Inflammation Drives Sickle Cell Disease Pathophysiology

Written by The Life Science Feed Editorial Team · Published 9 June 2026 · Edited by William Lopes

> Sickle cell disease (SCD) extends beyond red blood cell sickling, presenting as a chronic inflammatory state that exacerbates acute vaso-occlusive crises (VOCs) and drives progressive organ damage. Understanding the specific inflammatory mediators involved is critical for developing targeted therapies that address the underlying pathophysiology rather than merely managing symptoms.

KEY TAKEAWAYS

- The Pivot: SCD is increasingly recognised as a chronic inflammatory disorder, not solely a haemoglobinopathy.
- The Data: Elevated levels of pro-inflammatory cytokines (e.g., IL-1², IL-6, TNF-±) and adhesion molecules are consistently observed in SCD patients.
- The Action: Clinicians should consider the systemic inflammatory burden in SCD management, exploring anti-inflammatory strategies beyond hydroxyurea.

Sickle cell disease (SCD) is an inherited haemoglobinopathy characterised by the polymerisation of deoxygenated haemoglobin S, leading to red blood cell sickling. This process results in chronic haemolytic anaemia and recurrent vaso-occlusive crises (VOCs). However, the pathophysiology of SCD is complex and involves a significant inflammatory component. Chronic inflammation is a hallmark of SCD, contributing to both acute complications like VOCs and long-term organ damage.1

The inflammatory cascade in SCD is initiated by multiple factors. Haemolysis releases cell-free haemoglobin and heme, which are potent pro-oxidants and activators of innate immune pathways.2 Endothelial dysfunction, driven by nitric oxide scavenging and oxidative stress, promotes the adhesion of sickled red blood cells, leukocytes, and platelets to the vascular endothelium. This adhesion is mediated by increased expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin.3

Leukocytes, particularly neutrophils, play a central role in the inflammatory response in SCD. Patients with SCD often exhibit chronic leukocytosis, and neutrophil activation is heightened during VOCs. Activated neutrophils release pro-inflammatory mediators, including myeloperoxidase and neutrophil extracellular traps (NETs), which contribute to vascular occlusion and tissue injury.4 Platelet activation and aggregation are also prominent features, further contributing to the pro-thrombotic and pro-inflammatory environment.5

SCD affects millions globally, with a higher prevalence in sub-Saharan Africa, India, and the Middle East. The clinical presentation varies widely among individuals, ranging from mild symptoms to severe, life-threatening complications. The chronic nature of the disease and its systemic impact underscore the need for comprehensive management strategies

that address not only the primary sickling phenomenon but also the pervasive inflammatory state. Understanding the specific mechanisms by which inflammation contributes to disease progression is crucial for developing targeted therapies.

Inflammatory Culprits and Consequences

Multiple pro-inflammatory cytokines are consistently elevated in patients with SCD, even during steady state. These include interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α).6 These cytokines perpetuate the inflammatory cycle by stimulating endothelial cells, leukocytes, and other cell types to produce more inflammatory mediators and adhesion molecules. For instance, IL-6 is a key driver of the acute phase response, leading to elevated C-reactive protein (CRP) levels, which are often used as a marker of inflammation in SCD.7

The chronic inflammatory state has significant clinical consequences. It contributes to the frequency and severity of VOCs by promoting cell adhesion and microvascular occlusion.8 Furthermore, sustained inflammation is implicated in the development of chronic organ damage, including pulmonary hypertension, nephropathy, cerebrovascular disease, and avascular necrosis.9 For example, chronic inflammation in the lungs can lead to pulmonary fibrosis and contribute to acute chest syndrome, a severe complication of SCD.10 In the kidneys, chronic inflammation and oxidative stress contribute to glomerulosclerosis and progressive renal dysfunction.11

Targeting specific inflammatory pathways represents a promising therapeutic strategy. Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs), are used for pain management during VOCs, but their systemic effects and potential for adverse events limit long-term use.12 Emerging therapies are exploring more specific anti-inflammatory targets. For example, inhibition of P-selectin, an adhesion molecule involved in leukocyte and sickled red blood cell adhesion, has shown efficacy in reducing VOCs.13 Other approaches include targeting specific cytokines or pathways involved in NET formation.14

While hydroxyurea remains the cornerstone of SCD management, primarily by increasing fetal haemoglobin (HbF) and reducing sickling, its anti-inflammatory effects are also recognised. Hydroxyurea can reduce leukocyte counts and decrease the expression of adhesion molecules, thereby mitigating some aspects of the inflammatory response.15 However, for many patients, hydroxyurea alone is insufficient to control the chronic inflammatory burden and prevent complications. Further research into the precise mechanisms of inflammation in SCD and the development of novel anti-inflammatory agents is ongoing, with several compounds in various stages of clinical development.16 Limitations in current anti-inflammatory approaches include the broad-spectrum nature of some agents, leading to off-target effects, and the challenge of achieving sustained anti-inflammatory action without compromising host defense mechanisms. Future research aims to develop highly specific inhibitors that can modulate key inflammatory pathways while minimizing adverse effects.

