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REVIEW ARTICLE

# MOLECULAR CROSSTALK BETWEEN HYPOXIA INDUCIBLE FACTORS AND SICKLE CELL PATHOGENESIS: A NARRATIVE REVIEW

**Emmanuel Ifeanyi Obeagu[1,2]*, Ezeldine Abdalhabib[3], Wael Alzahrani[3]**
[1]*Division of Haematology, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.*
[2]*The Division of Molecular Medicine and Haematology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.*
[3]*Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Al Qurayyat, Jouf University, Saudi Arabia.*

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***Address for Correspondence:**
**Dr. Emmanuel Ifeanyi Obeagu**, Haematology, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.
Tel: +263-778025658;
E-mail: *emmanuelobeagu@yahoo.com*

## Abstract

Sickle cell disease (SCD) is a hereditary hemoglobin disorder marked by the polymerization of deoxygenated sickle hemoglobin (HbS), causing vaso-occlusion, hemolysis, and persistent inflammation, leading to substantial morbidity and mortality. Recent studies have found hypoxia-inducible factors (HIFs) to be crucial regulators in cellular reactions to low oxygen conditions, commonly seen in different tissues impacted by SCD. The activation of HIFs is essential in regulating erythropoiesis, vascular stability, and inflammation, which are all key to the pathophysiology of SCD. This review examines the molecular interactions between HIFs and essential disease processes, emphasizing their role in the intricate clinical presentations of SCD. HIFs, especially HIF-1, control various genes that play a role in erythropoiesis and the vascular reaction to low oxygen levels. In SCD, the rise in tissue hypoxia worsens erythropoietic dysregulation and leads to the atypical generation of sickled red blood cells, which are susceptible to early hemolysis. Moreover, HIFs stimulate inflammatory pathways by increasing the production of cytokines and adhesion molecules, resulting in endothelial dysfunction and microvascular blockages. The resulting inflammatory reaction drives a harmful cycle of blood vessel harm and organ injury, which is characteristic of complications in SCD.

**Keywords:** Erythropoiesis, hemolysis, hypoxia-inducible factors, inflammation, sickle cell disease.

## INTRODUCTION

Sickle cell disease (SCD) is an inherited hemoglobin disorder resulting from a single nucleotide mutation in the β-globin gene, causing valine to replace glutamic acid at the sixth position of the β-globin chain. This leads to the formation of sickle hemoglobin (HbS), which solidifies in low oxygen conditions, altering red blood cells (RBCs) into stiff, crescent-like shapes. These sickle-shaped RBCs have a higher tendency for hemolysis, decreased deformability, and increased adhesion, resulting in vaso-occlusion, tissue ischemia, chronic hemolytic anemia, and multiple organ issues like stroke, pulmonary hypertension, and kidney dysfunction[1-3]. Worldwide, SCD impacts more than 20–25 million individuals, with the greatest prevalence in sub-Saharan Africa, where roughly 2% of infants have homozygous SCD. Other regions with significant burdens include India, the Middle East, and some areas of the Americas, mirroring patterns of historical malaria prevalence[4-6]. Regardless of progress in disease management, such as hydroxyurea treatment, regular transfusions, and hematopoietic stem cell transplants, SCD still causes significant illness and early death, especially in under-resourced areas with restricted access to specialized care. Social factors, including poverty, unequal access to healthcare, and inadequate availability of disease-modifying treatments, intensify the challenges of SCD and underscore the pressing requirement for innovative, accessible solutions[7,8].

A defining characteristic of SCD is repeated tissue hypoxia, resulting from vaso-occlusive crises, persistent anemia, and microvascular impairment. Cells react to hypoxia mainly by activating hypoxia-inducible factors (HIFs), a group of transcription factors that control gene expression programs vital for cellular adaptation to low-oxygen conditions. HIFs consist of heterodimers formed by an oxygen-sensitive α-subunit (HIF-α) and a β-subunit (HIF-β) that is expressed constitutively. In normoxic conditions, prolyl hydroxylase domain-containing proteins (PHDs) hydroxylate HIF-α, leading to its degradation through

the von Hippel-Lindau (VHL) pathway via proteasomes. Hypoxia prevents this hydroxylation, resulting in the stabilization of HIF-α, which then moves to the nucleus, pairs with HIF-β, and attaches to hypoxia-response elements (HREs) to regulate the transcription of genes related to erythropoiesis, angiogenesis, metabolism, and inflammation[9-11]. Within the realm of SCD, the interaction between HIF signaling and the pathology of the disease is intricate and influenced by multiple factors. HIFs affect erythropoiesis and fetal hemoglobin (HbF) synthesis, helping to alleviate HbS polymerization and decrease sickling. They likewise control endothelial activation and the expression of adhesion molecules like intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which aid in vaso-occlusion and microvascular inflammation. Additionally, HIFs influence oxidative stress responses and the production of inflammatory cytokines (like TNF-α, IL-6), creating feedback loops that worsen tissue damage and organ dysfunction in SCD[12-15].

Therapeutically, focusing on HIF pathways offers a hopeful strategy for managing SCD. Prolyl hydroxylase inhibitors, as small-molecule HIF stabilizers, may boost HbF expression and enhance erythropoietic responses. Gene therapy strategies might also utilize HIF pathways to enhance hemoglobin switching. Nonetheless, HIF modulation poses possible risks, such as tumor formation, cardiovascular impacts, and unintended effects, requiring thorough assessment, especially in areas with a high disease burden and limited resources[16-18]. This narrative review seeks to deliver an extensive summary of the molecular interactions between HIFs and crucial pathophysiological processes in SCD. This review aims to establish a framework for comprehending the potential of HIF-targeted approaches to enhance outcomes for individuals with SCD by combining molecular insights with epidemiological and clinical aspects.

