing to ROS formation (MacKinney et al., 2019; DeVallance et al., 2023). XO-mediated degradation of oxyhemoglobin releases hemin and iron, triggering additional ROS formation (Schmidt et al., 2021, 2023). These, combined with the effects of ferroptosis-induced lipid peroxidation and the release of free iron, lead to hemolysis and the release of pro-inflammatory molecules such as TNF and IL-1β (Ansari and Gavins, 2019), further intensifying inflammatory responses in the endothelium and white blood cells of SCD patients (Möller et al., 2022).

8.1. Ferroptosis during ischemia/reperfusion injury in SCD

In SCD, recent discoveries highlight the critical role of ferroptosis in exacerbating tissue damage. Elevated levels of lipid peroxides and their metabolites, such as 4-HNEs and MDAs are consistently found across various tissues, particularly during IRI and iron overload situations (Hebbel et al., 2020). These accumulations are marked by increased protein oxidation, oxidant species, and lipid peroxidation products, especially in the kidney, liver, brain and lungs, indicating ferroptosis's significant role in SCD tissue damage (Kaul and Hebbel, 2000; Ajibola et al., 2019; Park et al., 2019; Antwi-Boasiako et al., 2020; Hebbel et al., 2020; Engwa et al., 2021).

Studies have shown that ferroptosis contributes to IRI in various organs, both in SCD and non-SCD patients, and that inhibiting ferroptosis may mitigate IRI (Yan et al., 2020; Chen et al., 2021c). Furthermore, ferroptosis-induced inflammation plays a critical role in lesion expansion within organs (Linkermann et al., 2013; Zhang et al., 2016).

In mouse models of SCD, an increase in blood heme levels and a decrease in hemopexin lead to higher free heme in cardiomyocytes. This triggers the activity of HMOX1, inducing ferroptosis and impairing heart function and cardiac contractility (Chattipakorn, 2022; Menon et al., 2022) (Fig. 3). Moreover, xanthine oxidase (XO) activity further contributes to this scenario by releasing free iron and promoting lipid peroxidation. (Schmidt et al., 2021, 2023). This is mirrored in conditions like thalassemia and hereditary hemochromatosis (Wang et al., 2017; Ginwalla et al., 2018; Sumneang et al., 2020; Fujikura et al., 2022; Wood, 2023), as well as in myocardial infarction, reperfusion injuries, and heart failure (Fang et al., 2023; Wang et al., 2023a), highlighting a pattern of cardiac iron toxicity.

This overactivity of pro-oxidation processes, coupled with weakened antioxidant defenses, underlies the pathophysiology of cardiac manifestations in SCD (Yu et al., 2021; Li et al., 2022; Wang et al., 2022). Elevated oxidative stress, mitochondrial iron overload, and dysregulation of the BACH1/HMOX1 axis contribute to ferroptosis. The involvement of GPX4 and the BACH1/ HMOX1 pathway in ferroptotic cell death may offer therapeutic targets, such as overexpressing SLC7A11 in cardiac cells to increase GSH levels and protect against ferroptosis in SCD (Chen et al., 2023a; Wang et al., 2023a).

HMOX1, a cytoprotective enzyme crucial for cardiovascular health, plays a complex role in SCD. It generates carbon monoxide and biliverdin, offering anti-inflammatory and anti-cell death benefits (Belcher et al., 2018; Gbotosho et al., 2021). However, HMOX1 overexpression can lead to iron (Fe^{2+}) buildup, causing ROS generation, lipid peroxidation, and ferroptosis (Kwon et al., 2015; Liu et al., 2023a). While HMOX1 mitigates ischemia–reperfusion and vascular injuries in SCD, it can also contribute to cardiac toxicity due to iron accumulation, as seen in SCD and beta-thalassemia (Garcia-Santos et al., 2018; Menon et al., 2022). Therefore, HMOX1's impact in SCD is context-dependent, necessitating a novel therapeutic approach to address its complex role in SCD toxicology.

8.2. Ferroptosis and iron in SCD

SCD is intricately associated with secondary iron overload, a condition that arises both from the disease's inherent pathology and the frequent blood transfusions that form a cornerstone of its management (Pirenne et al., 2021; Arthur and Stowell, 2023). This excess iron catalyzes lipid peroxidation by enhancing the activity of lipoxygenases and NADPH oxidase1 (NOX1) and promoting ROS production through the Haber–Weiss and Fenton reactions, contributing to cellular damage in SCD.

Rodrigues et al. (2018) explored the role of iron in the pathophysiology of sickle cell leg ulcers (SCLUs), a common complication of SCD (Rodrigues et al., 2018). Their research identified cutaneous free iron as a key factor in SCLU pathology. They demonstrated that deferoxamine (DFO), an iron chelator administered through a Transdermal Delivery System (DFO-TDDS), effectively improved wound healing in a murine model. This improvement was attributed to the chelation and removal of iron from the dermis, potentially preventing the generation of ROS and subsequent cellular damage. Given that ferroptosis involves accumulation of intracellular iron and lipid peroxides, these findings suggest that ferroptosis could be a contributing mechanism to delayed wound healing in SCLUs. This insight positions ferroptosis as a potential therapeutic target for enhancing wound healing in SCD patients and possibly in other skin and non-healing conditions characterized by ferroptosis-related complications (Bi et al., 2023).

Studies have consistently demonstrated a strong correlation between ferroptosis, iron accumulation, and heme dysregulation in SCD (Ashouri et al., 2021; Gbotosho et al., 2021). For example, transfusions with aged RBCs can exacerbate ferroptosis in splenic macrophages, leading to persistent tissue iron deposition, oxidative stress, inflammation, and capillary obstruction due to sickled RBCs accumulation (La et al., 2018).

