INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 12, Issue 8- 2025

Review Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2025.12.08.005

The Role of Ferroptosis in Sickle Cell Anemia: A Molecular Death Pathway in Focus

***Emmanuel Ifeanyi Obeagu**
Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.
*Corresponding author: Emmanuel Ifeanyi Obeagu, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe, emmanuelobeagu@yahoo.com,
ORCID: 0000-0002- 4538-0161

Abstract

Sickle cell anemia (SCA) is a hereditary hemoglobinopathy marked by chronic hemolysis, vaso-occlusion, and systemic inflammation. In recent years, ferroptosis—a form of regulated cell death driven by iron-dependent lipid peroxidation—has emerged as a potential contributor to the pathophysiology of SCA. Unlike apoptosis or necrosis, ferroptosis is triggered by oxidative stress, intracellular iron accumulation, and depletion of key antioxidants such as glutathione, all of which are features observed in patients with SCA. In SCA, chronic hemolysis results in excessive release of free heme and iron into circulation, promoting reactive oxygen species (ROS) generation and lipid membrane damage. The loss of glutathione and impaired activity of glutathione peroxidase 4 (GPX4), a central enzyme protecting against ferroptosis, further predispose erythrocytes, endothelial cells, and organ tissues to ferroptotic injury. The resulting oxidative damage amplifies inflammation, vascular dysfunction, and end-organ complications, suggesting that ferroptosis may serve as a central link between iron overload and disease progression in SCA.

Keywords: Sickle Cell Anemia, Ferroptosis, Oxidative Stress, Lipid Peroxidation, Iron Metabolism

Introduction

Sickle cell anemia (SCA) is a debilitating genetic blood disorder characterized by a single point mutation in the β-globin gene, leading to the formation of sickle hemoglobin (HbS). Under conditions of low oxygen tension, HbS polymerizes, causing red blood cells to assume a rigid, sickled shape. This deformation results in chronic hemolysis, vaso-occlusive crises, and multi-organ damage, contributing significantly to morbidity and mortality in affected individuals worldwide [1-3].Over the years, the focus of SCA research has extended beyond the mechanical and hemolytic complications of the disease to include the underlying molecular pathways that exacerbate tissue injury. One such emerging pathway is ferroptosis—a regulated, iron-dependent form of cell death distinct from apoptosis and necrosis. Ferroptosis is primarily driven by the accumulation of lipid peroxides, depletion of intracellular antioxidants, and dysregulated iron metabolism, all of which are central themes in the pathophysiology of SCA [4-6].The link between chronic hemolysis in SCA and iron metabolism is well established; repeated cycles of red blood cell destruction lead to the release of free heme and non-transferrin-bound iron into the circulation. This excess free iron participates in Fenton reactions, generating reactive oxygen species (ROS) that subsequently initiate lipid peroxidation—a hallmark of ferroptotic cell death. Therefore, the biochemical environment in SCA provides the essential triggers needed to activate ferroptosis [7-8].

Molecular regulators of ferroptosis, particularly glutathione peroxidase 4 (GPX4), play a pivotal role in controlling the oxidative state of cells. In healthy cells, GPX4 catalyzes the reduction of lipid hydroperoxides, preventing uncontrolled lipid peroxidation. However, in SCA, persistent oxidative stress coupled with diminished antioxidant defenses, including reduced glutathione levels, compromises GPX4 activity. This impairment accelerates lipid peroxidation and primes cells for ferroptotic death, thereby exacerbating tissue damage [9-10].The endothelial cells lining the vasculature are particularly vulnerable to ferroptosis due to their exposure to circulating iron and ROS. In SCA, endothelial dysfunction is a critical factor that underlies the development of vaso-occlusive events and organ injury. Ferroptosis in these cells can amplify inflammatory responses, promote the formation of microthrombi, and contribute to the cascade of vascular occlusion. Thus, endothelial ferroptosis emerges as a potential mechanism linking iron overload to the clinical manifestations observed in SCA [11-12].Emerging studies have begun to elucidate the intricate network of signaling pathways involved in mediating ferroptosis in various cell types, including those impacted by SCA. Key pathways involve the regulation of lipid metabolism by acyl-CoA synthetase long-chain family member 4 (ACSL4), modulation of intracellular iron homeostasis, and the redox control exerted by antioxidant systems. The interplay between these pathways ultimately determines the susceptibility of cells to ferroptotic death, highlighting potential molecular targets for therapeutic intervention [13].Therapeutic strategies aimed at modulating ferroptosis hold promise in mitigating the disease complications associated with SCA. Experimental interventions such as iron chelation therapy, administration of lipid peroxidation inhibitors, and supplementation with antioxidants like N-acetylcysteine (NAC) have shown potential in preclinical models. These approaches seek to restore the balance between oxidative stress and antioxidant defenses, thereby reducing ferroptotic cell death and its deleterious consequences [14-15].