The aim of this review is to explore the molecular crosstalk between HIFs and SCD pathogenesis, with a focus on understanding how HIFs influence key disease mechanisms, including endothelial dysfunction, inflammation, and erythropoiesis.

**Hypoxia-inducible factors and their role in sickle cell disease**

HIFs are master regulators of cellular adaptation to low oxygen environments. They orchestrate the transcription of numerous genes that modulate erythropoiesis, angiogenesis, metabolism, and inflammation. The HIF family consists primarily of three α-subunits—HIF-1α, HIF-2α, and HIF-3α—and a constitutively expressed β-subunit (HIF-β, also known as ARNT). HIF-α subunits are highly oxygen-sensitive: under normoxic conditions, they are hydroxylated by prolyl hydroxylase domain (PHD) enzymes, ubiquitinated by the von Hippel-Lindau (VHL) complex, and targeted for proteasomal degradation. Hypoxia inhibits PHD activity, allowing HIF-α stabilization, nuclear translocation, dimerization with HIF-β, and binding to hypoxia-response elements (HREs) in the promoter regions of target genes[16]. In SCD, chronic and episodic hypoxia is a defining feature, resulting from vaso-occlusion, hemolytic anemia, and impaired oxygen delivery. This hypoxic environment stabilizes HIFs, which in turn modulate multiple pathways central to disease pathogenesis (Table 1 and Table 2).

**Table 1: HIF-driven inflammatory and adhesion pathways contributing to vaso-occlusion in sickle cell disease.**

| Pathway/Target | HIF Isoform | Mechanism | Effect on SCD pathophysiology |
|---|---|---|---|
| VEGF (Vascular Endothelial Growth Factor) | HIF-1α, HIF-2α | Upregulates angiogenesis and vascular permeability | Promotes endothelial activation and contributes to microvascular occlusion |
| ICAM-1 (Intercellular Adhesion Molecule-1) | HIF-1α | Transcriptional upregulation under hypoxia | Enhances adhesion of sickled RBCs and leukocytes to endothelium |
| VCAM-1 (Vascular Cell Adhesion Molecule-1) | HIF-1α | Hypoxia-driven expression | Mediates RBC and leukocyte binding to endothelial cells, promoting vaso-occlusion |
| E-selectin / P-selectin | HIF-1α | Induced on endothelial surfaces | Facilitates leukocyte rolling and RBC adhesion in post-capillary venules |
| TNF-α (Tumor Necrosis Factor-alpha) | HIF-1α | Cytokine induction | Amplifies inflammatory cascade, endothelial activation, and vaso-occlusion |
| IL-6 (Interleukin-6) | HIF-1α | Upregulation under hypoxia | Promotes systemic inflammation and acute-phase response, worsening vaso-occlusive events |
| NF-κB Pathway | HIF-1α / HIF-2α | Cross-talk with HIF signaling | Enhances transcription of adhesion molecules and pro-inflammatory cytokines |
| Endothelin-1 | HIF-2α | Hypoxia-mediated upregulation | Vasoconstriction, increased vascular tone, exacerbating microvascular occlusion |
| MCP-1 (Monocyte Chemoattractant Protein-1) | HIF-1α | Induction under hypoxia | Recruits monocytes to endothelium, contributing to inflammation and vascular stasis |

**Isoform-Specific Roles: HIF-1α vs. HIF-2α**

HIF-1α and HIF-2α exhibit overlapping yet distinct functions, with tissue- and context-specific effects relevant to SCD.

**HIF-1α** is broadly expressed and regulates genes involved in glycolysis, angiogenesis, and acute cellular responses to hypoxia. In SCD, HIF-1α enhances the expression of adhesion molecules such as ICAM-1 and VCAM-1 on endothelial cells, promoting erythrocyte and leukocyte adhesion and contributing to vaso-occlusive crises.

**Table 2: Tissue-specific HIF responses and potential therapeutic intervention points in sickle cell disease.**

| Tissue/ Organ | Dominant HIF Isoform | Key HIF-Mediated Responses | Pathophysiological Consequences in SCD | Potential Therapeutic Interventions |
|---|---|---|---|---|
| Bone Marrow | HIF-1α, HIF-2α | EPO induction, erythroid progenitor proliferation, iron metabolism regulation | Ineffective erythropoiesis, chronic anemia, marrow expansion | HIF stabilizers to increase EPO and HbF, iron chelation to prevent overload |
| Endothelium (vascular) | HIF-1α | Upregulation of ICAM-1, VCAM-1, E-/P-selectin, VEGF | Enhanced RBC/leukocyte adhesion, microvascular occlusion, vaso-occlusive crises | HIF pathway inhibitors or adhesion blockers (anti-ICAM-1, anti-VCAM-1, P-selectin antagonists) |
| Lung/ Pulmonary Vasculature | HIF-2α | Endothelin-1 expression, vascular remodeling, angiogenesis | Pulmonary hypertension, hypoxemia | Selective HIF-2α modulators, endothelin receptor antagonists, vasodilators |
| Liver / Spleen | HIF-1α | Angiogenesis, inflammatory cytokine induction, extramedullary erythropoiesis | Organomegaly, local inflammation, ischemic injury | HIF modulators to balance erythropoiesis and inflammation; anti-inflammatory agents |
| Kidney | HIF-2α | EPO production, iron handling, metabolic adaptation | Risk of hyperviscosity, nephropathy | Targeted HIF-2α stabilization to enhance EPO without excessive RBC production; careful iron monitoring |
| Retina / Eye | HIF-1α | VEGF-driven angiogenesis | Retinopathy, neovascularization, vision loss | Anti-VEGF therapies; cautious HIF modulation to prevent pathological angiogenesis |
| Immune Cells / Leukocytes | HIF-1α | Cytokine and chemokine upregulation (TNF-α, IL-6, MCP-1) | Systemic inflammation, endothelial activation | Anti-inflammatory agents, selective HIF inhibitors to limit excessive immune activation |

It also induces pro-inflammatory cytokines (e.g., TNF-α, IL-6), amplifying vascular inflammation and endothelial dysfunction[4-6].