Interestingly, dietary iron restriction in SCD mouse models has been shown to mitigate vascular complications and organ damage, decreasing

leukocytosis, organ iron burden, and hemolysis, and reducing biomarkers of oxidative stress frequently linked with ferroptosis (Parrow et al., 2021). Pharmacological interventions, such as vamiferport, a ferroportin inhibitor, have also proven effective in mitigating the severity of SCD by reducing stress erythropoiesis and the presence of circulating mitochondria-rich RBCs (Nyffenegger et al., 2022). By limiting this risk, iron chelation therapy significantly improves overall patient outcome (Meerpohl et al., 2014; Ribeiro et al., 2019; Geneen et al., 2023).

Therefore, the intricate interplay between iron overload, lipid peroxidation, and ferroptosis in SCD underscores the critical importance of managing iron levels to mitigate cellular damage and enhance patient outcome.

8.3. Ferroptosis and inflammation in SCD

Based on our current understanding of ferroptosis and the immunopathophysiology of SCD, it is strongly suspected that ferroptosis contributes to inflammation in SCD or, at the very least, exhibit proinflammatory properties in this condition (Chen et al., 2021d; Tang et al., 2021; Chen et al., 2023b). Nevertheless, a direct correlation has not yet been definitively established. Inflammation in SCD, driven by factors such as infections and oxidative stress, may act as either protective or harmful response, highlighting the dual nature of inflammatory processes in this disease (Azevedo and Malmegrim, 2020; Beck et al., 2022). Significantly, ferroptosis is recognized as an immunostimulatory process associated with the release of damage-associated molecular patterns (DAMPs) in endothelial cells and immune cells. These include alarmins, heat shock proteins, HMGB1 (High mobility group box 1 protein), ATP, circulating DNA, immunogenic byproducts of lipid peroxidation, activating receptors (TLR2, TLR4, TLR9), CD14, and purinergic receptors, which collectively trigger an immune response aimed at clearing damaged cells and repairing tissue (Zhong et al., 2019; Zindel and Kubes, 2020; Conran and Embury, 2021; Luo et al., 2021; Chen et al., 2023b; Deng et al., 2023).

Sterile inflammation, defined as inflammation occurring in the absence of microorganisms, activates pathways such as neutrophil-gasdermin D (GSDMD) through caspase-4/11. This activation leads to the release of neutrophil extracellular traps (NETs), contributing to complications in SCD (Shen et al. 2013; Vats et al., 2022). Conversely, inflammatory conditions in SCD can create an environment that favors ferroptosis that potentially exacerbates the disease (NaveenKumar et al., 2018; Gbotosho et al., 2021, 2023; Salgar et al., 2023). This intricate relationship underscores the importance of further research to unravel the precise mechanisms by which ferroptosis influences inflammation in SCD and vice versa, offering insights into novel therapeutic strategies aimed at mitigating the impact of these interconnected processes on patient outcome.

8.3.1. Influence of ferroptosis on immune response and inflammatory dynamics in SCD

Ferroptosis exerts a significant influence on immune cells, impacting both their numbers and functionality (Tang et al., 2023). Moreover, it affects the secretion of immunomodulatory lipid mediators (LTB4, LTC4, LTD4 and PGE2), alongside the production of ROS and cytokines (IL-6, TNF). These factors can alter iron metabolism and increase oxidative stress in cells, suggesting its link to immune activation and inflammation (Sun et al., 2020; Deng et al., 2023; Tang et al., 2023; Tizabi et al. 2023). Iron overload, a contributing factor to increased stroke risk and disease severity in SCD, impacts leukocyte function (Walter et al., 2006; Weiss et al., 2019; Cercamondi et al., 2021). Additionally, macrophages, which are pivotal in recycling iron from aged erythrocytes, can undergo ferroptosis, affecting their immune activity (Ganz, 2016; Wang et al., 2017; Slusarczyk et al., 2023). M1 macrophages, also referred to as pro-inflammatory, inhibit cell proliferation and cause tissue damage while M2, or anti-inflammatory macrophages promote cell proliferation and tissue repair (Mills, 2012). The balance between M1 and M2 macrophage polarization influences their sensitivity to ferroptosis, thereby affecting inflammatory responses in various diseases. Significantly, M1 macrophages resist ferroptosis due to reduced ALOX15 activity (Kapralov et al., 2020), while erythrophagocytosis or the presence of external ferric ions can trigger ferroptosis in M2 macrophages (Gao et al., 2016; Hou et al., 2016).

In neutrophils, the activation of NOX1 and PADI4 plays a crucial role in the formation of NETs, where the release of myeloperoxidase triggers lipid peroxidation and ferroptosis (Chen et al., 2021d). This pathway illustrate how ferroptosis can influence immune responses (Sun et al., 2020). Additionally, neutrophil-derived microparticles, which release myeloperoxidase, have been implicated in causing damage to endothelial cells, further linking ferroptosis to immune-mediated tissue injury in SCD (Pitanga et al., 2014; Van Avondt et al., 2019, 2023).

Ferroptosis-induced sterile inflammation, driven by DAMPs, activates immune responses through pathways such as TLR4, AGER/RAGE, and STING1. This activation underscores the pivotal role of ferroptosis in bridging cell death to inflammation and immune modulation in SCD (Silva et al., 2009; Nyakundi et al. 2019; Wen et al., 2019; Dai et al., 2020a; Sun et al., 2020). Consequently, the efficacy of ferroptosis inhibitors in mitigating inflammation across various models supports the potential therapeutic value of targeting ferroptosis in SCD-related inflammation (Martin-Sanchez et al., 2017; Kong et al., 2019; Liu et al., 2020; Deng et al., 2023).