Aim

The primary aim of this review is to explore and elucidate the emerging role of ferroptosis as a critical molecular mechanism in the pathogenesis of sickle cell anemia (SCA), with a focus on its contribution to red blood cell injury, chronic inflammation, and end-organ damage.

Review Methods

In conducting this review on the role of ferroptosis in sickle cell anemia (SCA), a

comprehensive and systematic approach was adopted to gather, evaluate, and synthesize relevant literature. The review process was designed to ensure academic rigor, breadth of coverage, and relevance to current scientific and clinical contexts. A combination of electronic database searches, manual screening of reference lists, and cross-referencing of related studies was employed to retrieve high-quality peer-reviewed articles, research papers, and clinical reviews published on ferroptosis and its association with SCA. The primary databases used for the literature search included PubMed, Scopus, Web of Science, and Google Scholar, covering publications from the early 2000s to the most recent updates in 2025. Keywords and Medical Subject Headings (MeSH) terms such as *"ferroptosis," "sickle cell anemia," "lipid peroxidation," "iron metabolism," "oxidative stress," "glutathione," "GPX4," "erythrocyte injury,"* and *"therapeutic modulation"* were used either singly or in combination to capture a wide spectrum of relevant studies. Boolean operators (AND, OR) were employed to refine and broaden search results where necessary.

Inclusion criteria for selecting articles involved: studies published in English, research focusing specifically on ferroptosis and its molecular mechanisms, articles addressing the role of oxidative stress in SCA, and those evaluating therapeutic strategies targeting ferroptosis. Both in vitro and in vivo experimental studies, clinical trials, and high-quality review articles were considered. Exclusion criteria included articles lacking relevance to either SCA or ferroptosis, studies with insufficient methodological detail, and preprints not subjected to peer review.Each retrieved article was independently reviewed for relevance and quality. Data were extracted concerning molecular mechanisms, pathophysiological implications, therapeutic interventions, and gaps in knowledge. Special attention was paid to articles that provided novel insights into the regulation of ferroptosis, the intersection of iron metabolism and redox imbalance in SCA, and emerging therapeutic candidates. Articles were grouped and synthesized under thematic subheadings to provide a structured and coherent analysis.The review methodology emphasized critical appraisal, consistency in interpretation, and evidence-based synthesis. While this review is narrative in nature, the methodical selection and evaluation of sources were guided by the principles of transparency and replicability. Ultimately, this process ensured that the article presents an integrative, up-to-date perspective on ferroptosis as a promising target for molecular intervention in the context of sickle cell anemia.

Molecular Mechanisms of Ferroptosis in Sickle Cell Anemia (SCA)

Ferroptosis is a distinct form of regulated cell death characterized by the accumulation of lipid peroxides in an iron-dependent manner. Unlike apoptosis, necrosis, or autophagy, ferroptosis is specifically driven by metabolic disturbances in redox homeostasis and lipid metabolism. In the context of sickle cell anemia (SCA), where chronic hemolysis, oxidative stress, and iron overload are prevalent, the molecular machinery of ferroptosis becomes critically relevant in understanding disease progression and organ damage [16].At the core of ferroptosis is the peroxidation of polyunsaturated fatty acids (PUFAs) within cellular membranes. This process is initiated by iron-catalyzed Fenton reactions that generate reactive oxygen species (ROS), particularly hydroxyl radicals, which attack lipid bilayers. In SCA, chronic intravascular hemolysis leads to persistent release of free hemoglobin and heme into circulation. These hemolytic byproducts are potent pro-oxidants and major sources of labile iron that feed into the ferroptotic pathway by catalyzing lipid peroxidation in red blood cells, endothelial cells, and organ tissues [17].

