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Phospholipid Oxidation and Membrane Integrity in Sickle Cell Anemia

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Abstract

Sickle Cell Anemia (SCA) is a genetic blood disorder caused by the mutation of the β-globin gene, resulting in the production of hemoglobin S and the characteristic sickling of red blood cells (RBCs). One of the central pathophysiological mechanisms in SCA is oxidative stress, which significantly affects RBC membrane integrity through the oxidation of phospholipids. Phospholipid oxidation, driven by reactive oxygen species (ROS) and reactive nitrogen species (RNS), leads to alterations in the RBC membrane structure and function, contributing to hemolysis, increased blood viscosity, and vaso-occlusive crises. This review explores the mechanisms by which phospholipid oxidation disrupts RBC membrane integrity, the resulting impact on SCA pathogenesis, and the current therapeutic strategies aimed at mitigating oxidative damage. By examining the links between oxidative stress, phospholipid oxidation, and RBC membrane stability, this review highlights potential targets for novel therapeutic interventions in SCA.

Keywords: *Sickle Cell Anemia, Phospholipid Oxidation, Membrane Integrity, Oxidative Stress, Red Blood Cells*

Introduction

Sickle Cell Anemia (SCA) is a severe hereditary blood disorder caused by a single nucleotide mutation in the β-globin gene, leading to the production of hemoglobin S (HbS) instead of the normal hemoglobin A. This genetic defect results in the polymerization of HbS under low oxygen conditions, causing red blood cells (RBCs) to adopt a rigid, sickle-like shape. This morphological change impairs the RBCs' ability to traverse the microvasculature, leading to vaso-occlusive crises, chronic hemolysis, and a spectrum of clinical complications. Over the years, research has increasingly highlighted the multifaceted pathophysiology of SCA, where oxidative stress and its effects on RBC membranes have become central themes in understanding and managing the disease. One significant consequence of oxidative stress in SCA is the oxidation of phospholipids, a critical component of the RBC membrane. Phospholipids, including phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine, are fundamental to maintaining the structural integrity and functionality of the RBC membrane. Under conditions of oxidative stress, reactive oxygen species (ROS) and reactive nitrogen species (RNS) damage these phospholipids, initiating a cascade of lipid peroxidation reactions. This oxidative damage alters the physical properties of

the RBC membrane, leading to increased membrane permeability, cell fragility, and hemolysis. Thus, understanding the mechanisms by which phospholipid oxidation affects membrane integrity is crucial for developing effective therapies for SCA.[1-5]

Phospholipid oxidation in SCA starts with the attack of ROS on the polyunsaturated fatty acids present in the phospholipid bilayer of RBC membranes. This oxidative attack generates lipid peroxides and aldehyde byproducts, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), which further propagate oxidative damage and disrupt the membrane structure. The compromised RBC membrane not only affects cell stability but also impacts the cell's ability to function correctly within the circulatory system. This includes altered cell shape and increased susceptibility to hemolysis, which are key factors in the pathogenesis of SCA. The impact of phospholipid oxidation on RBC membrane integrity extends to the development of vaso-occlusive crises, a hallmark of SCA. Vaso-occlusive crises occur when sickled RBCs obstruct blood flow in the microvasculature, leading to tissue ischemia and pain. Oxidized phospholipids, particularly those causing the externalization of phosphatidylserine, act as pro-coagulant signals and promote RBC adhesion to the endothelium. This adhesion contributes to the formation of blood clots and microvascular blockages, exacerbating the severity and frequency of vaso-occlusive crises in SCA patients. The relationship between phospholipid oxidation and vaso-occlusive crises highlights the need for targeted therapeutic approaches to manage oxidative stress in SCA. Current treatments such as hydroxyurea, which increases fetal hemoglobin (HbF) and reduces oxidative stress, offer some relief but are not a cure. Research into additional therapies that specifically target oxidative damage to phospholipids is ongoing, with the goal of developing more effective treatments to manage both chronic and acute manifestations of the disease.[6-10]

