

Hypoxia, Inflammation, and Cytokine Crosstalk in Sickle Cell Disease: From Mechanisms to Modulation- A Narrative Review

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Abstract: Sickle cell disease (SCD) is a genetically inherited group of hemoglobinopathies characterized by the polymerization of hemoglobin S, chronic hemolytic anemia, and vaso-occlusion. The interplay between inflammation and hypoxia is central to the pathophysiologic manifestations of SCD and drives many of its complications. In this narrative review, we explore the bidirectional relationship between inflammatory pathways and hypoxic stress, with a focus on immune dysregulation, endothelial activation, and redox imbalance. The paper also highlights how mitochondrial dysfunction, reactive oxygen species (ROS) generation, glycolytic shifts affecting 2,3-diphosphoglycerate (2,3-DPG), and complement activation contribute to disease exacerbation. The review critically examines limitations of in vitro and animal models in mimicking the complex human pathophysiology, underscoring the need for translational research and clinical studies, especially in low- and middle-income countries (LMICs). Additionally, the paper evaluates emerging therapeutic interventions targeting inflammatory and hypoxia-related pathways, including small molecules, biologics, and gene-modifying strategies. Recognizing the heterogeneity in disease severity, this narrative review emphasizes the importance of personalized treatment approaches, integration of non-invasive biomarkers, and enhanced infrastructure for clinical trials in resource-limited settings.

Keywords: sickle cell disease, hypoxia, cytokines, inflammation, immune modulation

Introduction

Sickle cell disease (SCD) represents a group of inherited hemoglobinopathies characterized by the presence of abnormal hemoglobin S (HbS), which leads to the distortion of red blood cells into a sickle shape under deoxygenated conditions. Among these, sickle cell anemia (SCA) is the most severe and prevalent form, resulting from homozygous inheritance of the HbS gene.¹⁻³ The pathophysiology of SCD is complex and multifactorial, involving a dynamic interplay between hypoxia, inflammation, oxidative stress, and metabolic dysregulation. These interrelated processes collectively contribute to the hallmark clinical manifestations of the disease, including vaso-occlusive crises, hemolytic anemia, organ damage, and chronic pain.⁴⁻⁶ Hypoxia plays a central role in SCD pathogenesis by promoting sickling and polymerization of HbS, which impairs red blood cell deformability and vascular flow.^{7,8} Concurrently, inflammation is both a cause and consequence of these hypoxic episodes, characterized by activation of immune cells, cytokine release, and endothelial dysfunction. Oxidative stress further exacerbates cellular injury through excessive reactive oxygen species (ROS) production, in part originating from mitochondrial dysfunction and altered red blood cell metabolism.⁹⁻¹¹

Recent advances have expanded our understanding of the molecular mechanisms driving these processes, highlighting novel contributors such as the complement system's role in amplifying inflammation through damage-associated molecular patterns (DAMPs), and metabolic shifts involving glycolytic intermediates like 2,3-diphosphoglycerate (2,3-DPG), which modulate hemoglobin oxygen affinity and exacerbate hypoxia.¹²⁻¹⁵ Despite these insights, much of

the current knowledge is derived from reductionist in vitro models and animal studies, which may not fully recapitulate the complex human pathophysiology due to species-specific immune differences. The interplay between hypoxia and inflammation in sickle cell disease has been previously explored, with several studies highlighting the reciprocal amplification of hypoxic stress and inflammatory signaling pathways. Cytokine crosstalk, in particular, plays a critical role in modulating vascular occlusion, endothelial activation, and tissue injury. Despite existing literature, a comprehensive synthesis integrating these complex interactions remains valuable for advancing understanding and guiding therapeutic development. Key studies by Tan et al, Belcher et al, and Guarda et al have elucidated important aspects of this interplay, underscoring the need for ongoing integrative reviews that contextualize emerging molecular insights within the broader pathophysiology of sickle cell disease.^{16–18} This review aims to provide an updated and integrative overview of the pathophysiologic interactions between hypoxia and inflammation in SCD. The paper discusses emerging molecular targets and novel small-molecule therapeutic agents, with an emphasis on translational relevance.