Another central mechanism involves the depletion of intracellular glutathione (GSH) and subsequent inactivation of glutathione peroxidase 4 (GPX4), an enzyme essential for detoxifying lipid hydroperoxides. In SCA, high oxidative burden depletes GSH reserves and disrupts redox equilibrium, compromising GPX4's ability to neutralize lipid ROS. This creates a permissive

environment for lipid peroxide accumulation, thereby triggering ferroptosis in vulnerable cell types, especially within the vascular endothelium and renal epithelium [18].Iron metabolism dysregulation is a hallmark of SCA and plays a pivotal role in amplifying ferroptotic signaling. Transferrin saturation, elevated ferritin, and non-transferrin-bound iron levels are frequently observed in SCA patients. The iron-import protein transferrin receptor 1 (TfR1) and the iron-storage protein ferritin heavy chain (FTH1) are key modulators of intracellular iron availability. Their expression and degradation, particularly through ferritinophagy (autophagic degradation of ferritin), can enhance the labile iron pool and promote ferroptosis. In SCA, the increased activity of these iron-regulatory pathways escalates ferroptotic susceptibility [19].

Additionally, the enzyme acyl-CoA synthetase long-chain family member 4 (ACSL4) has emerged as a crucial determinant of ferroptosis sensitivity. ACSL4 facilitates the incorporation of PUFAs into phospholipids, creating substrates highly prone to peroxidation. Its upregulation has been observed in various inflammatory and oxidative contexts, including those resembling the pathophysiological environment of SCA. Furthermore, lysophosphatidylcholine acyltransferase 3 (LPCAT3) contributes to the remodeling of phospholipids, enhancing the incorporation of oxidizable fatty acids that can precipitate ferroptosis [20].Mitochondrial dysfunction and altered energy metabolism further potentiate ferroptotic cascades. In SCA, hypoxia-reperfusion cycles and chronic inflammation contribute to mitochondrial ROS production, which in turn accelerates lipid oxidation. The mitochondrial voltage-dependent anion channels (VDACs) and associated metabolic enzymes are implicated in the amplification of oxidative signals, although their precise role in SCA-related ferroptosis remains an area of ongoing investigation [21].Recent studies have also highlighted the involvement of nuclear factor erythroid 2–related factor 2 (NRF2), a master regulator of cellular antioxidant responses. While NRF2 activation generally confers protection against oxidative damage, its regulation is impaired in SCA, further exacerbating oxidative stress and ferroptotic vulnerability. Additionally, tumor suppressor protein p53 has been shown to suppress the expression of SLC7A11, a subunit of the cystine/glutamate antiporter system Xc–, which is critical for GSH biosynthesis. The repression of SLC7A11 thereby limits cystine uptake and glutathione production, sensitizing cells to ferroptosis—a mechanism likely to be relevant in SCA's inflammatory milieu [22-23].

Ferroptosis in Red Blood Cell Injury and Hemolysis

Red blood cells (RBCs) are the primary cellular targets affected in sickle cell anemia (SCA), and their structural and functional integrity is crucial for oxygen delivery and vascular health. In the sickling process, the polymerization of hemoglobin S under low oxygen tension causes RBCs to adopt rigid, crescent-like shapes, making them prone to hemolysis and entrapment within the microvasculature. While hemolysis has traditionally been attributed to mechanical fragility and oxidative stress, emerging evidence suggests that ferroptosis—an iron-dependent, lipid peroxidation-driven form of cell death—may be a central contributor to RBC injury in SCA [24].Though mature RBCs lack nuclei and mitochondria, they are not immune to regulated cell death. The susceptibility of RBCs to ferroptotic-like processes arises from their high heme and iron content, abundant polyunsaturated fatty acids in their membranes, and continuous exposure to oxidative stress. In SCA, oxidative stress is further intensified due to hemoglobin auto-oxidation, increased reactive oxygen species (ROS) production, and impaired antioxidant defenses, including glutathione depletion. These conditions favor lipid peroxidation within the RBC membrane, initiating a ferroptosis-like phenotype that compromises membrane integrity and promotes premature lysis [25-26].