Beyond therapeutic interventions, there is also growing interest in understanding the role of oxidative stress in the broader context of SCA complications. Oxidative stress is known to contribute to a range of SCA-related issues, including chronic pain, organ damage, and increased susceptibility to infections. By focusing on phospholipid oxidation as a central mechanism of oxidative damage, researchers aim to uncover new strategies for preventing these complications and improving the overall quality of life for SCA patients. Recent advancements in the field have also highlighted the potential of combining existing therapies with novel antioxidants and anti-inflammatory agents. For example, vitamin E and N-acetylcysteine (NAC) are being investigated for their ability to reduce oxidative damage and preserve RBC membrane integrity. These treatments offer hope for enhancing the effectiveness of SCA management strategies and addressing the oxidative stress that underlies many of the disease's complications. Additionally, there is a growing body of research exploring the role of iron chelation therapy in managing oxidative stress in SCA. Excess iron from repeated blood transfusions can exacerbate oxidative damage, and chelating agents like deferasirox and deferoxamine are used to reduce iron overload and its associated oxidative stress. These therapies provide another layer of intervention for managing oxidative damage in SCA and represent a critical component of comprehensive disease management.[11-15]

Phospholipid Oxidation in Sickle Cell Anemia

Phospholipid oxidation is a critical factor in the pathophysiology of Sickle Cell Anemia (SCA). This oxidative process affects the red blood cell (RBC) membrane, leading to a range of cellular dysfunctions that contribute to the disease's clinical manifestations. Sickle Cell Anemia arises from a point mutation in the β-globin gene, which causes the substitution of glutamic acid with valine at position 6 in the β-globin chain. This mutation leads to the production of hemoglobin S (HbS), which, under low oxygen conditions, polymerizes to form rigid, elongated structures that deform RBCs into a sickle shape. These sickled cells cause blockages in the microvasculature, leading to vaso-occlusive crises. One of the lesser understood but crucial aspects of SCA pathophysiology is the role of oxidative stress, which is exacerbated by HbS polymerization and contributes to further RBC damage. Oxidative stress in SCA is driven by the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These highly reactive molecules are generated as a byproduct of sickle hemoglobin polymerization and have the potential to damage various cellular components, including lipids, proteins, and nucleic acids. Among these targets, phospholipids in the RBC membrane are particularly susceptible to oxidative damage, which initiates a cascade of pathological events leading to increased RBC destruction and exacerbation of disease symptoms.[16-20]

Phospholipid oxidation begins with the attack of ROS on the polyunsaturated fatty acids (PUFAs) found in the phospholipid bilayer of RBC membranes. This oxidative attack results in the formation of lipid hydroperoxides, which are unstable and decompose into secondary products like malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). These byproducts can further propagate oxidative damage, leading to the formation of oxidized phospholipids. The oxidation process disrupts the normal structure of the phospholipid bilayer, altering membrane fluidity and permeability. ROS such as superoxide anions, hydrogen peroxide, and hydroxyl radicals are generated during the sickling process and exacerbate oxidative stress. These radicals react with the PUFAs in phospholipids, causing lipid peroxidation. The primary products of this reaction, including MDA and HNE, modify membrane proteins and lipids, leading to membrane dysfunction. The damaged membrane becomes more permeable, resulting in the leakage of intracellular components and contributing to the pathophysiology of SCA. The oxidation of phospholipids severely impacts RBC membrane integrity. One of the primary effects is increased membrane permeability. Oxidized phospholipids disrupt the lipid bilayer, causing it to become more permeable to ions and molecules. This increased permeability leads to the leakage of essential intracellular components, such as hemoglobin, potassium ions, and other solutes, which can contribute to RBC hemolysis.[21-25]

Hemolysis, or the breakdown of RBCs, is a central feature of SCA. The loss of RBCs from the circulation results in chronic anemia, which manifests as fatigue, weakness, and other symptoms. Additionally, the loss of membrane integrity affects the RBC's ability to navigate through small blood vessels. The sickled shape, combined with the effects of phospholipid oxidation, increases the rigidity of the RBCs, making it more difficult for them to traverse the microvasculature and increasing the risk of vaso-occlusive events. Phosphatidylserine (PS) is a phospholipid normally located on the inner leaflet of the RBC membrane bilayer. Oxidative stress causes PS to externalize to the outer leaflet, where it acts as a signal for phagocytosis and coagulation. This externalization serves as a 'eat-me' signal for macrophages, leading to increased clearance of RBCs from the