**HIF-2α** plays a more specialized role in erythropoietin (EPO) regulation and chronic adaptation to hypoxia. By inducing EPO expression in renal and hepatic tissues, HIF-2α stimulates erythropoiesis and reticulocyte production. While this compensatory mechanism can improve oxygen-carrying capacity, in SCD it may exacerbate erythrocyte sickling due to the preferential production of HbS-containing RBCs. HIF-2α is also implicated in long-term vascular remodeling and oxidative stress modulation, influencing disease progression[7-9].

**HIF-3α** is less studied in SCD and appears to function primarily as a negative regulator of HIF-1α and HIF-2α transcriptional activity, potentially fine-tuning hypoxic responses[17].

**HIF-mediated modulation of erythropoiesis and hemoglobin switching**

HIFs are critical regulators of erythropoiesis and fetal hemoglobin (HbF) induction. HbF inhibits HbS polymerization, mitigating sickling and hemolysis. Experimental studies suggest that HIF-1α stabilization can upregulate γ-globin gene expression either directly or via modulation of transcription factors such as BCL11A and KLF1. By promoting HbF production, HIF activation represents a potential therapeutic strategy to reduce disease severity in SCD[11,12].

**HIFs and Endothelial Dysfunction in SCD**

Endothelial activation is a central feature of SCD pathophysiology. HIF-1α enhances the expression of ICAM-1, VCAM-1, and selectins on endothelial surfaces, increasing RBC and leukocyte adherence. HIF-driven VEGF expression contributes to angiogenesis but also potentiates vascular permeability and inflammatory signaling, creating a feed-forward loop that exacerbates microvascular occlusion[13,14].

**HIFs and inflammatory signaling**

Chronic hypoxia in SCD leads to HIF-mediated induction of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. This cytokine milieu promotes leukocyte recruitment, oxidative stress, and endothelial injury. The interplay between HIFs, cytokine production, and adhesion molecule expression generates a self-perpetuating cycle of inflammation and vaso-occlusion, underlying many acute and chronic complications of SCD[15,16].

**Erythropoiesis and HIF activation in SCD**

A key characteristic of sickle cell disease is the formation of sickled red blood cells, which tend to undergo early destruction and have reduced oxygen transport capabilities. In reaction to tissue hypoxia, the body usually enhances erythropoiesis, the formation of new red blood cells, to address anemia. Hypoxia-inducible factors (HIF-1 and HIF-2) are crucial in this adaptive mechanism by controlling erythropoietin (EPO) synthesis, an essential hormone that promotes erythropoiesis in the bone marrow. In hypoxic conditions, HIFs become stable and enhance the transcription of the EPO gene, resulting in elevated EPO levels and increased production of red blood cells. In SCD, the hypoxic conditions created by sickled RBCs experiencing vaso-occlusion lead to ineffective

erythropoiesis, marked by the formation of abnormal, sickle-shaped red blood cells. Even with the elevated EPO levels, the abnormal RBCs still play a role in the cycle of hemolysis, anemia, and inflammation, worsening the condition. Moreover, the extended activation of HIFs in the bone marrow and various tissues may lead to the excessive generation of immature RBCs, which are less effective at transporting oxygen and are more susceptible to sickling in low oxygen environments[18-20].

**HIFs and inflammation in SCD**

Hypoxia and inflammation are interconnected in the pathophysiology of SCD. Tissue hypoxia, especially within the microvasculature, leads to the activation of HIFs, prompting the expression of different pro-inflammatory cytokines and adhesion molecules. These molecules play a vital role in attracting immune cells, including neutrophils and monocytes, to the area of vascular damage[21,22]. In SCD, sickled RBCs trigger the activation of endothelial cells, resulting in the expression of adhesion molecules like ICAM-1 and VCAM-1. These adhesion molecules aid in the binding of sickled RBCs and leukocytes to the endothelium, enhancing the creation of microvascular obstructions that lead to ischemia and tissue harm. HIFs additionally enhance the expression of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which play a role in the persistent inflammatory condition seen in SCD. The prolonged inflammatory response in SCD not only leads to the acute and chronic complications of the disease, including pain crises and organ damage, but also worsens the oxidative stress and endothelial dysfunction that are fundamental to vascular complications. Through the regulation of these inflammatory pathways, HIFs are crucial in the advancement of SCD and could serve as a possible therapeutic target for diminishing inflammation and averting additional vascular damage (Figure 1)[23,24].

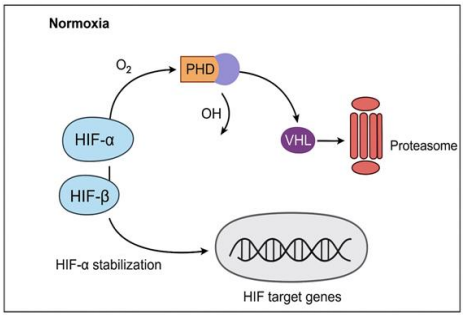


**Figure 1: HIF activation and regulation under hypoxia.**

**Endothelial dysfunction and vascular pathology in SCD**

Endothelial dysfunction is a key feature of sickle cell disease and is largely driven by the chronic hypoxic environment and the mechanical stress exerted by sickled RBCs on the blood vessel walls. HIFs play an important role in regulating vascular function by modulating the expression of various genes involved in endothelial cell activation, nitric oxide (NO) production, and vascular tone. In response to hypoxia, HIFs stimulate the expression of endothelial nitric oxide synthase (eNOS), which leads to the production of nitric oxide, a potent vasodilator that helps maintain vascular homeostasis[25,26]. However, in SCD, the balance between vasoconstrictors and vasodilators is disrupted, leading to endothelial injury and dysfunction. The activation of HIFs in SCD may exacerbate this imbalance by promoting the upregulation of pro-inflammatory genes while simultaneously impairing the vasodilatory function of nitric oxide. This disruption in vascular homeostasis contributes to the development of complications such as stroke, organ damage, and pain crises. By targeting HIFs and related pathways, it may be possible to mitigate endothelial dysfunction and improve vascular function in individuals with SCD[27,28].