Hemolysis in SCA results in the release of free hemoglobin, heme, and iron into circulation, amplifying oxidative injury and creating a feedback loop that predisposes surrounding RBCs

to further oxidative and ferroptotic damage. The oxidation of membrane lipids causes decreased deformability, membrane blebbing, and phosphatidylserine exposure, hallmarks of programmed erythrocyte death—or "eryptosis." Although not classical ferroptosis due to the lack of organelles in RBCs, eryptosis shares key molecular features with ferroptosis, including iron overload, lipid peroxidation, and glutathione imbalance [27].The antioxidant enzyme glutathione peroxidase 4 (GPX4), essential for mitigating lipid peroxides in nucleated cells, is absent in mature RBCs, rendering them particularly vulnerable to lipid peroxidation. Instead, RBCs rely on peroxiredoxins, catalase, and the glutathione system to defend against oxidative damage. In SCA, chronic oxidative stress depletes these protective systems, promoting ferroptotic injury. The deficiency in cellular mechanisms to repair oxidized lipids under such persistent stress conditions may lead to hemolytic episodes and contribute to the chronic anemia seen in SCA patients [28].Furthermore, repeated hemolysis contributes to endothelial dysfunction, nitric oxide scavenging, and vascular inflammation, all of which exacerbate disease severity. The ongoing destruction of RBCs releases pro-oxidant molecules into the extracellular space, including heme, which activates toll-like receptor 4 (TLR4) and triggers downstream inflammatory pathways. These interactions highlight the systemic ripple effects of ferroptotic-like RBC injury in promoting both local and systemic inflammation in SCA [29].Recent experimental models have demonstrated that pharmacological inhibition of lipid peroxidation can reduce hemolysis and improve RBC lifespan. For instance, ferrostatin-1 and liproxstatin-1, both ferroptosis inhibitors, have shown protective effects in oxidatively stressed erythrocytes by scavenging lipid radicals and preserving membrane architecture. These findings suggest that targeting ferroptotic pathways in RBCs may offer a novel therapeutic approach to reducing hemolysis and its downstream complications in SCA [29-30].

Vascular and Organ Damage Mediated by Ferroptosis

Ferroptosis plays a significant role in the pathophysiology of vascular and organ damage in sickle cell anemia (SCA), a disease marked by chronic hemolysis, inflammation, and end-organ dysfunction. The vascular endothelium, kidneys, liver, spleen, and lungs are among the most affected tissues in SCA, and emerging studies suggest that ferroptosis contributes to tissue injury through lipid peroxidation, oxidative stress, and iron toxicity. This iron-dependent cell death mechanism exacerbates microvascular occlusion, endothelial dysfunction, and progressive organ damage that characterizes severe sickle cell complications [31].The vascular endothelium is highly vulnerable to oxidative damage in SCA due to its constant exposure to hemolytic byproducts such as free hemoglobin, heme, and iron. These molecules catalyze the formation of reactive oxygen species (ROS), triggering lipid peroxidation and ultimately leading to ferroptotic death of endothelial cells. Damage to the endothelium promotes a pro-thrombotic, pro-adhesive phenotype that facilitates the adhesion of sickled erythrocytes and leukocytes, worsening vaso-occlusion and tissue ischemia. Moreover, the death of endothelial cells disrupts the vascular barrier, allowing further infiltration of inflammatory cells and amplifying local injury [32].

In the kidneys, ferroptosis contributes to the pathogenesis of sickle cell nephropathy, a common and serious complication of SCA. The renal tubular epithelium, particularly in the medulla where oxygen tension is low, is extremely susceptible to ferroptosis due to the presence of labile iron, oxidative stress, and frequent hypoxia-reperfusion injury. Studies in animal models have shown that inhibition of ferroptosis can reduce tubular cell death, proteinuria, and glomerular damage, indicating its central role in renal injury. The chronic activation of ferroptotic pathways may also lead to progressive fibrosis and eventual loss of renal function in SCA patients [33].The liver and spleen, as major iron-handling and blood-filtering

organs, are also sites of significant ferroptotic damage. In the liver, excess iron accumulation from repeated hemolysis and transfusions overwhelms antioxidant defenses, leading to hepatocyte lipid peroxidation and ferroptosis. This contributes to liver dysfunction, inflammation, and fibrosis. Similarly, the spleen, which plays a role in filtering abnormal erythrocytes, experiences iron overload and oxidative damage, impairing its function and promoting splenic atrophy—particularly in pediatric SCA cases. These changes can diminish immune surveillance and increase susceptibility to infections [34].