circulation and further exacerbating anemia. Moreover, externalized PS acts as a pro-coagulant signal, enhancing the adhesion of sickled RBCs to the endothelial cells of blood vessels. This increased adhesion promotes the formation of blood clots and contributes to the development of vaso-occlusive crises, a major clinical manifestation of SCA. These crises cause acute pain, organ damage, and other severe complications. The products of lipid peroxidation, such as MDA and HNE, are not only indicators of oxidative stress but also play a role in the progression of SCA. Elevated levels of these products correlate with increased oxidative damage and are associated with the clinical severity of the disease. Monitoring the levels of these biomarkers can provide insights into the extent of oxidative damage and the effectiveness of therapeutic interventions aimed at reducing oxidative stress.[26-30]

Research has shown that high levels of MDA and HNE are associated with increased hemolysis and a greater frequency of vaso-occlusive crises. These findings underscore the importance of targeting oxidative stress and phospholipid oxidation in the management of SCA. Several therapeutic strategies have been developed to target phospholipid oxidation and manage oxidative stress in SCA. Hydroxyurea is a well-established treatment that, beyond increasing fetal hemoglobin levels, exerts antioxidant effects that help reduce oxidative damage. By lowering ROS levels and thereby reducing oxidative stress, hydroxyurea helps to stabilize the RBC membrane and decrease the frequency of vaso-occlusive crises. Another promising approach is the use of antioxidants such as vitamin E and N-acetylcysteine (NAC). Vitamin E, a lipid-soluble antioxidant, protects phospholipids from oxidative damage and preserves RBC membrane integrity. NAC, a precursor to the antioxidant glutathione, helps to reduce oxidative stress and improve RBC function. Both of these agents have shown potential in clinical trials for managing oxidative stress in SCA patients.[31-35]

Impact on Red Blood Cell Membrane Integrity

Phospholipid oxidation has profound effects on red blood cell (RBC) membrane integrity in Sickle Cell Anemia (SCA). The oxidation of phospholipids disrupts membrane structure and function, contributing significantly to the disease's pathophysiology. Phospholipids are fundamental components of the RBC membrane, contributing to its structural integrity and flexibility. The RBC membrane is composed of a phospholipid bilayer interspersed with proteins that maintain cell shape, facilitate gas exchange, and regulate membrane permeability. Phospholipid oxidation leads to the peroxidation of polyunsaturated fatty acids within the bilayer, generating lipid peroxides and secondary oxidation products like malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE). These oxidative products cause structural damage by altering the physical properties of the lipid bilayer. Oxidized phospholipids disrupt membrane fluidity and increase rigidity, which affects the RBC's ability to deform and traverse the microvasculature. The membrane's altered properties lead to a loss of its biconcave shape and contribute to the sickling process. This structural destabilization exacerbates RBC damage and hemolysis, both of which are central features of SCA. One of the primary consequences of phospholipid oxidation is increased RBC membrane permeability. Oxidized phospholipids cause the lipid bilayer to become more permeable to ions and molecules, which disrupts the osmotic balance of the cell. This increased permeability results in the leakage

of intracellular components such as hemoglobin, potassium ions, and other vital solutes. The loss of these components leads to cell swelling, dehydration, and eventually cell rupture.[36-40]

The process of hemolysis, or the destruction of RBCs, is a critical aspect of SCA pathology. The compromised membrane integrity due to phospholipid oxidation accelerates RBC hemolysis, contributing to chronic anemia and associated symptoms such as fatigue, pallor, and weakness. Hemolysis also releases free hemoglobin into the bloodstream, which can cause further complications, including increased oxidative stress and endothelial damage. Phospholipid oxidation alters several key properties of the RBC membrane, including its deformability and stability. Under oxidative stress, the RBC membrane becomes more rigid and less flexible. This decreased deformability impairs the RBC's ability to navigate through small blood vessels, which is essential for normal circulation. The sickled shape of RBCs, exacerbated by membrane damage, leads to increased blood viscosity and contributes to vaso-occlusive crises, a hallmark of SCA. Additionally, the oxidative modification of membrane proteins and lipids can lead to the formation of membrane aggregates and microvesicles. These structural changes further compromise the cell’s ability to maintain its normal shape and function, exacerbating the clinical manifestations of SCA, such as pain crises and organ damage.[41-45]