**HIFs and the immune response in SCD**

The immune response in SCD is intricate and encompasses both the innate and adaptive immune systems. Sustained inflammation, caused by HIF activation, results in the attraction of immune cells to regions of tissue injury and blocked blood vessels. The activation of neutrophils, monocytes, and T lymphocytes plays a role in the persistent inflammatory condition that defines SCD. HIFs enhance the expression of chemokines and adhesion molecules, which aid in attracting immune cells and intensifying the inflammatory cycle. The ongoing immune activation not only leads to pain and organ damage related to SCD but also hinders the body's capacity to manage inflammation and heal tissue injuries. Modulating HIF-driven immune responses could help lessen the inflammatory reaction in SCD, decrease the occurrence of pain crises, and mitigate the advancement of organ damage[8,9].

**Molecular crosstalk: HIFs and erythropoiesis in sickle cell disease**

HIFs are crucial regulators of erythropoiesis, the process by which new RBCs are produced to maintain adequate oxygen delivery to tissues. In SCD, a genetic disorder caused by the production of sickle hemoglobin (HbS), the pathophysiology is significantly influenced by the dysfunctional properties of RBCs, which tend to sickle under low oxygen conditions. This results in a variety of clinical manifestations, including anemia, vaso-occlusion, and tissue damage[29-31].

**Erythropoiesis and oxygen sensing by HIFs**

In a healthy person, erythropoiesis is a carefully controlled process that guarantees the production of enough RBCs to transport oxygen throughout the body. In typical oxygen levels, HIFs are quickly broken down, but in low oxygen situations, prevalent in SCD because of RBC sickling and subsequent tissue ischemia, HIFs are stabilized. HIFs, mainly HIF-1 and HIF-2, control essential genes that are part of the erythropoietic response. A crucial gene is EPO, mainly generated by the kidneys when oxygen levels are low, and it promotes erythropoiesis in the bone marrow. In SCD, the persistent low-oxygen environment caused by microvascular blockage and hemolysis triggers HIFs to boost EPO synthesis. Even though this adaptive mechanism seeks to counteract the anemia produced by

the heightened destruction of sickled RBCs, it fails to address the underlying issue of the disease, which is the unusual polymerization of HbS when oxygen levels are low. Consequently, while erythropoiesis rises, the bone marrow generates irregular, sickled RBCs that are ineffective in oxygen delivery and susceptible to early destruction[32,33].

**The role of HIFs in ineffective erythropoiesis in SCD**

Ineffective erythropoiesis is a key feature of SCD. This process happens when the bone marrow generates RBCs more rapidly to counteract the anemia triggered by sickling and hemolysis, yet numerous newly created RBCs are destroyed early. The heightened turnover of RBCs creates a detrimental cycle of anemia and compensatory erythropoiesis. Although HIFs strive to boost RBC production through the induction of EPO expression, they may worsen ineffective erythropoiesis associated with SCD. The relationship between HIFs and erythropoiesis in SCD is intricate. Activation of HIF-1 and HIF-2 results in the synthesis of EPO as well as additional factors affecting hematopoiesis, including hypoxia-inducible factor 2-alpha (HIF-2α) and vascular endothelial growth factor (VEGF), both of which play roles in angiogenesis and the growth of the erythropoietic environment. Nevertheless, the heigh-tened erythropoiesis frequently results in a significant quantity of immature, non-functional RBCs because of the inefficient synthesis of HbA and the excessive generation of HbS. This leads to an abnormal quantity of sickled red blood cells that can't carry out the usual physiological roles of oxygen transport and exacerbate additional issues in SCD, such as vaso-occlusion and hemolytic crises. Furthermore, HIFs also affect the differentiation and maturation of erythroid progenitors. The stabilization of HIFs in the bone marrow during low oxygen levels encourages the maturation of these progenitors into immature RBCs, which are less efficient at transporting oxygen and more prone to sickling. These undeveloped cells play a role in the inefficacy of erythropoiesis in SCD, since they cannot persist in circulation and are swiftly removed by the spleen and liver, resulting in anemia and an ongoing need for erythropoietic activity [34-36].

**HIFs and the regulation of fetal hemoglobin (HbF) in SCD**

One of the most exciting aspects of HIFs in SCD is their role in the reactivation of fetal hemoglobin (HbF) production. Fetal hemoglobin is a form of hemoglobin that is normally expressed in the fetus and during early infancy, but its production significantly decreases after birth. In SCD, the expression of HbF has been shown to reduce the severity of the disease because HbF does not undergo polymerization in low-oxygen conditions, unlike HbS. HIFs, particularly HIF-1, have been implicated in the reactivation of HbF production in adult red blood cells. Studies have shown that the activation of HIF-1, under conditions of hypoxia, can lead to the upregulation of gamma-globin genes, which encode the subunits of HbF. This process has been identified as a promising therapeutic target for SCD, as increasing the proportion of HbF in the blood can reduce sickling and alleviate symptoms such as pain crises and vaso-occlusion. The molecular mechanisms by which HIFs regulate HbF expression are still being elucidated, but this avenue of research has the potential to lead to new treatments for SCD that leverage the body's natural hypoxic response to reduce disease severity[37-39].

**Tissue-specific hypoxia-inducible factor responses in sickle cell disease**

HIFs exhibit tissue-specific expression and activity, which critically shapes the pathophysiology of SCD. The chronic and episodic hypoxia characteristic of SCD leads to differential stabilization of HIF-1α and HIF-2α across various organs, resulting in distinct cellular responses that contribute to disease complications.