In the lungs, ferroptosis is implicated in the development of acute chest syndrome (ACS) and pulmonary hypertension—two major life-threatening complications in SCA. Pulmonary endothelial cells and alveolar epithelial cells are exposed to oxidative stress and iron toxicity, particularly during vaso-occlusive episodes. The resultant ferroptotic cell death compromises pulmonary microcirculation and gas exchange, fostering inflammation and vascular remodeling. Additionally, iron-induced ferroptosis may amplify hypoxia-induced signaling, further worsening pulmonary vascular resistance [35].Systemically, the chronic activation of ferroptotic pathways in multiple organs contributes to the multi-organ dysfunction observed in severe SCA. The release of damage-associated molecular patterns (DAMPs) from ferroptotic cells can exacerbate systemic inflammation, perpetuating a vicious cycle of tissue injury and immune activation. This interplay between ferroptosis, inflammation, and organ dysfunction underscores its central role in disease progression [35-36].

Therapeutic Potential of Ferroptosis Modulation in Sickle Cell Anemia (SCA)

The growing understanding of ferroptosis as a key driver of red blood cell destruction, vascular dysfunction, and end-organ damage in sickle cell anemia (SCA) has opened new avenues for therapeutic intervention. Targeting ferroptosis represents a novel molecular strategy that complements traditional treatments like hydroxyurea, blood transfusions, and hematopoietic stem cell transplantation. By modulating ferroptotic pathways, it may be possible to attenuate oxidative damage, preserve cellular integrity, and alleviate chronic inflammation, thereby addressing multiple pathological processes of SCA simultaneously [37].Pharmacological inhibition of ferroptosis has emerged as a promising therapeutic strategy. Small-molecule ferroptosis inhibitors such as ferrostatin-1, liproxstatin-1, and vitamin E derivatives have demonstrated efficacy in preclinical models by scavenging lipid peroxides and preserving membrane stability. These compounds act by halting the lipid peroxidation cascade that drives ferroptosis, thereby reducing cellular injury and death. In SCA models, such interventions have shown potential in prolonging erythrocyte lifespan, reducing hemolysis, and mitigating organ injury, especially in the kidneys and lungs [38].

Iron chelation therapy, traditionally used to manage iron overload in transfused SCA patients, also holds relevance in the context of ferroptosis modulation. Agents such as deferoxamine, deferasirox, and deferiprone reduce labile iron pools that fuel ferroptotic reactions. By limiting iron availability, these chelators diminish ROS production and lipid peroxidation, thus interrupting the ferroptotic cascade. While their primary indication is iron overload, their role in directly countering ferroptosis warrants further exploration in SCA-specific contexts [39].Another important axis of therapeutic intervention is glutathione metabolism. The antioxidant glutathione (GSH) is a crucial defender against oxidative stress, and its depletion in SCA creates a pro-ferroptotic environment. Strategies aimed at restoring glutathione levels—such as supplementation with N-acetylcysteine (NAC) or enhancing cysteine uptake via system Xc^- activators—can replenish intracellular antioxidant reserves and bolster resistance to ferroptosis. Adjunct therapies that support glutathione peroxidase 4 (GPX4) activity or mimic its function may further fortify cellular

defense mechanisms against lipid peroxidation [40].

Gene therapy and gene editing technologies also offer exciting opportunities for ferroptosis modulation. By correcting hemoglobinopathies or enhancing the expression of antioxidant genes, these approaches could indirectly reduce ferroptosis susceptibility. For example, upregulating fetal hemoglobin (HbF) reduces hemoglobin S polymerization and oxidative burden, thereby minimizing one of the upstream triggers of ferroptosis. Additionally, CRISPR-Cas9–mediated modulation of ferroptosis-related genes (e.g., ACSL4, SLC7A11, or GPX4) may offer precise and lasting protection against ferroptotic cell death [39.Importantly, combination therapy approaches that integrate ferroptosis inhibitors with current SCA treatments hold potential for synergistic effects. For instance, combining hydroxyurea—which increases HbF and reduces hemolysis—with lipid peroxidation blockers or iron chelators may offer enhanced protection against RBC fragility and organ damage. Such integrated strategies could yield improved quality of life and clinical outcomes in patients with moderate to severe disease [40].