One of the direct consequences of phospholipid oxidation is the externalization of phosphatidylserine (PS) to the outer leaflet of the RBC membrane. Under normal conditions, PS is located on the inner leaflet, but oxidative stress causes it to flip to the outer leaflet, where it acts as a signal for phagocytosis and coagulation. Externalized PS is recognized by macrophages, leading to increased clearance of RBCs from circulation, which worsens anemia. Additionally, PS externalization enhances the formation of blood clots by acting as a pro-coagulant signal. This effect contributes to the development of vaso-occlusive crises by promoting RBC adhesion to the endothelium and the activation of the clotting cascade. The effects of phospholipid oxidation on RBC membrane integrity have significant implications for the lifespan of RBCs and the progression of SCA. The increased hemolysis resulting from membrane damage shortens the lifespan of RBCs, leading to chronic anemia and the need for regular blood transfusions. Repeated transfusions can lead to iron overload, which itself exacerbates oxidative stress and further complicates disease management. The shortened RBC lifespan also contributes to the chronic nature of SCA. As RBCs are destroyed more rapidly, the body must produce new cells to replace those lost. This ongoing demand for erythropoiesis can lead to additional complications, including splenomegaly and increased risk of infections due to splenic dysfunction. Phospholipid oxidation and its effects on the RBC membrane contribute to several secondary complications of SCA. The compromised membrane integrity and increased hemolysis can lead to a range of issues, including the development of acute chest syndrome, stroke, and organ damage. These complications are often a result of both the direct effects of membrane damage and the downstream consequences of increased hemolysis and vaso-occlusive events.[46-50]

Acute chest syndrome, for example, is a serious complication that can arise from the sickling of RBCs in the pulmonary vasculature, leading to lung inflammation and infection. Similarly, the increased risk of stroke is associated with vaso-occlusive events and the promotion of coagulation pathways due to oxidized phospholipids and externalized PS. Lipid peroxidation products such as

MDA and HNE serve as biomarkers for oxidative stress and are used to assess the severity of SCA. Elevated levels of these biomarkers are associated with increased membrane damage and more severe disease manifestations. Monitoring these biomarkers can provide valuable insights into the degree of oxidative stress and the effectiveness of therapeutic interventions aimed at reducing oxidative damage. Clinical studies have shown that higher levels of MDA and HNE correlate with more frequent vaso-occlusive crises and greater hemolysis in SCA patients. These findings underscore the importance of targeting oxidative stress in therapeutic strategies and using biomarkers to guide treatment decisions. Current therapeutic strategies for managing phospholipid oxidation and oxidative stress in SCA include the use of hydroxyurea, antioxidants, and iron chelation therapy. Hydroxyurea, a standard treatment for SCA, not only increases fetal hemoglobin levels but also has antioxidant properties that help reduce oxidative stress and stabilize the RBC membrane. Antioxidants such as vitamin E and N-acetylcysteine (NAC) are also used to counteract oxidative damage. Vitamin E, a lipid-soluble antioxidant, helps protect phospholipids from oxidation and improve RBC membrane stability. NAC, a precursor to glutathione, enhances the body's antioxidant defenses and reduces oxidative stress. Both treatments have shown promise in clinical trials for improving RBC membrane integrity and reducing the frequency of vaso-occlusive crises.[51-55]

Phospholipid Oxidation and Vaso-Occlusive Crises

Phospholipid oxidation plays a significant role in the development and exacerbation of vaso-occlusive crises in Sickle Cell Anemia (SCA). These crises are a hallmark of the disease and involve the obstruction of blood flow due to sickled red blood cells (RBCs), leading to acute pain, organ damage, and other severe complications. Understanding the relationship between phospholipid oxidation and vaso-occlusive crises provides insights into the disease mechanisms and highlights potential therapeutic targets for managing these painful episodes. Vaso-occlusive crises in SCA are primarily caused by the sickling of RBCs, which leads to the blockage of blood vessels and reduced oxygen delivery to tissues. Phospholipid oxidation, a consequence of oxidative stress, significantly exacerbates these crises. Oxidative stress in SCA results from the overproduction of reactive oxygen species (ROS) during the sickling process. These ROS initiate the peroxidation of phospholipids in the RBC membrane, which disrupts the cell's structural integrity and enhances its propensity to sickle. The process of phospholipid oxidation creates a cascade of harmful effects. Oxidized phospholipids generate secondary products such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), which contribute to further oxidative damage and inflammation. This damage not only affects the RBCs but also the endothelial cells lining the blood vessels, promoting adhesion and contributing to the formation of microinfarcts and vaso-occlusive events.[56-60]