Aim

The aim of this review is to provide an in-depth exploration of the intricate interplay between hypoxia, inflammation, and cytokine dysregulation in Sickle Cell Disease (SCD).

Review Methods

In this review, a comprehensive analysis of the existing literature on the role of hypoxia, inflammation, and cytokine dysregulation in Sickle Cell Disease (SCD) was conducted. The objective was to gather and synthesize data from various sources to explore the complex mechanisms that contribute to the pathophysiology of SCD, focusing particularly on how hypoxia and inflammation interact to worsen disease outcomes. The review methods involved a systematic approach to literature selection, data extraction, and critical analysis. A systematic search was performed using electronic databases such as PubMed, Scopus, and Web of Science to identify relevant peer-reviewed articles published within the last two decades. Keywords such as “hypoxia” “inflammation” “cytokines” “sickle cell disease” “immune activation” and “pathophysiology” were used to refine the search and ensure the inclusion of relevant studies. Both experimental and clinical research articles were considered, providing a broad spectrum of evidence regarding the molecular, cellular, and clinical aspects of SCD. Articles that addressed the mechanistic pathways of hypoxia, the role of pro-inflammatory cytokines, and their impact on SCD pathophysiology were included in the review. Studies that explored therapeutic approaches targeting these pathways were also prioritized.

The screening process followed a set of inclusion and exclusion criteria. Included studies were those that provided detailed insights into the hypoxia-inflammation axis in SCD, while excluded studies were those that did not focus on the molecular or immunological aspects of the disease or lacked relevance to the current understanding of the disease’s pathogenesis. The selected studies were further categorized into three primary sections: (1) the role of hypoxia in SCD, (2) the involvement of inflammatory pathways and cytokine dysregulation, and (3) the crosstalk between hypoxia and cytokines in the progression of the disease. Each study was carefully analyzed to assess its findings, methodology, and relevance to the review objectives. The therapeutic potential of modulating the hypoxia–inflammation axis was explored by reviewing recent clinical trials and experimental treatments aimed at targeting cytokines, inflammatory pathways, and hypoxic signaling in SCD. This included an assessment of novel therapies such as gene editing, anti-inflammatory treatments, and hypoxia-modulating agents. The review also evaluated challenges in translating these approaches into clinical practice, highlighting gaps in current research and suggesting future directions for investigation. The aim was to provide a comprehensive overview of the state of research and to offer insights into potential therapeutic strategies for SCD management.

Hypoxia in Sickle Cell Disease

Hypoxia, defined as a deficiency in tissue oxygenation, plays a central role in the pathophysiology of Sickle Cell Disease (SCD). It is both a trigger and consequence of the hallmark events that characterize this genetic blood disorder. SCD results from a mutation in the β -globin gene, leading to the production of hemoglobin S (HbS). Under deoxygenated

conditions, HbS undergoes polymerization, causing red blood cells (RBCs) to assume a rigid, sickled shape. These deformed cells have reduced deformability, are more adhesive, and are prone to hemolysis and vascular obstruction. The compromised microcirculatory flow due to sickling and vaso-occlusion significantly limits oxygen delivery to tissues, creating a chronic state of hypoxia that extends across multiple organ systems.^{16,17} The physiological impact of hypoxia in SCD is extensive. At the cellular level, reduced oxygen availability activates hypoxia-inducible factors (HIFs), particularly HIF-1 α , which serve as transcriptional regulators of genes involved in angiogenesis, metabolism, erythropoiesis, and inflammation. While these adaptations aim to preserve oxygen homeostasis, their persistent activation in SCD may contribute to pathologic outcomes. For instance, HIF-1 α upregulates vascular endothelial growth factor (VEGF) and erythropoietin (EPO), promoting neovascularization and compensatory erythropoiesis. However, the continuous need for RBC production may favor the release of immature erythrocytes with impaired functionality, exacerbating anemia and oxygen transport deficits.^{18,19}