**1. Bone marrow and erythropoietic tissues**

The bone marrow is a primary site of HIF activation in response to hypoxia induced by chronic anemia in SCD. HIF-2α predominates in the regulation of EPO production, which stimulates erythropoiesis. While increased EPO-mediated erythropoiesis aims to compensate for anemia, in SCD it can exacerbate ineffective erythropoiesis due to accelerated production of sickle red blood cells, contributing to marrow expansion, extramedullary hematopoiesis, and reticulocytosis. HIF-1α also supports glycolytic metabolism in erythroid precursors, enabling survival under hypoxic stress[3].

**2. Vascular endothelium**

Endothelial cells are highly responsive to HIF-1α stabilization under hypoxic and ischemic conditions. HIF-1α induces the expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and pro-inflammatory cytokines, promoting the adhesion of sickled erythrocytes and leukocytes to the endothelium. These interactions drive vaso-occlusion, microvascular ischemia, and tissue damage. HIF-2α in endothelial cells contributes to angiogenic responses via VEGF upregulation, which may lead to abnormal vascular remodeling and increased vascular permeability [4–6].

**3. Spleen**

The spleen, a highly vascular and oxygen-sensitive organ, is particularly susceptible to HIF-mediated responses. Hypoxia in the splenic microenvironment triggers HIF-1α and HIF-2α activation, which can exacerbate red pulp congestion and contribute to splenic infarction—a common complication in SCD. HIF-driven inflammatory signaling within splenic endothelial and immune cells further amplifies local tissue injury and functional asplenia over time[7,8].

**4. Liver and kidney**

HIF-2α is the dominant isoform regulating EPO expression in the kidney and, to a lesser extent, the liver. In SCD, chronic hypoxia elevates HIF-2α activity, promoting erythropoietic compensation. However, excessive HIF-2α activation may also enhance iron metabolism and oxidative stress pathways, contributing to organ injury. In the kidney, HIF activation influences glomerular endothelial function, tubular metabolism, and susceptibility to chronic kidney disease, which is a major SCD complication[9-11].

**5. Lung**

Pulmonary tissue experiences recurrent hypoxia during vaso-occlusive episodes, leading to HIF-1α stabilization in alveolar epithelial and vascular endothelial cells. HIF-1α-mediated upregulation of VEGF and pro-inflammatory cytokines contributes to pulmonary vascular remodeling, endothelial dysfunction, and predisposition to pulmonary hypertension a life-threatening SCD complication. HIF-2α may further influence chronic hypoxic adaptation in pulmonary vasculature, affecting vascular tone and remodeling[12-14].

**6. Central nervous system**

Neurons and glial cells respond to hypoxia through HIF-1α activation, which promotes angiogenesis, metabolic adaptation, and cell survival. In SCD, repeated hypoxic episodes can induce maladaptive HIF signaling, leading to cerebral vasculopathy, ischemic injury, and increased stroke risk. HIF-mediated inflammatory responses in brain endothelial cells may further exacerbate blood-brain barrier dysfunction and neurovascular complications[15,16].

**HIFs, hypoxia, and the endothelial activation in SCD**

Endothelial dysfunction is another key component of the inflammatory response in SCD. Hypoxia and sickling lead to alterations in the endothelial cell lining of blood vessels, which contribute to vascular inflammation and the promotion of vaso-occlusive events. Inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1) and VCAM-1 are upregulated in response to hypoxia, and HIFs are instrumental in this process. In SCD, endothelial cells are activated by several factors, including the low oxygen tension that characterizes many tissues in the disease[40]. HIF-1, through the induction of VEGF (vascular endothelial growth factor) and NOS, helps regulate endothelial responses to hypoxia. While VEGF promotes angiogenesis and attempts to restore oxygen delivery, it can also contribute to vascular permeability and leukocyte extravasation, which are both hallmarks of inflammation in SCD. Moreover, the increased expression of NOS can lead to nitric oxide overproduction, which, while intended to counteract vasoconstriction, can also contribute to oxidative stress and endothelial damage in the setting of SCD. Furthermore, the chronic activation of HIFs in endothelial cells can contribute to the persistent endothelial dysfunction observed in SCD. This dysfunction leads to the chronic inflammation that fuels disease complications such as stroke, organ damage, and chronic pain. HIFs also modulate the expression of pro-inflammatory enzymes like cyclooxygenase-2 (COX-2), which mediates the production of prostanoids such as prostaglandins that further exacerbate inflammatory responses[41].

**HIFs and leukocyte recruitment in SCD**

Aside from activating endothelial cells, HIFs significantly influence the activity of circulating leukocytes in SCD. The activation of HIF-1α has been demonstrated to enhance the expression of adhesion molecules on leukocytes, facilitating their migration to inflamed tissues. This process entails the increased expression of integrins and selectins on leukocyte surfaces, aiding their attachment to endothelial cells and movement into tissues. In SCD, tissue hypoxia and inflammation frequently occur, and the influx of neutrophils and monocytes to injury or blocked vessels worsens the inflammatory cycle and results in heightened tissue damage[42]. Neutrophils, especially, are crucial contributors to the inflammatory reactions observed in SCD. HIF-1α increases neutrophil migration to inflamed areas by controlling the expression of chemokines and adhesion molecules like ICAM-1. Upon reaching the inflammation site, neutrophils secrete numerous pro-inflammatory mediators, such as reactive oxygen species (ROS), which may lead to oxidative harm and exacerbate endothelial dysfunction. These mechanisms are essential for the development of vaso-occlusion, since the clustering of sickled RBCs and activated leukocytes results in the creation of occlusive thrombi in minor vessels, which further reduces tissue oxygenation and intensifies the inflammatory response[43].