8.3.2. Heme-induced ferroptosis as a trigger for inflammation in SCD

Ferroptosis may also significantly impact inflammation in SCD through its involvement in intravascular hemolysis and heme metabolism. Elevated heme levels, resultant from iron overload and hemolysis, exacerbate disease severity and affect the immune landscape in SCD immunopathology (Dutra et al., 2014; Erdei et al., 2018; Pitanga et al., 2016, 2021; Vogel et al., 2021). Heme-induced ferroptosis, primarily driven by increased intracellular iron from heme catabolism and subsequent lipid peroxidation, introduces a critical pathway, although non-canonical mechanisms involving labile iron also play a role (NaveenKumar et al., 2018; Li et al., 2023c; Silva, 2023). Furthermore, the interaction of cell-free hemoglobin with nitric oxide reduces its vasodilatory and anti-inflammatory capabilities, further implicating ferroptosis in SCD's pathogenesis through increased oxidative stress and hypercoagulability (Morris et al., 2005; Belcher et al., 2014; Merle et al., 2018; Frimat et al., 2019).

Moreover, heme activates redox-sensitive pathways, including NF-κB and NLRP3 inflammasome, leading to elevated levels of pro-inflammatory mediators (IL-1β, caspase-1, IL-18, and LTB4). These molecular events link to ferroptosis through mechanisms of lipid peroxidation and oxidative DNA damage, further connecting these processes to inflammation in SCD (Dutra et al., 2014; Pitanga et al., 2016; Vogel et al., 2021; Hopp et al., 2023; Salgar et al., 2023). Additionally, introducing ferroptosis inducers to cancer cells has shown an elevation in proteins linked to NF-κB activation, such as phosphorylated p65 and IκBα, followed by a rise in pro-inflammatory cytokines shortly after ferroptosis induction (Li et al., 2021). Ferrostatin-1, a ferroptosis inhibitor, effectively reduces inflammation in LPS-stimulated HUVECs by lowering HMGB1, IL-6, and TNF-α expression Similarly, the use of ferroptosis inhibitors in a mouse model of iron overload disease has been shown to suppress NRF2 and NF-κB signaling, reducing the levels of IL-1β and TNF-α, thereby illustrating how ferroptosis inhibitors can modulate inflammatory dynamics (Salama and Omar, 2021; Salama et al., 2022). These findings offer a comprehensive understanding of the intersection between ferroptosis and immune responses in SCD, paving the way for potential therapeutic strategies (Gbotosho et al., 2021, 2023).

In summary, ferroptosis and inflammation are intricately interconnected processes, with each influencing the onset and progression of the other in SCD. The release of hemoglobin, heme, and free iron during

vaso-occlusion and hemolysis leads to exacerbated oxidative stress, vascular dysfunction, inflammation, and ferroptosis. The complex interplay of these factors, coupled with the activation of various inflammatory pathways, underscores ferroptosis's central role in SCD progression, suggesting it may offer novel therapeutic targets and interventions.

9. Therapeutic strategy targeting ferroptosis in SCD

The connection between ferroptosis and SCD has sparked significant interest in exploring ferroptosis as a potential therapeutic target, especially given its promise for mitigating the disease's burden. Initially, the focus of research on ferroptosis was primarily on its induction for cancer treatment. However, the scenario has gradually shifted towards inhibiting ferroptosis to manage conditions marked by the accumulation of lipid peroxides, such as ischemia–reperfusion injuries, iron toxicity, and other prevalent issues in SCD (Fig. 4).

Consequently, addressing the shortfall in antioxidant defense in SCD becomes essential for controlling the propagation of phospholipid peroxides via a one-electron reduction process (Marwah et al., 2002; Ren et al., 2008; Delesderrier et al., 2019; Dosunmu-Ogunbi et al., 2019). This imbalance leads to an escalation in lipid peroxidation, underscoring the imperative for therapeutic strategies aimed at restoring equilibrium. These strategies include limiting lipid peroxidation, neutralizing radicals, and repairing oxidative damage, highlighting the critical need for intervention (Gizi et al., 2011; Vona et al., 2021). Research into ferroptosis has pinpointed specific inhibitors, including iron chelators, lipophilic radical-trapping antioxidants, and other targets that indirectly bolster antioxidant defenses. These findings offer promising treatment venues for countering ferroptosis and iron overload in SCD, showcasing the dynamic and evolving landscape of therapeutic development in this area (Table 1).

9.1. Hydroxyurea

Hydroxyurea (HU) stands as a pivotal therapeutic agent in managing SCD, operating through diverse mechanisms. Its primary efficacy in SCD stems from its ability to induce HbF production, effectively mitigating HbS polymerization and, consequently, reducing vaso-occlusive crises (Telen, 2016). Moreover, HU exerts a myelosuppressive effect, lowering the number of activated blood cells and thereby reducing vaso-occlusive events and inflammation. Furthermore, it enhances nitric oxide bioavailability, aiding in vasodilation and reducing ischemic injury in SCD (Osunkwo et al., 2020). Despite its benefits, HU can precipitate side effects like neutropenia and gastrointestinal issues, necessitating careful monitoring (Osunkwo et al., 2020).

Additionally, HU is known for its antioxidant and iron-chelating properties, potentially playing a role in preventing ferroptosis by reducing levels of ROS, boosting nitric oxide synthesis, and stimulating the NRF2 pathway in HUVECs (Santana et al., 2020). SCD patients under HU treatment have exhibited an increase in HbF levels, a decrease in lipid peroxidation levels, and bolstered antioxidative defenses (de