In vascular tissues, hypoxia exerts profound effects on endothelial function. Endothelial cells exposed to low oxygen levels exhibit increased expression of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin, which facilitate the adherence of sickled erythrocytes and leukocytes to the vessel wall. This endothelial activation not only contributes to the pathogenesis of vaso-occlusive crises (VOCs) but also fosters a pro-thrombotic and inflammatory microenvironment. Additionally, hypoxia impairs the bioavailability of nitric oxide (NO), a critical vasodilator and anti-inflammatory mediator. Reduced NO levels further disrupt vascular tone, increase oxidative stress, and heighten the risk of vascular occlusion and endothelial injury.^{20,21} Organs with high oxygen demands, such as the brain, lungs, and kidneys, are particularly vulnerable to the effects of hypoxia in SCD. In the brain, chronic hypoxia may contribute to silent cerebral infarcts and overt strokes—both of which are significant causes of morbidity in affected children and adults. In the pulmonary system, hypoxia is implicated in the development of acute chest syndrome (ACS), a leading cause of hospitalization and mortality in SCD. Repeated hypoxic episodes also contribute to the development of pulmonary hypertension, a condition associated with increased mortality. Similarly, in the kidneys, hypoxia-induced injury to the renal medulla can lead to hyposthenuria, proteinuria, and progressive renal dysfunction.²²

Hypoxia in SCD is not merely a passive consequence of vascular occlusion—it is also an active modulator of systemic inflammation and immune dysregulation. Through HIF signaling and other pathways, hypoxia induces the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-1 beta (IL-1 β), which amplify immune cell activation and recruitment. This interplay between hypoxia and inflammation creates a vicious cycle that perpetuates endothelial injury, tissue ischemia, and multi-organ damage. Furthermore, hypoxia influences leukocyte behavior, promoting neutrophil extracellular trap (NET) formation and oxidative bursts, which further exacerbate vascular and tissue injury.³ From a clinical perspective, understanding and addressing hypoxia in SCD is essential for comprehensive patient management. Strategies aimed at preventing or minimizing hypoxic episodes—such as adequate hydration, prompt treatment of infections, use of hydroxyurea to reduce sickling, and blood transfusions to improve oxygen-carrying capacity—are key components of care. Novel therapies that directly target hypoxia pathways are also emerging. For example, agents that stabilize HIF-1 α are being explored for their potential to promote erythropoiesis without the deleterious effects of excessive sickling. Similarly, drugs that modulate NO signaling or reduce oxidative stress may help mitigate the downstream consequences of hypoxia in vascular tissues.²³

Inflammatory Pathways and Cytokine Dysregulation in Sickle Cell Disease

Sickle Cell Disease (SCD) is increasingly recognized as a chronic inflammatory condition, with a distinct profile of immune activation and cytokine imbalance that persists even in steady-state phases. In addition to the genetic defect in hemoglobin synthesis, a dysregulated inflammatory response contributes substantially to the clinical complications observed in SCD, such as vaso-occlusive crises (VOCs), acute chest syndrome, stroke, and chronic organ damage. The inflammatory pathways activated in SCD are multifaceted, involving innate and adaptive immune components, endothelial cells, and the persistent release of pro-inflammatory cytokines and chemokines.^{24,25} A hallmark of the inflammatory state in SCD is the chronic activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway. NF- κ B is a transcription factor that regulates genes responsible for cytokine production, leukocyte adhesion, and cellular survival. In SCD, recurrent hemolysis and ischemia-reperfusion injury

stimulate Toll-like receptors (TLRs) on monocytes and endothelial cells, leading to NF- κ B activation. This results in the upregulation of adhesion molecules—such as VCAM-1, ICAM-1, and P-selectin—and the release of a broad spectrum of inflammatory mediators including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β). These molecules not only exacerbate leukocyte recruitment but also promote endothelial dysfunction, setting the stage for recurrent vascular occlusion and tissue ischemia.^{26–28}