One of the direct effects of phospholipid oxidation is increased RBC adhesion to the endothelial cells of blood vessels. Oxidized phospholipids on the RBC membrane can interact with endothelial adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), leading to enhanced RBC adhesion to the vessel wall. This increased adhesion is a critical factor in the development of vaso-occlusive crises. Phosphatidylserine (PS) externalization, a consequence of phospholipid oxidation, plays a

significant role in this process. PS on the outer leaflet of the RBC membrane acts as a pro-coagulant signal, enhancing the interaction between RBCs and the endothelial surface. This interaction facilitates the formation of blood clots and further contributes to the obstruction of blood flow, leading to vaso-occlusive crises. Oxidized phospholipids not only affect RBCs but also cause damage to endothelial cells, which line the blood vessels. These lipids can induce endothelial cell dysfunction through the activation of inflammatory pathways. For instance, oxidized phospholipids can stimulate the release of pro-inflammatory cytokines and adhesion molecules from endothelial cells, which promotes the recruitment of inflammatory cells and further exacerbates vascular inflammation. The inflammatory response triggered by oxidized phospholipids results in endothelial activation, which increases the expression of adhesion molecules and the production of inflammatory mediators. This endothelial dysfunction contributes to the pathogenesis of vaso-occlusive crises by facilitating the adhesion of sickled RBCs and the formation of thrombi, which obstruct blood flow and lead to acute pain and tissue ischemia.[61-65]

Phospholipid oxidation affects the coagulation cascade, which is a critical component of vaso-occlusive crises. Oxidized phospholipids can act as coagulant signals by exposing PS on the RBC membrane, which promotes the activation of the coagulation cascade. This pro-coagulant state enhances thrombus formation and contributes to blood vessel occlusion during vaso-occlusive crises. Increased activation of the coagulation cascade leads to the formation of fibrin clots and the obstruction of blood vessels. This coagulation process is amplified by the externalization of PS, which serves as a scaffold for the assembly of coagulation complexes and the propagation of the clotting response. Consequently, the interplay between phospholipid oxidation and the coagulation cascade is a key factor in the severity of vaso-occlusive crises. Phospholipid oxidation impairs RBC deformability, which exacerbates the tendency of these cells to sickle and cause vaso-occlusive crises. Oxidative damage to the phospholipid bilayer disrupts membrane fluidity and elasticity, making it more difficult for RBCs to change shape in response to changes in blood flow. Decreased deformability of sickled RBCs further contributes to the blockage of small blood vessels and the formation of microinfarcts. The rigid, inflexible nature of oxidized RBCs exacerbates the symptoms of vaso-occlusive crises by impeding the flow of blood through the microvasculature and increasing the risk of vascular occlusion.[66-70]

Biomarkers of phospholipid oxidation, such as MDA and HNE, have been used to assess the extent of oxidative stress and its relationship to vaso-occlusive crises. Elevated levels of these biomarkers correlate with increased oxidative damage and the severity of vaso-occlusive events in SCA patients. Monitoring these biomarkers can provide insights into the effectiveness of therapeutic interventions aimed at reducing oxidative stress. For example, therapies that lower MDA and HNE levels may help to prevent or reduce the frequency of vaso-occlusive crises, offering potential strategies for disease management. Several therapeutic strategies aim to manage phospholipid oxidation and its effects on vaso-occlusive crises. Hydroxyurea, a commonly used medication in SCA, not only increases fetal hemoglobin levels but also has antioxidant properties that reduce oxidative stress and stabilize the RBC membrane. This dual action helps to mitigate the impact of phospholipid oxidation and reduce the frequency of vaso-occlusive crises. Antioxidants such as vitamin E and N-acetylcysteine (NAC) are also employed to counteract oxidative damage. Vitamin E, a lipid-soluble antioxidant, protects phospholipids from oxidation and improves RBC

membrane stability. NAC, which replenishes glutathione, enhances the body's antioxidant defenses and helps to manage oxidative stress. Both treatments have demonstrated potential in clinical trials for reducing the incidence of vaso-occlusive crises in SCA patients. Combination therapies that address both oxidative stress and vaso-occlusive crises offer a promising approach to managing SCA. By combining antioxidants with other treatments such as hydroxyurea, researchers aim to achieve synergistic effects that improve patient outcomes. For example, combining vitamin E with hydroxyurea may offer enhanced protection against oxidative damage and reduce the frequency of vaso-occlusive crises.[71-73]