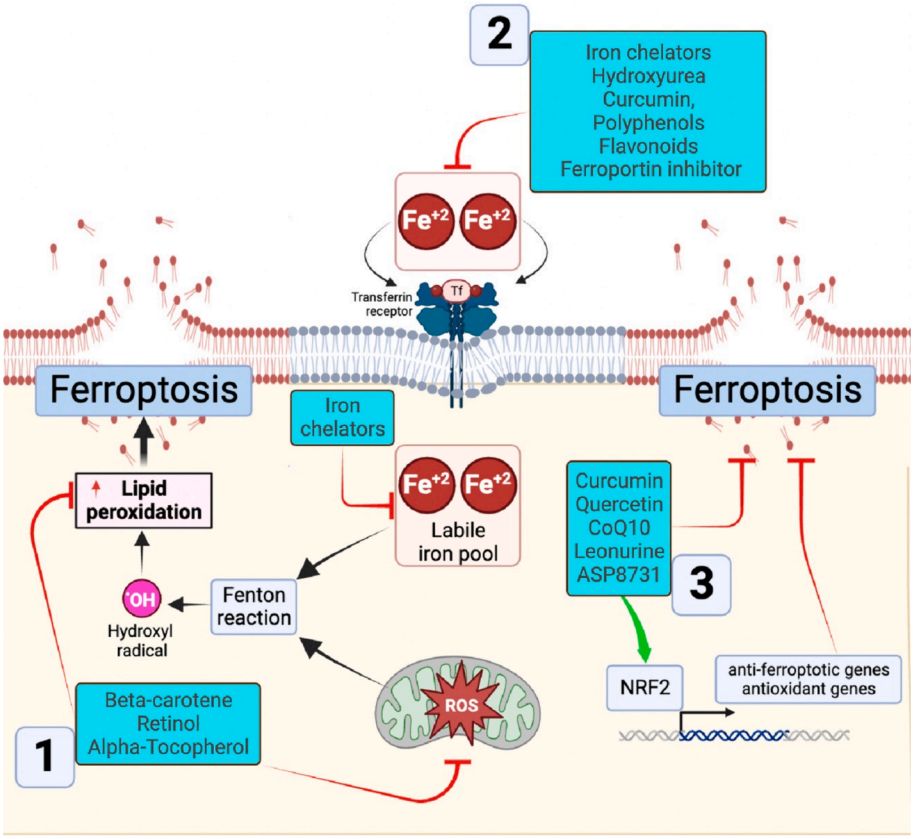

Fig. 4. Proposed Mechanism of Anti-Ferroptosis Therapeutics in Sickle Cell Disease (SCD). (1) Radical Scavenging and Lipid Peroxide Inhibition: Antioxidants such as beta-carotene, alpha-tocopherol, and retinol act as radical scavengers, preventing lipid peroxidation, a key driver of ferroptosis. These agents thwart the formation of lipid hydroperoxides. Alpha-tocopherol, alongside its derivatives, modulates ferroptosis by specifically inhibiting LOX enzymes. Additionally, polyphenols and other bioactive compounds from plants serve as potent peroxyl radical scavengers, contributing to the anti-ferroptotic defense. (2) Iron Sequestration: Iron chelators mitigate ferroptosis by arresting both the non-enzymatic, iron-catalyzed autooxidation of lipids and the enzymatic oxidation mediated by the LOX enzyme family, which contains non-heme iron. (3) Nrf2 Pathway Activation: The pharmacological activation of Nrf2-target genes imparts a strong anti-ferroptotic action by upregulating genes that combat oxidative stress and inhibit ferroptosis. Nrf2 serves as a key transcriptional regulator for the expression of various antioxidant and protective proteins. HMOX1: Heme oxygenase 1; LOX: Lipoxygenase; ROS: Reactive oxygen species; TF: Transferrin.

Table 1
Natural and synthetic inhibitors of ferroptosis offer potential therapeutic benefits for Sickle Cell Disease.

Compound	Nature of the compound	Targets	Functions	References
Hydroxyurea	Synthetic	Iron ROS	Iron chelation; antioxidant, decrease LPOx, increase HbF levels	(Chitambar and Wereley, 1995; de Torres et al., 2012; Silva et al., 2013; Santana et al., 2020; Santos Neto et al., 2020; Renó et al., 2021;)
Deferiprone	Synthetic	Iron	Iron chelation; reduction of ROS and LPOx	(Bruzzese et al., 2023; Hamdy et al., 2023; Scarpellini et al., 2023)
Deferoxamine	Synthetic	Iron	Iron chelation; reduction of ROS	(Bruzzese et al., 2023; Hamdy et al., 2023; Scarpellini et al., 2023)
Deferasirox	Synthetic	Iron	Increase of iron excretion; inhibition of lipid peroxidation	(Bruzzese et al., 2023; Hamdy et al., 2023; Scarpellini et al., 2023)
Vitamin E	Natural	GPX4; LPOx, ROS	Free radical scavenger; synergistic function with GPX4; reduction of ROS	(Khanna et al., 2003; Wortmann et al., 2013 Kagan et al., 2017; Hu et al., 2021; Saito, 2021; Lan et al., 2022)
Vitamin A	Natural	Peroxyl radicals, LPOx, ROS	Free radical scavenger, inhibition LPOx	(Rózanowska et al., 2005; Jakaria et al., 2023)
Carotenoids	Natural	Singlet molecular oxygen, ROS	Singlet quenching, Inhibition of LPOx	(Do et al., 2023; Terao, 2023)
Lutein	Natural	SLC7A11/ IRF/GPX4	Inhibition of LPOx, decrease ROS	(Liu et al., 2023b).
Lycopene	Natural	Nrf2/HO-1; System Xc-	Inhibition of LPOx; decrease ROS, modulation of iron metabolism	(Wang et al., 2023b)
Leonurine	Natural	Nrf2	Suppression of NF-κB, decrease ROS	(Salama et al., 2022)
Coenzyme Q10	Natural	FSP1-CoQ10-NAD(P)H; Nrf2	Inhibition of LPOx, decrease ROS	(Thakur et al., 2013; Valverde et al., 2016; Samimi et al., 2024)
Curcumin	Natural	Iron, LPOx, ROS	Iron chelation; decrease ROS	(Badria et al., 2015; Valverde et al., 2016; Guerrero-Hue et al., 2019; Kajarabille and Latunde-Dada, 2019; Kose et al., 2019; Yang et al., 2021; Zheng et al., 2021; Wei et al., 2022)
Quercetin	Natural	Iron, ROS, LPOx	Inhibition of lipid peroxidation, iron chelation; decrease ROS	(Syed et al., 2020; Adeniyi et al., 2022; Feng et al., 2023)
Resveratrol	Natural	GPX4, LPOx, ROS	Inhibition of LPOx; decrease ROS; increase of GPX4 expression	(Liu et al., 2022b; Silva et al., 2022; Wang et al., 2023c).
Zileuton	Synthetic	ALOX5; iron	Inhibition of LPOx; decrease ROS, inhibit leukotriene synthesis	(Patel et al., 2009; Sinha et al., 2019; Sun et al., 2023)
Baicalin/ Baicalein	Natural	ALOX12 and ALOX15; GPX4; System Xc-	Reduction of ROS, increase of GPX4 and SLC7A11 expression	(Dai et al., 2021b; Duan et al., 2021; Lone et al., 2023)
ASP8731	Synthetic	BACH1; Nrf2	Disruption of the heme signaling pathway, Inhibition of LPOx; decrease ROS	(Nishizawa et al., 2020; Nataraja et al., 2021; Belcher et al., 2023; Irikura et al., 2023)