Hemolysis, a constant feature of SCD, is another critical driver of inflammation. Free hemoglobin released into the plasma during intravascular hemolysis scavenges nitric oxide (NO), a potent anti-inflammatory and vasodilatory molecule. The resultant NO depletion contributes to vasoconstriction, platelet activation, and further endothelial injury. Simultaneously, the release of damage-associated molecular patterns (DAMPs), such as heme and high mobility group box 1 protein (HMGB1), further amplifies immune activation. These DAMPs engage TLR4 and other pattern recognition receptors (PRRs) on innate immune cells, intensifying the production of IL-8, monocyte chemoattractant protein-1 (MCP-1), and other chemokines that drive neutrophil and monocyte infiltration into tissues.^{2,29} Neutrophils, which are often elevated and activated in SCD, play a prominent role in mediating inflammation and vascular injury. Upon activation, these cells release neutrophil extracellular traps (NETs), which are web-like structures composed of DNA, histones, and granule proteins designed to trap pathogens. However, in SCD, excessive NET formation contributes to thrombosis and endothelial damage. The interaction between activated neutrophils and sickled red cells within the microvasculature aggravates the occlusive process. Additionally, neutrophil-derived enzymes, such as myeloperoxidase (MPO) and elastase, further disrupt the vascular endothelium and enhance oxidative stress.^{30,31}

Adaptive immunity also contributes to the chronic inflammatory landscape in SCD. Although traditionally less emphasized, recent studies have highlighted the role of T cells in modulating inflammatory responses. For example, Th17 cells, characterized by the production of interleukin-17 (IL-17), are often increased in SCD patients and are associated with heightened inflammatory responses. Regulatory T cells (Tregs), which normally suppress inflammation, may be functionally impaired in SCD, leading to unchecked immune activation. Furthermore, the chronic antigenic stimulation from repeated infections and tissue damage may promote immune exhaustion and skewed cytokine production patterns.³² Importantly, cytokine dysregulation in SCD is not limited to pro-inflammatory mediators. Anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β) may be dysregulated or insufficient to counterbalance the inflammatory burden. This imbalance further perpetuates a state of immune dysregulation and prevents resolution of inflammation, even during asymptomatic periods. The net result is a state of low-grade chronic inflammation punctuated by acute inflammatory flares during VOCs.³³ From a therapeutic standpoint, targeting inflammatory pathways and cytokine dysregulation offers promising avenues for intervention. Hydroxyurea, the current standard therapy, has been shown to reduce leukocyte count, lower levels of circulating inflammatory cytokines, and improve endothelial function. Emerging agents such as voxelotor (which increases hemoglobin oxygen affinity) may also indirectly modulate inflammation by preventing sickling and reducing vascular adhesion. Furthermore, specific anti-cytokine therapies, such as TNF- α blockers and IL-1 β inhibitors, are being investigated for their potential to attenuate inflammation and reduce clinical complications in SCD.³⁴

Crosstalk Between Hypoxia and Cytokines in Sick Cell Disease

SCD is characterized by recurrent episodes of tissue hypoxia and ischemia-reperfusion injury due to vaso-occlusion. These hypoxic events play a pivotal role in orchestrating a complex and dynamic interaction with the immune system, particularly through the modulation of cytokine expression. The crosstalk between hypoxia and cytokines not only amplifies inflammation but also contributes to endothelial dysfunction, leukocyte adhesion, and end-organ damage—hallmarks of SCD pathophysiology.^{35,36} Hypoxia acts as a potent activator of inflammatory responses by stabilizing hypoxia-inducible factors (HIFs), primarily HIF-1 α , a transcription factor that regulates genes involved in oxygen homeostasis, glycolysis, angiogenesis, and immune signaling. In SCD, HIF-1 α is frequently upregulated due to chronic and acute oxygen deprivation, which promotes the transcription of numerous pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and vascular endothelial growth factor (VEGF). These cytokines not only facilitate leukocyte recruitment but also increase vascular permeability and perpetuate endothelial activation, creating a vicious cycle of inflammation and hypoxia.³⁷