Conclusion

Ferroptosis has emerged as a pivotal contributor to the pathophysiology of sickle cell anemia (SCA), linking red blood cell fragility, chronic inflammation, and progressive organ damage through a distinct iron-dependent mechanism of regulated cell death. Unlike traditional forms of cell death such as apoptosis or necrosis, ferroptosis is uniquely driven by lipid peroxidation and iron overload—both of which are profoundly dysregulated in SCA. This molecular pathway not only exacerbates hemolysis but also contributes to endothelial dysfunction, renal impairment, hepatic injury, and pulmonary complications, thereby amplifying the multisystem burden of the disease. Targeting key regulators of this pathway—including iron metabolism, antioxidant defense mechanisms (e.g., glutathione and GPX4), and lipid oxidation enzymes—offers promising opportunities for intervention. Pharmacological inhibitors of ferroptosis, iron chelators, and agents that restore redox balance represent innovative strategies that may complement existing treatments such as hydroxyurea and transfusion therapy. Moreover, advances in gene therapy and precision medicine have the potential to manipulate ferroptosis-related genes to provide long-lasting protection against oxidative injury and organ failure.

List of Abbreviations

ACSL4 – Acyl-CoA Synthetase Long-Chain Family Member 4
GPX4 – Glutathione Peroxidase 4
GSH – Glutathione
HbS – Hemoglobin S
LPCAT3 – Lysophosphatidylcholine Acyltransferase 3
NAC – N-Acetylcysteine
Nrf2 – Nuclear Factor Erythroid 2–Related Factor 2
PUFA-PLs – Polyunsaturated Fatty Acid-Containing Phospholipids
RBCs – Red Blood Cells
ROS – Reactive Oxygen Species
SCA – Sickle Cell Anemia
System Xc^- – Cystine/Glutamate Antiporter

References

1. Obeagu EI, Obeagu GU. Living with sickle cell in Uganda: A comprehensive perspective on challenges, coping strategies, and health interventions. Medicine (Baltimore). 2024;103(51): e41062.
2. Obeagu EI, Adias TC, Obeagu GU. Advancing life: innovative approaches to enhance survival in sickle cell anemia patients. Ann Med Surg (Lond). 2024;86(10):6021-6036.
3. Russo A, Patanè GT, Calderaro A, Barreca D, Tellone E, Putaggio S. Crosstalk Between Sickle Cell Disease and Ferroptosis. International Journal of Molecular Sciences. 2025;26(8):3675.