**The Role of HIFs in hypoxic endothelial activation in SCD**

In SCD, the intermittent episodes of tissue hypoxia, often induced by microvascular occlusion from sickled RBCs, lead to the activation of HIFs, particularly HIF-1α. Under normal oxygen conditions, HIF-1α is rapidly degraded, but in hypoxic conditions, it stabilizes and translocates to the nucleus, where it binds to hypoxia-responsive elements (HREs) to activate the transcription of genes involved in adaptive responses. In endothelial cells, HIF-1α regulates several key pathways that influence vascular tone, permeability, and inflammation[8]. These include the upregulation of VEGF, NOS, and adrenomedullin, all of which play important roles in endothelial cell survival, angiogenesis, and vasodilation. However, while HIF-1α mediates adaptive responses to hypoxia, its persistent activation in SCD can exacerbate endothelial dysfunction. The upregulation of VEGF and NOS in response to hypoxia may initially help to improve oxygen delivery by promoting angiogenesis and vasodilation. Yet, chronic activation of these pathways can also contribute to endothelial damage by increasing vascular permeability, which results in plasma leakage and the exacerbation of tissue ischemia and inflammation. Moreover, the overproduction of NO due to increased NOS activity may lead to oxidative stress, which further impairs endothelial function and promotes the pathogenesis of vascular occlusion, a hallmark of SCD[40].

**HIF-1α and endothelial inflammation in SCD**

Endothelial activation in SCD is characterized by an inflammatory response that involves the upregulation of adhesion molecules, such as VCAM-1, ICAM-1, and E-selectin. These molecules facilitate the adhesion of leukocytes, particularly neutrophils, to the endothelium, which is a crucial step in the inflammatory cascade that leads to vascular occlusion. HIF-1α plays a significant role in modulating this process by increasing the expression of these adhesion molecules, thereby enhancing leukocyte recruitment to sites of hypoxic injury. This inflammatory response

further aggravates endothelial dysfunction, as the accumulated neutrophils and monocytes release pro-inflammatory cytokines, ROS, and proteolytic enzymes that can cause endothelial cell injury and impair vascular integrity[41]. In SCD, the sickling of RBCs, hemolysis, and the release of cell-free hemoglobin from lysed cells all contribute to endothelial activation. Hemoglobin, when released into the plasma, can bind to pattern recognition receptors on endothelial cells, activating inflammatory signaling pathways and further promoting endothelial dysfunction. This vicious cycle of RBC sickling, hemolysis, and inflammation exacerbates the effects of hypoxia and places an immense burden on the endothelium. The role of HIFs in promoting endothelial inflammation via upregulation of adhesion molecules and pro-inflammatory cytokines underscores the importance of targeting the HIF-mediated pathways in the management of vascular complications in SCD[42].

**HIFs and nitric oxide regulation in SCD**

The regulation of NO by HIFs is a critical aspect of endothelial function in SCD. Nitric oxide is a potent vasodilator and plays an important role in maintaining vascular tone and promoting blood flow. In healthy individuals, NO helps to counterbalance vasoconstriction and maintains smooth blood flow through the vessels. However, in SCD, the persistent endothelial dysfunction and hemolysis lead to decreased bioavailability of NO, contributing to the vasoconstriction and impaired circulation that characterizes the disease[33]. HIF-1α, through its regulation of NOS, may contribute to the regulation of NO production in endothelial cells. While the induction of NOS in response to hypoxia is adaptive, chronic activation of this pathway can be maladaptive in SCD. Increased NOS activity leads to the overproduction of NO, which can result in the formation of peroxynitrite a reactive nitrogen species that causes oxidative damage to the endothelium. This oxidative stress further exacerbates endothelial dysfunction and contributes to the pathogenesis of vaso-occlusion. The balance between NO production and its oxidative byproducts is crucial in determining the extent of endothelial damage in SCD. HIFs, by modulating this delicate balance, play a central role in regulating the vascular responses to sickling and hemolysis[44].

**HIFs and vascular remodeling in SCD**

Vascular remodeling refers to the structural changes that occur in response to chronic injury, inflammation, and ischemia. In SCD, the chronic episodes of microvascular occlusion and tissue hypoxia lead to adaptive changes in the vasculature, including thickening of the vessel walls, increased vascular permeability, and endothelial cell proliferation. HIFs, through the regulation of genes involved in angiogenesis, such as VEGF, contribute to these remodeling processes. While the initial intent of vascular remodeling is to improve tissue perfusion and restore oxygen supply, in SCD, these adaptive responses can be maladaptive, leading to the formation of fragile, dysfunctional blood vessels that are prone to further occlusion and rupture[45]. Chronic vascular remodeling can lead to irreversible damage to small vessels, especially in organs that are particularly susceptible to hypoxia, such as the spleen, kidney, and brain. The vascular changes associated with SCD can also lead to the development of pulmonary hypertension, stroke, and renal failure, all of which are common complications of the disease[46].

**Therapeutic implications**

The role of HIFs in endothelial dysfunction and other vascular complications in SCD presents an intriguing opportunity for therapeutic intervention. Given the significant impact of HIFs on the pathophysiology of SCD, especially in the context of hypoxia, inflammation, and vascular remodeling, targeting the molecular pathways regulated by HIFs could provide novel avenues for treatment. However, several challenges need to be addressed before such therapies can be effectively implemented in clinical practice.