The bidirectional relationship is further evidenced by the ability of cytokines to influence hypoxic signaling. For instance, TNF- α and IL-1 β , which are elevated in SCD patients, can induce HIF-1 α stabilization even under normoxic conditions by promoting oxidative stress and inhibiting prolyl hydroxylases, the enzymes responsible for HIF-1 α degradation. This cytokine-induced pseudo-hypoxia exacerbates HIF-driven gene expression, promoting further cytokine release and contributing to a feed-forward loop of inflammation and hypoxia. Additionally, IL-6 enhances the expression of C-reactive protein (CRP) and fibrinogen, acute phase proteins that further drive vascular inflammation and thrombotic risk.⁴ Endothelial cells serve as key mediators in the hypoxia–cytokine interplay. Under hypoxic conditions, endothelial cells express higher levels of adhesion molecules such as E-selectin, P-selectin, ICAM-1, and VCAM-1, which facilitate the tethering and transmigration of leukocytes into tissues. Cytokines such as IL-8 and MCP-1 are concurrently upregulated, driving chemotaxis and local immune cell accumulation. This endothelial activation is both a cause and consequence of hypoxia, as occluded vessels reduce oxygen delivery and initiate a pro-inflammatory cascade that further impairs perfusion.⁷

Moreover, the hypoxic microenvironment influences immune cell behavior and phenotype. Neutrophils exposed to hypoxia exhibit enhanced survival and a primed phenotype characterized by increased production of reactive oxygen species (ROS) and release of neutrophil extracellular traps (NETs). These activated neutrophils contribute to endothelial injury and promote vaso-occlusion. Similarly, hypoxia shapes macrophage polarization toward a pro-inflammatory M1-like phenotype, which produces high levels of TNF- α , IL-1 β , and IL-12. These cytokines further stimulate endothelial cells and promote a hostile vascular milieu.⁶ The adaptive immune system is not spared from hypoxia-induced changes. T cells under hypoxic stress demonstrate altered differentiation and cytokine production, with increased Th17 polarization and reduced regulatory T cell (Treg) function. Elevated IL-17 levels in SCD have been associated with increased inflammation, vascular damage, and pain sensitization. Hypoxia thus reinforces a skewed immune profile that favors inflammation and diminishes tolerance mechanisms.³⁸ Importantly, the interplay between hypoxia and cytokines in SCD is influenced by the frequency and duration of vaso-occlusive episodes. Chronic hypoxia in tissues such as the bone marrow, spleen, and kidneys leads to persistent low-grade inflammation and fibrosis, while acute hypoxic events result in cytokine surges and systemic inflammatory responses. These dynamics underline the importance of therapeutic timing and target selection to modulate both hypoxia and cytokine activity effectively (Figure 1).⁵

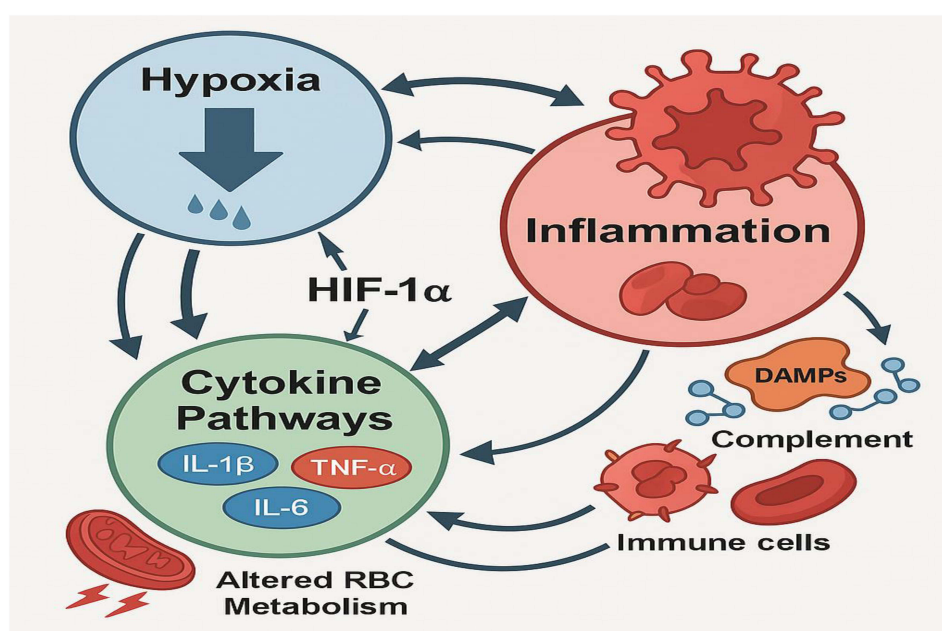


Figure 1 The Bidirectional Interactions among Hypoxia, Inflammation, and Cytokine Pathways.