4. Menon AV, Liu J, Tsai HP, Zeng L, Yang S, Asnani A, Kim J. Excess heme upregulates heme oxygenase 1 and promotes cardiac ferroptosis in mice with sickle cell disease. Blood, The Journal of the American Society of Hematology. 2022;139(6):936-941.
5. Fortuna V, Lima J, Oliveira GF, Oliveira YS, Getachew B, Nekhai S, Aschner M, Tizabi Y. Ferroptosis as an emerging target in sickle cell disease. Current Research in Toxicology. 2024; 7:100181.
6. Xi C, Pang J, Zhi W, Chang CS, Siddaramappa U, Shi H, Horuzsko A, Pace BS, Zhu X. Nrf2 sensitizes ferroptosis through l-2-hydroxyglutarate–mediated chromatin modifications in sickle cell disease. Blood, The Journal of the American Society of Hematology. 2023;142(4):382-396.
7. Obeagu EI, Obeagu GU. Malnutrition in sickle cell anemia: Prevalence, impact, and interventions: A Review. Medicine (Baltimore). 2024 ;103(20): e38164.
8. Obeagu EI, Obeagu GU. Managing gastrointestinal challenges: Diarrhea in sickle cell anemia. Medicine (Baltimore). 2024;103(18): e38075.
9. Menon AV, Tsai HP, Kim J. Cardiac iron overload promotes ferroptosis and cardiac dysfunction in mice with sickle cell disease. The FASEB Journal. 2020;34(S1):1-.
10. Haroun E, Lim SH, Dutta D. GBT1118, a Voxelotor Analog, Ameliorates Hepatopathy in Sickle Cell Disease. Medicina. 2024;60(10):1581.
11. Beckman JD, Sparkenbaugh EM. The invisible string of coagulation, complement, iron, and inflammation in sickle cell disease. Current opinion in hematology. 2023;30(5):153-8.
12. Obeagu EI, Obeagu GU. Management of diabetes mellitus patients with sickle cell anemia: Challenges and therapeutic approaches. Medicine (Baltimore). 2024;103(17): e37941.
13. Maddah R, Etemad S, Amiri BS, Ghaderi H, Zarei H, Faghihkhorasani F, Rezaeeyan H. Evaluation of Genes and Molecular Pathways Involved in Pathogenesis of Sickle Cell Anemia: A Bioinformatics Analysis and Future Perspective. Iranian Journal of Public Health. 2024;53(6):1404.
14. Zhu X, Oseghale AR, Nicole LH, Li B, Pace BS. Mechanisms of NRF2 activation to mediate fetal hemoglobin induction and protection against oxidative stress in sickle cell disease. Experimental Biology and Medicine. 2019;244(2):171-182.
15. Xi C, Palani C, Takezaki M, Shi H, Horuzsko A, Pace BS, Zhu X. Simvastatin-Mediated Nrf2 Activation Induces Fetal Hemoglobin and Antioxidant Enzyme Expression to Ameliorate the Phenotype of Sickle Cell Disease. Antioxidants. 2024;13(3):337.
16. Obeagu EI, Ubosi NI, Obeagu GU, Egba SI, Bluth MH. Understanding apoptosis in sickle cell anemia patients: Mechanisms and implications. Medicine. 2024;103(2): e36898.
17. Menon AV, Liu J, Tsai HP, Zeng L, Yang S, Asnani A, Kim J. Excess heme upregulates heme oxygenase 1 and promotes cardiac ferroptosis in mice with sickle cell disease. Blood, The Journal of the American Society of Hematology. 2022;139(6):936-491.
18. Fortuna V, Lima J, Oliveira GF, Oliveira YS, Getachew B, Nekhai S, Aschner M, Tizabi Y. Ferroptosis as an emerging target in sickle cell disease. Current Research in Toxicology. 2024; 7:100181.
19. Bell V, Varzakas T, Psaltopoulou T, Fernandes T. Sickle cell disease update: new treatments and challenging nutritional interventions. Nutrients. 2024;16(2):258.
20. Obeagu EI, Obeagu GU. Immunization strategies for individuals with sickle cell anemia: A narrative review. Medicine (Baltimore). 2024 Sep 20;103(38): e39756.