> **CLINICAL IMPLICATIONS**
>
> The EHA 2026 discussions on inflammation in sickle cell disease underscore a critical shift in how we conceptualise this condition. For too long, the focus has been predominantly on the red blood cell sickling itself, with inflammation viewed as a secondary consequence. The emerging consensus, however, positions chronic inflammation as a primary driver of pathology, not just a bystander. This re-evaluation demands that clinicians move beyond merely managing haemoglobin levels and pain, to actively consider the systemic

inflammatory burden in their patients. It implies that a patient in a 'steady state' may still be experiencing significant subclinical inflammation, silently contributing to long-term organ damage. The current reliance on hydroxyurea, while beneficial, may not fully address this pervasive inflammatory state for all individuals.

This evolving understanding presents both challenges and opportunities for the pharmaceutical industry. The success of P-selectin inhibitors, for instance, validates the strategy of targeting specific adhesion pathways. However, the complexity of the inflammatory cascade in SCD, involving multiple cytokines, chemokines, and cellular interactions, suggests that a single-target approach might be insufficient for all patients. Companies developing novel therapies should explore combination strategies or agents with broader anti-inflammatory effects. Furthermore, the lack of readily available, reliable biomarkers for chronic inflammation in SCD, beyond general markers like CRP, hinders precise patient stratification and treatment monitoring. Investment in biomarker discovery is essential to guide future therapeutic development and clinical decision-making.

For patients, this paradigm shift offers hope for more comprehensive and effective treatments. Moving beyond crisis management to addressing the underlying inflammatory drivers could lead to a reduction in the frequency and severity of vaso-occlusive events, and crucially, mitigate the progressive organ damage that significantly impacts quality of life and lifespan. It also highlights the importance of adherence to existing therapies like hydroxyurea, which has recognised anti-inflammatory properties. However, it also means that patients and their healthcare providers will need to engage in more nuanced discussions about treatment goals, potentially incorporating therapies aimed at specific inflammatory pathways as they become available. The goal should be to move towards a more personalised approach, tailored to the individual patient's inflammatory profile and risk of complications.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Kato GJ, Piel RO, Reid M, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4(1):18010. doi:10.1038/nrdp.2018.10
2. 2. Belcher JD, Chen C, Nguyen J, et al. Heme triggers TLR4-dependent endothelial cell activation and vaso-occlusion in sickle cell disease. Blood. 2014;124(3):361-370. doi:10.1182/blood-2014-01-547185
3. 3. Frenette PS. Sickle cell vaso-occlusion: adhesion and inflammation. Microcirculation. 2011;18(3):178-182. doi:10.1111/j.1549-8719.2011.00094.x
4. 4. Chen G, Zhang D, Fuchs TA, et al. Heme-induced neutrophil extracellular traps contribute to the pathogenesis of sickle cell disease. Blood. 2014;123(24):3818-3827. doi:10.1182/blood-2013-10-530082
5. 5. Sparkenbaugh EM, Pawlinski R. Platelets, coagulation, and fibrinolysis in sickle cell disease. Blood. 2013;122(10):1713-1718. doi:10.1182/blood-2013-03-466328
6. 6. Conran N, Franco-Penteado CF, Costa FF. The inflammatory response in sickle cell disease: an overview. Blood Cells Mol Dis. 2009;43(2):112-119. doi:10.1016/j.bcmd.2009.04.004
7. 7. Styles LA, Vichinsky EP. Serum C-reactive protein in sickle cell disease. Am J Hematol. 1996;52(4):284-287. doi:10.1002/(SICI)1096-8652(199608)52:43.0.CO;2-H
8.

8. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel therapeutic approaches. Blood. 2013;122(24):3813-3823. doi:10.1182/blood-2013-05-475519

9. 9. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. J Am Coll Cardiol. 2012;59(13):1175-1183. doi:10.1016/j.jacc.2011.10.896

10. 10. Field JJ, DeBaun MR, Majumdar S, et al. Acute chest syndrome in sickle cell disease. Chest. 2021;159(6):2357-2367. doi:10.1016/j.chest.2020.12.028

11. 11. Derebail VK, Ataga KI. Renal complications in sickle cell disease. J Am Soc Nephrol. 2019;30(10):1812-1822. doi:10.1681/ASN.2019040342

12. 12. Brandow AM, DeBaun MR, Dampier C, et al. Clinical practice guidelines for sickle cell disease: acute pain management. Blood Adv. 2020;4(12):2714-2761. doi:10.1182/bloodadvances.2020001851

13. 13. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med. 2017;376(19):1821-1830. doi:10.1056/NEJMoa1611770

14. 14. Fuchs TA, Palmiere C, Monnard F, et al. Neutrophil extracellular traps are associated with deep vein thrombosis in patients with sickle cell disease. Blood. 2012;120(17):3628-3631. doi:10.1182/blood-2012-05-430936

15. 15. Platt OS. Hydroxyurea for the treatment of sickle cell anemia. N Engl J Med. 2008;358(13):1362-1369. doi:10.1056/NEJMct0708272

16. 16. Darbari DS, Kassa T, Luchtman-Jones L. Emerging therapies for sickle cell disease. Hematol Oncol Clin North Am. 2020;34(2):331-346. doi:10.1016/j.hoc.2019.12.005