Therapeutic Modulation of the Hypoxia–Inflammation Axis in Sickle Cell Disease

Therapeutic targeting of the hypoxia–inflammation axis in SCD represents a promising and evolving frontier in disease management, aimed at attenuating the underlying pathophysiological processes that fuel vaso-occlusion, tissue damage, and chronic complications. Given the bidirectional relationship between hypoxia and inflammation, interventions that can simultaneously disrupt this deleterious cycle have the potential to significantly improve clinical outcomes.^{9,10} Pharmacologic agents that stabilize red blood cells and reduce hemolysis indirectly mitigate tissue hypoxia. Hydroxyurea, the cornerstone of SCD therapy, increases fetal hemoglobin (HbF) levels, which reduces sickling and improves red cell rheology. By decreasing the frequency of vaso-occlusive episodes and hemolytic burden, hydroxyurea diminishes episodes of hypoxia and the downstream inflammatory cascade. Clinical studies have demonstrated reductions in circulating cytokines such as IL-6 and TNF- α in patients receiving hydroxyurea, highlighting its dual benefit on oxygen delivery and immune modulation.^{39,40} Direct targeting of inflammatory mediators has also garnered significant attention.⁴¹

Targeting hypoxia-inducible factors (HIFs) themselves is another promising strategy. Pharmacologic HIF inhibitors have been explored in oncology and chronic inflammatory diseases, and similar approaches may benefit SCD by limiting the transcription of pro-inflammatory and pro-angiogenic genes induced under hypoxic stress. Conversely, selective HIF stabilizers such as roxadustat have shown potential to improve erythropoiesis and oxygen delivery in anemia, and their nuanced application in SCD requires careful balancing between therapeutic benefit and exacerbation of inflammation.⁴² Antioxidants and agents targeting oxidative stress may also play a supportive role in modulating the hypoxia–inflammation interplay. As oxidative stress exacerbates both HIF stabilization and cytokine production, drugs like L-glutamine—recently approved for reducing SCD complications—help buffer redox imbalances and may attenuate downstream inflammatory signaling. Similarly, omega-3 fatty acids, N-acetylcysteine, and other nutraceuticals have shown anti-inflammatory effects and may complement standard therapies.⁴³

Emerging biologic therapies represent a promising frontier in the management of sickle cell disease by targeting specific components of the inflammatory and vaso-occlusive pathways. These agents include monoclonal antibodies and recombinant proteins designed to inhibit key adhesion molecules, cytokines, or complement factors involved in the pathophysiology of SCD. For example, crizanlizumab, a monoclonal antibody targeting P-selectin, was developed to reduce vaso-occlusive crises by preventing leukocyte and platelet adhesion to the endothelium; however, recent reports of adverse effects have led to its withdrawal in some regions, highlighting the need for cautious evaluation of biologic safety profiles. Other biologics under investigation include inhibitors of interleukin-1 β and tumor necrosis factor- α , which aim to modulate the heightened inflammatory milieu characteristic of SCD. While gene therapies and curative interventions are gaining ground, biologics provide alternative or adjunctive options, especially for patients ineligible for curative approaches. Ongoing clinical trials continue to refine the therapeutic landscape by assessing efficacy, safety, and patient-specific responses to these targeted treatments (Table 1).^{44,45}

Table 1 Emerging Small-Molecule Agents Targeting Hypoxia-Linked Pathophysiological Pathways

Agent	Primary Target(s)	Pathophysiological Pathway Affected	Mechanism of Action
Roxadustat	HIF prolyl hydroxylase (PHD)	Hypoxia signaling, erythropoiesis	Stabilizes HIF- α , enhances erythropoietin and iron metabolism genes
MitoQ	Mitochondrial ROS	Oxidative stress, mitochondrial dysfunction	Scavenges mitochondrial ROS, preserves membrane potential
Dimethyl fumarate	NRF2 pathway	Antioxidant defense, inflammation	Activates NRF2, suppresses NF- κ B-mediated inflammation
CP-17 (Complement Inhibitor)	C3 convertase	Complement activation, inflammation	Inhibits C3 cleavage, prevents downstream complement activation

(Continued)

Table 1 (Continued).