Torres et al., 2012; Silva et al., 2013). In pre-clinical models, HU has been demonstrated to diminish lipid peroxidation products, thereby reducing oxidative stress in the liver, brain, and spinal cord of rats (Santos Neto et al., 2020). Furthermore, HU functions as an efficacious metal chelator by targeting the di-iron center of ribonucleotide reductase, inhibiting cellular proliferation and displaying its antitumor activity (Nyholm et al., 1993; Offenbacher et al., 2009). In CCRF-CEM cells, treatment with HU has been shown to decrease iron uptake and increase the expression of iron-regulatory proteins, indicating a complex interaction between HU, iron metabolism, and cellular growth mechanisms (Chitambar and Wereley, 1995). Supporting these findings, treating RBCs *in vitro* with 0.8 mM HU for 1 h resulted in decreased lipid peroxidation and Fe^{3+} levels, and it stimulated the enzymes of the pentose phosphate pathway, essential for replenishing the primary

cellular antioxidant and preserving redox balance (Renó et al., 2021). Furthermore, combining HU with iron chelators like deferiprone and deferasirox has proven effective in mitigating iron overload, leading to decreased serum ferritin levels and reduced iron accumulation in liver and heart tissues (Italia et al., 2013). The concurrent use of HU with deferasirox in SCD patients is considered safe, although the comprehensive implications of this combination require further investigation (Wong et al., 2021). Therefore, HU represents a significant stride forward in SCD management, underscoring the need for continuous research to refine its application and manage its side effects. While the direct effect of HU on ferroptosis has not been clearly outlined, understanding its influence on iron-dependent enzymes and iron uptake provides a foundational basis for further exploration of its potential impact on ferroptosis-related pathways.

9.2. Traditional iron chelators

In SCD management, iron chelation therapy emerges as indispensable for addressing iron overload, typically resulting from repeated blood transfusions. It is recommended for patients exhibiting high serum ferritin levels or significant liver iron concentration, employing agents such as deferiprone, deferoxamine, and deferasirox (Bruzzese et al., 2023; Hamdy et al., 2023). Notably, these therapies aim to counterbalance iron accumulation by enhancing iron excretion and mitigating iron toxicity, thereby inhibiting lipid peroxidation and ferroptosis (Scarpellini et al., 2023). Particularly, the synergistic use of chelating drugs, especially the combination of deferoxamine and deferiprone, has gained widespread adoption. Deferiprone has shown comparable results to deferoxamine in reducing iron overload in children and adults with SCD (Hamdy et al., 2023).

Deferiprone, effective in reducing cardiac iron, is preferred for its cost-effectiveness and lower toxicity, although regular MRI monitoring is recommended for patients on chronic transfusion therapy to assess liver iron and cardiac function. Deferasirox, an oral chelator with high Fe^{3+} affinity, has been effective in reducing liver iron and preventing hemosiderin accumulation, with side effects being manageable (Entezari et al., 2022). Furthermore, deferiprone has emerged as arguably the safest option, demonstrating efficacy comparable to deferoxamine and deferasirox in iron reduction, presenting itself as a viable treatment alternative. Safety assessments reveal that deferiprone is associated with lower incidences of adverse events compared to deferasirox, emphasizing its superior safety profile (Arrey Agbor et al., 2024).

The primary aim of iron chelating therapy in SCD is to rapidly reduce tissue iron levels to prevent organ damage, especially in cases of an existing organ failure. The decision to initiate therapy is based on transfusion frequency, iron deposition levels, and hepatic/cardiac dysfunction, typically starting when serum ferritin exceeds 1000–1500 μg/L or liver iron concentration surpasses 3–5 mg/g dry weight. Despite the benefits, deferiprone's risks, such as agranulocytosis and liver dysfunction, underscore the challenges of chelation therapy, often affecting patient adherence (Ferraresi et al., 2023; Geneen et al., 2023).

9.3. Broad spectrum radical-trapping antioxidants

Broad-spectrum radical-trapping antioxidants (RTAs) play a pivotal role in stopping autoxidation chain reactions within lipid membranes by neutralizing radicals, resulting in stable, non-radical products, and preserving cell membrane integrity. However, their effectiveness is finite and relies on adequate GSH levels, indicating that they cannot indefinitely prevent ferroptosis (Gulcin, 2020). Despite the variable efficacy of antioxidants, their importance in reducing ferroptosis in SCD requires further investigation.