21. Obeagu EI, Akinleye CA, Obeagu GU. The role of nucleation in sickle cell pathophysiology: opportunities for innovative treatments. Ann Med Surg (Lond). 2024;87(3):1341-1350.
22. Obeagu EI, Obeagu GU. Managing emotional and physical stress in sickle cell anemia: a review of effective strategies and approaches. Ann Med Surg (Lond). 2025;87(3):1370-1382.
23. Dilli PP, Obeagu E, Tamale A, Ajugwo A, Pius T, Makeri D. Update on the practice of premarital screening for sickle cell traits in Africa: a systematic review and meta-analysis. BMC Public Health. 2024;24(1):1467.
24. D'Alessandro A, Keele GR, Hay A, Nemkov T, Earley EJ, Stephenson D, Vincent M, Deng X, Stone M, Dzieciatkowska M, Hansen KC. Ferroptosis regulates hemolysis in stored murine and human red blood cells. Blood. 2025;145(7):765-783.
25. Wang Q, Zennadi R. The role of RBC oxidative stress in sickle cell disease: from the molecular basis to pathologic implications. Antioxidants. 2021;10(10):1608.
26. Chen Z, Jiang J, Fu N, Chen L. Targetting ferroptosis for blood cell-related diseases. Journal of Drug Targeting. 2022;30(3):244-258.
27. Salgar S, Bolívar BE, Flanagan JM, Anum SJ, Bouchier-Hayes L. The NLRP3 inflammasome fires up heme-induced inflammation in hemolytic conditions. Translational Research. 2023; 252:34-44.
28. Wang H, You X, Wang J, Chen X, Gao Y, Wang M, Zhang W, Zhang J, Yu Y, Han B, Qi M. MFSD7C protects hemolysis-induced lung impairments by inhibiting ferroptosis. Nature Communications. 2024;15(1):8226.
29. Chattipakorn N. Cardiac ferroptosis: new jigsaw in SCD puzzles. Blood, The Journal of the American Society of Hematology. 2022;139(6):811-812.
30. Liu Y, Zhong H, Bao W, Mendelson A, An X, Shi P, Chou ST, Manwani D, Yazdanbakhsh K. Patrolling monocytes scavenge endothelial-adherent sickle RBCs: a novel mechanism of inhibition of vaso-occlusion in SCD. Blood, The Journal of the American Society of Hematology. 2019;134(7):579-590.
31. Yu Y, Yan Y, Niu F, Wang Y, Chen X, Su G, Liu Y, Zhao X, Qian L, Liu P, Xiong Y. Ferroptosis: a cell death connecting oxidative stress, inflammation and cardiovascular diseases. Cell death discovery. 2021;7(1):193.
32. Wu H, Chen L, Lu K, Liu Y, Lu W, Jiang J, Weng C. HMGB2 Deficiency Mitigates Abdominal Aortic Aneurysm by Suppressing Ang-II-Caused Ferroptosis and Inflammation via NF-κβ Pathway. Mediators of inflammation. 2023;2023(1):2157355.
33. Ding S, Jiang J, Zhang G, Yu M, Zheng Y. Ambient particulate matter exposure plus chronic ethanol ingestion exacerbates hepatic fibrosis by triggering the mitochondrial ROS-ferroptosis signaling pathway in mice. Ecotoxicology and environmental safety. 2023; 256:114897.
34. Liu Y, Pal M, Bao W, Shi PA, Lobo CA, An X, Manwani D, Zhong H, Yazdanbakhsh K. Type I interferon is induced by hemolysis and drives antibody-mediated erythrophagocytosis in sickle cell disease. Blood, The Journal of the American Society of Hematology. 2021;138(13):1162-1171.
35. Qin S, Zhu C, Chen C, Sheng Z, Cao Y. An emerging double-edged sword role of ferroptosis in cardiovascular disease. International Journal of Molecular Medicine. 2024 ;55(1):16.
36. Bhatt S, Argueta DA, Gupta K, Kundu S. Red blood cells as therapeutic target to treat sickle cell disease. Antioxidants & Redox Signaling. 2024;40(16-18):1025-1049.
37. Gonçalves E, Smaoui S, Brito M, Oliveira JM, Arez AP, Tavares L. Sickle cell disease: current drug treatments and functional foods with therapeutic potential. Current Issues in Molecular Biology. 2024;46(6):5845-5865.
38. Bou-Fakhredin R, De Franceschi L, Motta I, Eid AA, Taher AT, Cappellini MD. Redox Balance in β-Thalassemia and sickle cell disease: a love and hate relationship. Antioxidants. 2022;11(5):967.

39. Conran N, De Paula EV. Thromboinflammatory mechanisms in sickle cell disease–challenging the hemostatic balance. Haematologica. 2020;105(10):2380.
40. Gotardo ÉM, Brito PL, Gushiken LF, Chweih H, Leonardo FC, Costa FF, Conran N. Molecular and cellular effects of in vivo chronic intravascular hemolysis and anti-inflammatory therapeutic approaches. Vascular pharmacology. 2023; 150:107176.

Access this Article in Online	
	Website: www.ijcrcps.com
Quick Response Code	Subject: Hematology
DOI: 10.22192/ijcrcps.2025.12.08.005	

How to cite this article:
Emmanuel Ifeanyi Obeagu. (2025). The Role of Ferroptosis in Sickle Cell Anemia: A Molecular Death Pathway in Focus. Int. J. Curr. Res. Chem. Pharm. Sci. 12(8): 44-53.
DOI: http://dx.doi.org/10.22192/ijcrcps.2025.12.08.005

