Inflammatory Mediators of Endothelial Injury in Sickle Cell Disease

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KEYWORDS

• Inflammation • Mediators • Sickle cell

KEY POINTS

- Inflammation plays a critical role in the complex pathophysiology of sickle cell disease (SCD) and drives both the acute and chronic processes leading to vascular injury.
- Mediators of inflammation, such as cellular adhesion molecules, cytokines, leukotrienes (LTs), and nuclear factor (NF)-κB signaling factors, represent potential therapeutic targets in SCD.

INTRODUCTION

SCD is now recognized as a complex disease characterized by acute and chronic inflammation. The incidence of nearly every clinical manifestation of SCD correlates with white blood cell (WBC) count, indicating a role for leukocytes and inflammation in the pathophysiology of SCD. Leukocytosis is common in SCD patients and is manifested by elevation in monocyte and neutrophil counts,[1–3] accompanied by elevated levels of circulating inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin (IL)-1, and IL-8. Elevated levels of these cytokines have been shown to exacerbate sickling in experimental models and correlate with clinical vasoocclusive severity. Leukocytosis is associated with a decreased life expectancy and, when observed in infancy, predicts future disease severity.[4,5] Clinically, elevated baseline WBC counts have been associated with acute chest syndrome (ACS), decline in lung function, and ischemic stroke in children with sickle cell anemia (SCA).[6–8] Reports of acute vasoocclusive pain events, ACS multiorgan failure, and death after administration of myeloid colony-stimulating factors (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) suggest that the association of leukocytosis and poor outcome may be causal. The reduced incidence of vasoocclusive pain and ACS episodes in patients on hydroxyurea (HU) is thought due, in part, to the myelosuppressive effect of the drug.[9]

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Genetic associations with inflammation also support the involvement of inflammatory pathways in the pathophysiology of SCD and may partly explain the phenotypic heterogeneity of the disease. Associations between variants in the transforming growth factor β1 (TGF-β)/bone morphogenetic protein 6 pathway and pulmonary hypertension, stroke, and osteonecrosis in SCD have been replicated in 4 independent studies.[10–14]

Studies showing an increased risk of severe disease in SCA patients with elevated levels of TNF-α receptor-1 (TNF-R1) and vascular cell adhesion molecule (VCAM)-1 are supported by findings from a genome-wide association study of a link between disease severity and polymorphisms in VCAM-1 and in ADP-ribosylation factor guanine nucleotide-exchange factor 2 (*ARFGEF2)*, a gene involved in TNF-R1 release.[15]

Another recent gene-centric association identified an association between ACS and a variant (rs6141803) located in close proximity to a gene (*COMMD7)* that is highly expressed in pulmonary endothelial cells (ECs), interacts with NF-κB signaling, and is differentially expressed when exposed to oxidant heme species.[16]

Individuals with SCA who express the integral red blood cell (RBC) membrane glycoprotein, Duffy antigen receptor for chemokines (DARC), were found to have higher steady-state WBC counts and levels of DARC-binding chemokines; IL-8; and regulated on activation, normal T cell expressed and secreted (RANTES) compared with individuals who were negative for the allele, FY^*B^{null}.[17] The DARC modulates the bioavailability of proinflammatory chemokines, including RANTES (CCL5) and IL-8 (CXCL8), which are inactivated once bound to RBCs.

Gene expression studies have shown that sickle RBCs, either directly or indirectly, promote endothelial up-regulation of TNF-α and IL-1 genes.[18–20] Jison and colleagues[21] demonstrated differential expression of 112 genes involved in inflammation, heme metabolism, cell cycle regulation, antioxidant responses, and angiogenesis in peripheral blood mononuclear cells from SCD patients at baseline.

The importance of the vascular endothelium and its participation in the inflammatory response in SCD has become increasingly appreciated and is convincingly related to its activation by inflammatory stimuli and abnormal expression of adhesion molecules. Circulating ECs from individuals with SCA exhibit an activated phenotype with abnormal expression of adhesion molecules, selectins, tissue factor (TF), and up-regulated heme oxygenase-1 (HO-1).[22–24] Biologic modifiers triggering endothelial activation during sickle vasoocclusive episodes include hypoxia; oxidant molecules; cytokines, in particular TNF-α and IL-1; and thrombin.[25,26]

Adhesive interactions between sickle RBCs, leukocytes, platelets, and the vascular endothelium cause vasoocclusion, ischemia, and reperfusion injury that result in acute vasoocclusive pain episodes, ACS and, over time, ischemic organ damage. The development of sickle cell mouse models that mimic sickle cell vasoocclusion and ischemia-reperfusion injury in humans has provided critical information about the pathobiology of SCD. Because inflammation plays a significant role in the development of acute clinical manifestations and chronic vascular injury in SCD, pharmacologic strategies aimed at pathways of inflammation may have both therapeutic and preventative value.

This review summarizes the accumulated evidence from clinical and experimental studies that implicate the inflammatory response in the development of vascular injury associated with SCD. Despite the broad impact of inflammation on acute complications and chronic vascular disease in SCD, no directed antiinflammatory therapies for the treatment or prevention of vasoocclusive events currently exist. An integrated approach using a combination of therapeutic agents directed at individual components of the inflammatory response may ultimately be necessary to make a clinical impact on this debilitating disease.