**Targeting HIFs to modulate endothelial dysfunction in SCD**

The therapeutic potential of targeting HIFs lies in their ability to modulate key endothelial functions, including vascular tone, permeability, and inflammation. Pharmacological agents that can stabilize or inhibit HIF activity could be explored to either reduce or enhance specific aspects of HIF-mediated responses. For instance, HIF stabilizers, such as roxadustat, which are already used in the treatment of anemia in chronic kidney disease, could potentially be used in SCD to improve tissue oxygenation by enhancing erythropoiesis and alleviating the effects of chronic hypoxia. This could reduce the activation of inflammatory pathways in endothelial cells, thus mitigating vascular occlusion and tissue damage. Additionally, therapies targeting HIF-induced pro-inflammatory pathways hold promise for alleviating endothelial activation and leukocyte recruitment. By inhibiting the upregulation of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin, it may be possible to reduce the infiltration of immune cells into the endothelium, thereby decreasing the inflammatory response that contributes to vaso-occlusion. Such approaches may not only help in the prevention of acute vaso-occlusive crises but also provide long-term benefits by limiting the chronic inflammatory damage seen in SCD[41,42].

**Modulating nitric oxide production**

Another therapeutic avenue involves modulating the production of NO in response to HIF activation. In SCD, nitric oxide dysfunction is central to the pathogenesis of endothelial dysfunction, as decreased NO bioavailability leads to vasoconstriction and impaired blood flow. Conversely, excessive NO production, due to chronic HIF activation, may lead to oxidative stress and the formation of harmful byproducts like peroxynitrite. Fine-tuning the balance of NO synthesis through HIF modulation could potentially help in maintaining endothelial integrity while avoiding the detrimental effects of oxidative damage. Pharmacological agents that target the NOS pathway or NO signaling could complement current therapies aimed at improving vascular health in SCD patients[43].

**Risks of hypoxia-inducible factor modulation in sickle cell disease**

HIFs are central regulators of erythropoiesis, angiogenesis, metabolism, and inflammation. While therapeutic modulation of HIF pathways via pharmacologic stabilizers or gene-targeted strategies offers promising avenues for improving hemoglobin production and mitigating SCD pathology, such interventions are associated with significant potential risks that must be carefully considered.

**1. Tumorigenic potential**

HIF activation promotes cell survival, proliferation, and angiogenesis. Chronic or excessive stabilization of HIF-1α or HIF-2α can create a pro-tumorigenic environment by enhancing VEGF-mediated vascular growth, suppressing apoptosis, and stimulating glycolytic metabolism in susceptible cells. Preclinical studies suggest that long-term HIF activation may increase the risk of hematologic malignancies or solid tumors, particularly in tissues with high proliferative capacity[3].

**2. Cardiovascular and vascular effects**

HIF modulation can significantly influence vascular tone and remodeling. Elevated HIF-1α levels increase endothelin-1 production and endothelial adhesion molecule expression (ICAM-1, VCAM-1), potentially exacerbating vaso-occlusion, hypertension, and pulmonary arterial remodeling in SCD patients. HIF-2α activation in the pulmonary vasculature may similarly contribute to pulmonary hypertension and right ventricular strain. These effects necessitate careful monitoring, especially in individuals with pre-existing cardiopulmonary complications[4-6].

**3. Exacerbation of Inflammatory Responses**

HIF stabilization can amplify inflammatory signaling by promoting the transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) and adhesion molecules. While some inflammation is necessary for tissue repair and adaptation to hypoxia, excessive or prolonged HIF-driven inflammation may worsen endothelial dysfunction, microvascular occlusion, and organ damage in SCD. Redundant or overlapping inflammatory pathways may also limit the therapeutic benefit of HIF modulation[7,8].

**4. Iron and oxidative stress dysregulation**

HIFs regulate genes involved in iron metabolism, including transferrin and ferroportin. HIF-mediated erythropoietic stimulation increases iron utilization, which may exacerbate iron overload in patients receiving chronic transfusions. Furthermore, HIF activation can alter ROS production, potentially increasing oxidative stress and contributing to hemolysis and vascular injury[9,10].

**5. Off-target effects and tissue-specific variability**

HIF modulators may exert differential effects across tissues due to isoform- and context-specific expression. For example, while HIF-2α stabilization in the kidney enhances erythropoiesis, similar activation in the pulmonary vasculature may aggravate hypertension. Likewise, HIF-1α-induced angiogenesis may benefit ischemic tissues but promote pathological neovascularization in the retina or liver. These tissue-specific responses highlight the need for targeted delivery systems and careful dosing strategies[11-13].

**Gene therapy and HIF regulation**

Gene therapy represents another promising approach for modulating HIFs and their downstream effects in SCD. Since HIFs play an essential role in adaptive responses to hypoxia, manipulating their expression or activity at the genetic level could lead to long-term benefits. For example, gene editing techniques, such as CRISPR/Cas9, could be utilized to modify genes involved in HIF regulation, providing a potential means of enhancing tissue oxygenation and reducing the deleterious effects of hypoxia-induced endothelial dysfunction. Moreover, gene therapies aimed at enhancing the production of anti-inflammatory cytokines or modulating the expression of adhesion molecules could be explored to reduce vascular inflammation and improve endothelial function[48].

**Gene therapy in sickle cell disease: Cost, accessibility, and ethical considerations**

Gene therapy represents a transformative approach to the management of SCD, offering the potential for a definitive cure by correcting the underlying β-globin mutation or reactivating HbF production. Strategies include lentiviral vector-mediated gene addition, CRISPR-Cas9–based gene editing to disrupt repressors such as BCL11A, and autologous hematopoietic stem cell (HSC) transplantation following ex vivo modification. Early clinical trials have demonstrated promising efficacy, with many patients achieving durable HbF induction, improved hemoglobin levels, and reduced vaso-occlusive complications[1-4].

**1. Cost**

Gene therapy for SCD is currently associated with extremely high upfront costs, often exceeding several hundred thousand U.S. dollars per patient. The high cost arises from the complex ex vivo manipulation of autologous HSCs, specialized manufacturing facilities, stringent quality control, and the need for intensive pre- and post-treatment monitoring. These financial demands limit accessibility to patients in high-income countries and present an even greater barrier in sub-Saharan Africa, India, and other regions with high disease prevalence[5,6].