9.3.1. Vitamin E and homologs

Vitamin E, an oil-soluble RTA, has proven effective in inhibiting ferroptosis in various cell types, both *in-vitro* and *in-vivo*. Its ability to scavenge peroxyl radicals is attributed to its high affinity for unpaired electrons (Saito, 2021). Vitamin E includes eight fat-soluble compounds, categorized as tocopherols when their polyprionid chain is saturated and as tocotrienols when unsaturated. Its protective role is evident in studies on endothelial cells lacking GPX4, where vitamin E deficiency can lead to thrombotic events and increased ferroptosis (Wortmann et al., 2013). In hematopoietic stem and progenitor cells, the absence of GPX4 causes lipid peroxidation and ferroptosis, which can be counteracted by α-tocopherol. This highlights the cooperative role of GPX4 and vitamin E in maintaining lipid redox homeostasis and preventing ferroptosis (Hu et al., 2021). Additionally, the synergistic function of GPX4 and vitamin E is crucial in controlling reticulocyte maturation, stress erythropoiesis, and iron homeostasis, signifying their essential role in cellular protection, particularly in SCD (Wortmann et al., 2013; Altamura et al., 2020).

Antioxidants like vitamin E and N-acetyl cysteine protect against ferroptosis induced by classical inducers or GPX4 depletion, in part by inhibiting lipoxygenase activity and reducing hydroperoxide cytotoxicity (Khanna et al., 2003; Kagan et al., 2017). Vitamin E also enhances anti-oxidative processes by inhibiting ferroptosis through the PI3K/AKT/mTOR signaling pathway (Lan et al., 2022). In exploring therapeutic potentials for treating ferroptosis in SCA, initial studies, such as those by Gbenebitse et al. have indicated that vitamin E supplementation may enhance blood flow viscosity and reduce resistance by lowering plasma lipid peroxidation levels (Gbenebitse et al., 2005). More recent research has demonstrated that alpha-tocopherol can inhibit heme-stimulated neutrophil adhesion, CD11a/CD11b activation, NFκB translocation, and ROS generation in neutrophils post-heme stimulation (Miguel et al., 2021). Furthermore, studies on nanostructured vitamin E analogues have shown promising results in improving several hematological parameters and inhibiting sickle RBCs, suggesting a potential involvement of ferroptosis in these mechanisms (Ahmed et al., 2021). In sum, the effectiveness of vitamin E in scavenging peroxyl radicals and functioning synergistically with GPX4 makes it a promising therapeutic agent for treating conditions such as SCA. It has the potential to improve blood flow, reduce oxidative stress, and influence ferroptosis-related mechanisms.

9.3.2. Vitamin A and carotenoids

Retinol (Vitamin A) and its precursor beta-carotene, play a significant role in the antioxidative defense system, especially in the context of SCD. Although high-dose vitamin A supplementation exhibited a limited effect on serum retinol levels, it mildly improved erythrocyte indices, growth status, and muscle function in SCD children (Brownell et al., 2020). Remarkably, Vitamin A has been found to inhibit ferroptosis more effectively than α-tocopherol, neutralizing peroxyl radicals through the formation of carbon-centered radical adducts and preventing the propagation of lipid peroxidation through electron transfer (Rózanowska et al., 2005; Jakaria et al., 2023). Carotenoids, including beta-carotene, lycopene, and lutein, show promising potential as therapeutic agents in managing complications associated with ferroptosis (Do et al., 2023; Terao, 2023). Specifically, beta-carotene has demonstrated ability to inhibit methylmercuric chloride-induced lipid peroxidation in mice (Andersen and Andersen, 1993), and suppress erastin-induced ferroptosis in a RAS–RAF–MEK-dependent oxidative cell death pathway (Yagoda et al., 2007).

Lutein supplementation has been found to attenuate endothelial ferroptosis by upregulating the interferon regulatory factor (a transcription factor), indirectly regulating the expression of solute carrier family 7 member 11 (SLC7A11) and GPX4 (Liu et al., 2023b). Lycopene has proven effective in inhibiting neurotoxicity and ferroptosis by modulating iron metabolism, reducing lipid peroxidation, and activating the cysteine transporter and NRF2/HO-1 signaling pathway (Wang et al., 2023b). Furthermore, supplementation with lycopene notably counteracted the rise in lipid peroxidation, reversed the suppression of the cysteine/glutamate antiporter, and mitigated splenic cell death caused by environmental-chemical pollutants-induced ferroptosis

(Dai et al., 2021a). However, the anti-ferroptotic effects of beta-carotene and other carotenoids, such as lycopene, require further investigation in the context of hemoglobinopathies.

9.3.3. NRF2 pathway activators

The role of NRF2, a regulatory protein that controls antioxidant enzyme expression, is increasingly recognized as critical in cellular defense against oxidative damage in SCD (Xi et al., 2023). Thus, NRF2 may play various roles, including regulating the β-globin gene, activating heme oxygenase-1, reducing NF-κB activation, suppressing adhesion molecule expression, and decreasing both inflammation and the release of pro-inflammatory cytokines in SCD (Kaspar et al., 2009; He et al., 2020; Panda et al., 2022). It also suppresses L-2-hydroxyglutarate (L2HG) production, a metabolite implicated in epigenetic modifications and the regulation of genes linked to metabolic processes, oxidative stress, and ferroptotic responses (Xi et al., 2023). Pharmacological activation of NRF2 shows protective effects against ROS stress and ferroptosis in SCD models (Fan et al., 2017; Chauhan and Zennadi, 2023; Duarte et al., 2023), highlighting the NRF2-SLC7A11-GPX4 axis as a promising therapeutic target in conditions marked by iron overload and oxidative stress, such as in SCD (Shakya et al., 2023). Particularly, leonurine, a natural alkaloid, has shown hepatoprotective benefits in SCD by reducing iron-induced hepatotoxicity, primarily through suppressing ferroptosis and reducing oxidative damage and inflammation. These effects are achieved by enhancement of NRF2 nuclear translocation and suppression of NF-κB (Salama et al., 2022).