Agent	Primary Target(s)	Pathophysiological Pathway Affected	Mechanism of Action
2-Deoxy-D-glucose (2-DG)	Hexokinase	Altered glycolysis, metabolic reprogramming	Blocks glycolysis, reduces lactate and 2,3-DPG accumulation
Apabetalone (RVX-208)	BET proteins	Inflammation, vascular dysfunction	Epigenetic modulation of inflammatory gene expression
Omaveloxolone	NRF2 and mitochondrial biogenesis	Oxidative stress, mitochondrial dysfunction	Enhances antioxidant response and mitochondrial function
PT2385	HIF-2 α	Hypoxia-driven transcription	Inhibits HIF-2 α -mediated gene expression
Zilucoplan	Complement component C5	Terminal complement activation, inflammation	Prevents MAC formation and inflammation
RAGE-aptamer	Receptor for Advanced Glycation End-products	DAMP signaling, inflammation	Inhibits RAGE-mediated DAMP signaling and cytokine release

Discussion

This review highlights the complex interplay between hypoxia, inflammation, and cytokine crosstalk in the pathophysiology of sickle cell disease (SCD). The multifaceted mechanisms—including oxidative stress driven by mitochondrial ROS, altered red blood cell metabolism with elevated 2,3-DPG levels, and immune activation involving the complement system and damage-associated molecular patterns (DAMPs)—create a self-perpetuating cycle that exacerbates vascular injury, inflammation, and clinical complications in SCD. The integration of emerging therapeutic agents targeting these pathways underscores a shift towards more precise, mechanism-based treatments that go beyond symptomatic management.⁴⁶ Despite the progress in understanding these interrelated processes, significant challenges remain. Experimental models, both in vitro and animal, while invaluable, do not fully replicate the human disease milieu due to species-specific differences in immune responses and the complex systemic interactions present in SCD patients. This limitation underscores the need for increased investment in well-designed human studies and clinical trials, particularly in resource-limited settings where SCD burden is highest. The establishment of infrastructure and expertise at sickle cell centers in low- and middle-income countries will be crucial for advancing translational research and biomarker discovery.⁴⁷

Furthermore, the heterogeneous clinical phenotypes seen in SCD necessitate personalized approaches to therapy. While gene therapy and curative interventions show promise, accessibility and suitability for all patients remain limited. Thus, the continuous development and rigorous evaluation of biologics, small-molecule inhibitors, and adjunctive therapies remain essential. Enhanced understanding of cytokine networks and immune regulation may also identify novel targets and predictive biomarkers for treatment response and disease progression.⁴⁸ Future research should prioritize the integration of multi-omics approaches, including transcriptomics, proteomics, and metabolomics, to dissect the molecular signatures underlying hypoxia-inflammation interactions. Additionally, non-invasive monitoring tools and standardized biomarker panels could facilitate early detection of disease exacerbations and guide therapeutic decisions. Collaboration between basic scientists, clinicians, and public health stakeholders will be key to translating mechanistic insights into improved patient outcomes.

Conclusion

Understanding the multifaceted pathogenesis of hypoxia-induced oxidative stress and inflammation requires a comprehensive view of cellular, metabolic, and immunological pathways. Central to this is the role of mitochondrial reactive oxygen species (ROS) production under hypoxic conditions, which amplifies oxidative damage and perpetuates tissue injury. Altered glycolysis and increased 2,3-diphosphoglycerate (2,3-DPG) levels further exacerbate

deoxygenation by reducing hemoglobin-oxygen affinity. The immune system's response is similarly intricate, with damage-associated molecular patterns (DAMPs) activating the complement cascade and fueling a proinflammatory milieu. While in vitro and animal models have provided crucial insights into these mechanisms, limitations remain—especially concerning species-specific immune differences and the translational relevance of findings. Thus, integrating human-based data with improved modeling strategies is essential for advancing therapeutic interventions.

Disclosure

The author reports no conflicts of interest in this work.

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