**2. Accessibility and infrastructure**

Effective delivery of gene therapy requires sophisticated infrastructure, including apheresis units, stem cell processing laboratories, cryopreservation facilities, and specialized clinical teams for conditioning regimens and transplantation. Many high-burden regions lack these resources, making large-scale implementation challenging. Additionally, long-term follow-up is essential to monitor for potential adverse events such as insertional mutagenesis, off-target gene editing effects, and late hematologic complications, further complicating accessibility[7,8].

**3. Ethical considerations**

Gene therapy in SCD raises several ethical issues:

**Equity:** There is a risk that high-cost curative therapies may exacerbate existing health disparities, providing access predominantly to wealthier populations while the majority of affected individuals remain untreated.

**Informed consent:** Gene editing and ex vivo modification involve complex scientific concepts. Ensuring patients and families fully understand the risks, benefits, and uncertainties is critical, particularly in pediatric populations.

**Long-term safety:** The long-term consequences of genomic modification remain uncertain. Ethical responsibility includes rigorous post-treatment monitoring and transparent communication of potential risks.

**Resource allocation:** Prioritization of expensive curative therapies may divert resources from broader public health interventions, such as neonatal screening, hydroxyurea therapy, and transfusion programs, which benefit larger patient populations[9-11].

**Clinical trial data, off-target effects, and implementation barriers of HIF-targeted therapies in sickle cell disease**

HIF modulation represents a promising therapeutic avenue in SCD, primarily aiming to enhance erythropoiesis, induce HbF, and mitigate hypoxia-driven vascular injury. Despite encouraging preclinical evidence, translation into human clinical trials remains in the early stages, and several challenges must be addressed for safe and effective implementation.

**1. Clinical trial data**

Current clinical data on HIF-targeted therapies in SCD are limited, with most evidence derived from small-scale studies or trials in other anemia-related disorders, such as chronic kidney disease (CKD).

**HIF Prolyl Hydroxylase Inhibitors (PHIs):** Agents such as roxadustat, daprodustat, and vadadustat have demonstrated efficacy in increasing hemoglobin levels by stabilizing HIF-α subunits and upregulating erythropoietin in CKD patients. Preclinical SCD models show that HIF stabilization can induce HbF production and improve erythrocyte survival, yet no large-scale human SCD trials have been completed[1-4].

**Fetal hemoglobin induction:** HIF stabilization in vitro has been linked to reactivation of γ-globin genes, suggesting a potential therapeutic effect in reducing sickling. Pilot studies in human erythroid progenitor cultures confirm this mechanism but clinical translation is pending[5,6].

**Gene therapy approaches:** Emerging strategies combine HIF modulation with gene editing techniques targeting HbF repressors (e.g., BCL11A). While early-phase studies are promising, they remain experimental, with limited patient numbers and follow-up duration[7].

**2. Off-target effects**

HIF-targeted interventions carry the risk of unintended systemic effects due to the widespread roles of HIFs:

**Tumorigenesis:** Chronic HIF activation may increase angiogenesis and cell proliferation, raising concerns about cancer risk in long-term therapy[8].

**Cardiovascular complications:** HIF-1α can upregulate endothelin-1, adhesion molecules, and pro-inflammatory cytokines, potentially exacerbating vaso-occlusion, hypertension, and pulmonary vascular remodeling[9].

**Iron and metabolic dysregulation:** HIF-induced changes in iron metabolism, glycolysis, and oxidative stress may exacerbate hemolysis or organ injury[10].

**Tissue-specific variability:** Differential HIF isoform activation in organs (e.g., HIF-2α in kidney vs. HIF-1α in pulmonary vasculature) may result in organ-specific adverse effects, complicating dosing and targeting[11].

**3. Implementation barriers**

Several factors limit the translation of HIF-targeted therapies from bench to bedside, especially in regions most affected by SCD:

**Access and cost:** The high cost of novel therapeutics and need for specialized monitoring may restrict availability to high-income countries, leaving most SCD patients underserved[12].

**Infrastructure limitations:** HIF modulators may require clinical oversight for dosing adjustments, adverse effect monitoring, and combination with standard therapies (e.g., hydroxyurea, transfusions). Resource-limited settings often lack the necessary infrastructure for safe implementation[13].

**Regulatory and ethical considerations:** The long-term safety profile of HIF stabilizers remains uncertain. Regulatory authorities require robust evidence of efficacy and safety before widespread adoption. Ethical concerns include equitable access and risk–benefit communication to patients[14].

**Integration with existing therapies:** HIF-targeted therapies must be carefully integrated with standard-of-care approaches to avoid overlapping toxicity or counterproductive effects, such as excessive erythrocytosis or iron overload[15].

## CONCLUSION

The interaction between HIFs and SCD provides important understanding of the pathophysiology of this debilitating disorder. HIFs play a key role in the body's reaction to lack of oxygen, and their activation in SCD is involved in essential mechanisms like endothelial dysfunction, inflammation, and changed erythropoiesis. Focusing on HIF pathways may provide exciting treatment possibilities, especially by improving oxygen supply, decreasing endothelial activation, and minimizing inflammatory reactions. Nonetheless, the intricacy of HIF signaling and its widespread impacts necessitate thorough attention in therapeutic development. Current therapies, including hydroxyurea and blood transfusions, mainly focus on alleviating SCD symptoms, whereas HIF-targeted strategies seek to alter the fundamental pathophysiological mechanisms.

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## AUTHOR'S CONTRIBUTION

**Obeagu EI:** conceived the idea, writing the manuscript, literature survey. **Abdalhabib E:** formal analysis, data processing. **Alzahrani W:** literature survey. Final manuscript was checked and approved by all authors.

## DATA AVAILABILITY

The empirical data used to support the study's conclusions are available upon request from the corresponding author.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest**.**

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