CoQ10, acting as a natural lipophilic radical-trapping antioxidant that neutralizes lipid peroxides, is crucial for the FSP1-CoQ10-NAD(P)H pathway. It plays a central role in cellular redox processes, providing key defense against ferroptosis. In patients with SCD, CoQ10 administration has been shown to markedly reduce inflammation, oxidative stress markers, and the frequency of vaso-occlusive crises, highlighting its therapeutic efficacy in addressing SCD-related complications (Thakur et al., 2013). Additionally, the flavoprotein FSP1, encoded by the gene AIFM2, is identified as a NRF2 target gene (Dodson et al., 2019; Dai et al., 2020b, 2020c; Kim et al., 2023). This suggests that agents such as CoQ10, in conjunction with leonurine, could regulate a spectrum of target genes by activating NRF2, which are crucial for reducing lipid peroxide accumulation, preserving cell membrane integrity, and averting the progression of the ferroptotic cascade in SCD (Salama et al., 2022; Samimi et al., 2024). Nonetheless, further research is necessary to fully understand the roles of NRF2 activators and the mechanisms of ferroptosis in SCD towards developing more effective therapies.

9.3.4. Polyphenols

Polyphenols, a broad category of naturally occurring organic compounds characterized by their multiple phenol structures, are ubiquitous throughout the plant kingdom. They enrich the flavor, color, and health benefits of a variety of nutrients, including fruits, vegetables, tea, wine, and chocolate. The molecular structure of polyphenols enables them to neutralize free radicals, bind metal ions like iron, and modulate antioxidant defense mechanisms. However, their effectiveness is contingent upon factors such as the administered dose, treatment duration, and the specific type of cell or tissue targeted, making their biological impact highly context-dependent (Stepanic et al., 2015; Eghbaliferiz and Iranshahi, 2016). By neutralizing free radicals and averting the oxidative stress responsible for lipid peroxidation, polyphenols play a crucial role in protecting cells and potentially mitigating ferroptosis (Kajarabille and Latunde-Dada, 2019).

Curcumin, a natural polyphenol derived from turmeric, is known for its anticancer, antioxidant, and anti-inflammatory properties, exhibiting significant potential as a ferroptosis inhibitor through its iron-chelating capabilities (Badria et al., 2015; Guerrero-Hue et al., 2019; Yang et al., 2021; Wei et al., 2022). A recent study has shown that curcumin and CoQ10, individually and in combination, alleviate chronic hyperalgesia in SCD (Valverde et al., 2016; Joshi et al., 2022). Alongside curcumin, other flavonoids and polyphenols, possess iron-chelating abilities and play a role in modulating redox state in SCD (Kalpravidh et al., 2010; Thakur et al., 2013; Badria et al., 2015; Kajarabille and Latunde-Dada, 2019; Kose et al., 2019; Zheng et al., 2021). However, their limited solubility and bioavailability have led to research for analogues with better pharmacokinetics (Hao et al., 2023). At the molecular level, curcumin modulates various pro-inflammatory pathways, including NF-κB and PI3K/Akt/mTOR, and impacts SCD treatment by influencing the NRF2 signaling pathway (Hasanzadeh et al., 2020; Zheng et al., 2021).

Quercetin, a flavonoid and natural antioxidant (Landis et al. 2022), operates chiefly by inhibiting lipid peroxidation through mechanisms such as NRF2 activation, xanthine oxidase enzyme inhibition, iron chelation, and direct elimination of hydroxyl and superoxide anion radicals (Feng et al., 2023). It has been shown to inhibit the polymerization of isolated HbS and stabilize the membranes of sickle erythrocytes (Syed et al., 2020; Adeniyi et al., 2022), effectively inhibiting RBC dehydration, hemolysis, and vascular adhesion (Al Balushi et al., 2019). Moreover, quercetin offers a protective effect against ROS production in SCA patients, especially those under hydroxyurea treatment (Henneberg et al., 2013). A study demonstrated that a single dose of quercetin (200 mg/kg body weight) effectively reduced hypoxia reoxygenation (H/R)-induced pathophysiology in NY1DD mice, a mild SCD model, suggesting a novel strategy for treating severe SCD pathophysiology when combined with the inherent high oxygen affinity of RBCs in this mouse model (Thangaswamy et al., 2021).

Resveratrol (RV), a natural phytoalexin found in grapes and a variety of dietary sources, is renowned for its potent antioxidant and anti-inflammatory properties (Malaguarnera, 2019; Meng et al., 2021). It inhibits ribonucleotide reductase, similar to hydroxyurea (Rodrigue et al., 2001) and promotes the expression of γ-globin genes, leading to increased HbF levels (Fibach et al., 2012; Theodorou et al., 2016; Mukherjee et al., 2022). Additionally, resveratrol prevents the lipid peroxidation of cell membranes (Tadolini et al., 2000) and has shown efficacy in protecting against cerebral ischemic injury by significantly reducing lipid peroxidation (Lin et al., 2021). Recent research indicates that resveratrol inhibits ferroptosis by activating the KAT5/GPX4 pathway (Liu et al., 2022b) and enhances the expression of SOD2 and catalase, thereby decreasing ROS and lipid peroxidation via the SIRT3/FoxO3a pathway (Wang et al., 2023c). In SCD mouse models, resveratrol treatment has been found to improve NO-mediated relaxations, normalize PDE5 expression, and lower markers of lipid peroxidation in priapism (Silva et al., 2022). These findings collectively demonstrate resveratrol's significant anti-ferroptotic effects, underscoring its potential as a therapeutic agent against ferroptosis in SCD.