Therapeutic Interventions Targeting Phospholipid Oxidation

Addressing phospholipid oxidation in Sickle Cell Anemia involves several therapeutic strategies aimed at reducing oxidative stress and preserving membrane integrity. One of the primary approaches is the use of antioxidant therapies to neutralize ROS and prevent phospholipid oxidation. Agents such as hydroxyurea, vitamin E, and N-acetylcysteine (NAC) are commonly used in clinical practice and research for their antioxidant properties. Hydroxyurea, a standard treatment for SCA, has been shown to reduce oxidative stress by increasing the production of fetal hemoglobin (HbF) and decreasing ROS levels. While its primary benefit comes from increasing HbF, hydroxyurea also has secondary effects on reducing oxidative damage and improving RBC membrane stability. Vitamin E, a well-known antioxidant, protects against lipid peroxidation by scavenging free radicals and breaking the chain reaction of lipid peroxidation. Supplementation with vitamin E has been shown to reduce oxidative stress markers and improve clinical outcomes in SCA patients, including a reduction in hemolysis and an improvement in RBC membrane integrity. N-acetylcysteine (NAC) acts as a precursor for glutathione, a key intracellular antioxidant. NAC supplementation helps replenish glutathione levels, neutralizes ROS, and reduces oxidative damage to phospholipids and other cellular components. Clinical studies have demonstrated that NAC can effectively reduce oxidative stress and improve RBC function in SCA patients. Another approach to managing oxidative stress involves iron chelation therapy. Excess iron from repeated blood transfusions can catalyze ROS formation and exacerbate oxidative damage. Deferasirox and deferoxamine are iron chelators that reduce iron-induced oxidative stress by binding free iron and facilitating its excretion. These therapies help decrease oxidative damage to phospholipids and maintain RBC membrane integrity. Targeted therapies that address phospholipid oxidation and membrane damage are also under investigation. For example, sevuparin, a novel agent, has shown potential in reducing oxidative stress and improving RBC function. By targeting both the sickling process and oxidative stress, sevuparin represents a promising therapeutic avenue for managing SCA.[68-73]

Conclusion

Phospholipid oxidation is a pivotal factor in the pathogenesis of Sickle Cell Anemia (SCA), influencing the stability of red blood cell (RBC) membranes, contributing to hemolysis, and exacerbating vaso-occlusive crises. Through mechanisms such as increased RBC adhesion, endothelial dysfunction, and the activation of the coagulation cascade, phospholipid oxidation plays a critical role in the development and progression of the disease's complications. Agents

such as hydroxyurea, vitamin E, and N-acetylcysteine (NAC) have demonstrated efficacy in reducing oxidative stress and improving clinical outcomes in SCA. Hydroxyurea, in particular, offers both antioxidant effects and increases fetal hemoglobin levels, which collectively help to manage the disease. Vitamin E and NAC also show promise in stabilizing the RBC membrane and reducing oxidative damage.

Drugs like nitric oxide donors and statins provide additional therapeutic options by targeting oxidative stress and enhancing vascular function. Nitric oxide donors help to improve blood flow and reduce vaso-occlusive crises, while statins offer both lipid-lowering and antioxidant benefits. Agents such as deferoxamine and deferasirox address the problem of iron overload from blood transfusions. By removing excess iron, these chelators reduce oxidative stress and prevent further damage to RBC membranes. Advances in gene therapy, including techniques like CRISPR-Cas9 and lentiviral vector-based approaches, offer potential long-term solutions for SCA by correcting the genetic defects that cause the disease. These methods aim to increase fetal hemoglobin levels and reduce oxidative stress at a fundamental level.

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