9.4. Inhibitors of arachidonate lipoxygenases (ALOX)

Arachidonate lipoxygenases, enzymes rich in non-heme iron, play a pivotal role in catalyzing lipid peroxidation and are key to the process of ferroptosis (Shah et al., 2018). In patients with SCD, there is a notable increase in the expression of Arachidonate 5-lipoxygenase (ALOX5) in blood mononuclear cells, contributing to lipid peroxidation and ongoing inflammation (Patel et al., 2009). Consequently, targeting ALOX5 emerges as a promising strategy for SCD treatment. Zileuton, a selective ALOX5 inhibitor, interrupts leukotriene synthesis, effectively reducing lipid peroxidation, ferroptosis, and the adherence of polymorphonuclear neutrophils and sickle RBCs to the pulmonary vasculature in rats (Haynes et al., 2006). Classified as an iron ligand type inhibitor of ALOX5, Zileuton acts both as an iron chelator and a redox inhibitor (Sinha et al., 2019), receiving positive feedback in clinical trials involving children and adults (Eiymo et al., 2013). Additionally, its efficacy in lowering IL-13 production in murine splenic lymphocytes further underscores its therapeutic potential in managing SCD (Sun et al., 2023).

Baicalin and its aglycone form, baicalein, are flavonoids known to specifically inhibit ALOX12 and ALOX15, boasting significant

antioxidant, anti-inflammatory, anticancer, and neuroprotective effects (Hu et al., 2022). A recent study highlighted baicalin's ability to significantly reduce sickling in an animal model of SCD, cutting the sickling rate by 46 % (Lone et al., 2023). With their capacity to prevent ferroptosis by boosting the expression of GPX4 and SLC7A11 (Dai et al., 2021b; Duan et al., 2021), these flavonoids show promising therapeutic potential for SCD management.

9.5. *Inhibitor of heme signaling pathway*

ASP8731, a novel small molecule inhibitor of the transcription factor BACH1, plays a multifaceted role in SCD management. It exhibits anti-inflammatory and anti-vaso-occlusive properties while also inducing HbF production (Nataraja et al., 2021; Belcher et al., 2023). By inhibiting BACH1, ASP8731 potentially augments NRF2 function and disrupts the heme signaling pathway, contributing to its ability to inhibit ferroptosis. Moreover, ASP8731 increases HMOX1 and FTH1 mRNA in HepG2 liver cells, reduces VCAM1 mRNA, and stabilizes GSH levels in endothelial cells, alongside reducing microvascular stasis and boosting the expression of HMOX1 and gamma-globin in mouse and *ex-vivo* models (Nishizawa et al., 2020; Irikura et al., 2023).These findings highlight the therapeutic promise of BACH1 inhibition in SCD, particularly in preventing ferroptosis and offering a new horizon in the treatment landscape.

10. Conclusion

As we deepen our understanding of the intricate interactions between iron, ferroptosis, and inflammation in SCD, the potential for groundbreaking therapeutic strategies becomes increasingly apparent. The role of iron-mediated lipid peroxidation in ferroptosis, especially in the context of chronic hemolysis and ischemia–reperfusion injury, points to potential new possibilities for targeted SCD treatment. Although much more work in this area is needed, already hints of suppression of ferroptosis via the FSP1/CoQ10 pathway, presents a promising area for drug development.

The targeting of enzymes like LOXs and NOX1, central to lipid peroxidation, may transform SCD management, offering more precise and effective interventions. This approach underscores the critical intersection of toxicological science and disease management. Additionally, the integration of genomic, metabolic, and single-cell RNA sequencing data is set to offer deeper molecular insights into SCD, revealing novel biomarkers and therapeutic targets. Indeed, very recently, the U.S. Food and Drug Administration approved two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of SCD in patients 12-years and older (FDA News Release 12/08/2023).

In the context of personalized medicine, advancements in genomic and proteomic technologies are poised to enable treatments tailored to individual patient profiles. Investigating the role of environmental factors such as heavy metals like lead, zinc, magnesium, and copper in SCD could uncover new therapeutic avenues, emphasizing the need to consider external toxicological influences in disease progression and treatment.

Furthermore, exploring antioxidant therapies, particularly targeting the NRF2 pathway, is crucial in managing the toxicological aspects of oxidative stress in SCD. Combined with established treatments such as hydroxyurea, these therapies could notably enhance patient outcomes.

The development and implementation of non-invasive biomarkers for SCD monitoring and therapy response are critical, representing a significant advancement in patient care. These biomarkers can play a pivotal role in detecting toxicological stress responses in patients, enhancing the efficacy and safety of treatments.

In summary, exploration of molecular and cellular mechanisms in SCD, especially concerning iron toxicity, ferroptosis, and oxidative stress, is rapidly evolving. This progress highlights the importance of anti-ferroptosis strategies within the broader context of iron toxicology in SCD. Continuous research is vital to refine these strategies and their clinical applications.

Funding statement

This study was supported by a grant-in-aid from the Coordination of Higher Education Personnel Improvement/Institutional Internationalization Program (CAPES/Print) under Grant Number 88887.894766/2023-00, the Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB) under Grant Number PET0002/2022, and the Federal University of Bahia, Ministry of Education, Brazil. YT was partially supported by NIH/NIGMS (2 SO6 GM08016-39). MA was supported in part by NIEHS R01ES10563 and R01ES07331. SN was supported by NIH (1R01HL125005, 5U54MD007597, and 1UM1AI26617).

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Vitor Fortuna: Conceptualization, Writing – original draft, Writing – review & editing. **Jaqueline Lima:** Writing – original draft. **Gabriel F. Oliveira:** Writing – original draft. **Yasmin S. Oliveira:** Writing – original draft. **Bruk Getachew:** Writing – original draft. **Sergei Nekhai:** Conceptualization, Writing – review & editing. **Michael Aschner:** Conceptualization, Writing – review & editing. **Yousef Tizabi:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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