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The Interplay among Immune Response, Inflammation, Oxidative Stress and Sickle Cell Anaemia Pathogenesis

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Abstract

Sickle Cell Anemia (SCD) stands as a life-threatening hematological condition primarily prevalent in sub-Saharan Africa. It originates from a genetic mutation in the β-chain hemoglobin gene, leading to the substitution of valine for glutamic acid. This genetic alteration gives rise to an aberrant hemoglobin variant known as hemoglobin S (HbS). Under deoxygenated conditions, HbS undergoes polymerization, causing red blood cells to assume a rigid, sickle-like shape and significantly reducing their lifespan. Scientific investigations have underscored a robust correlation between oxidative stress, inflammation, immune response, and the development of sickle cell disease. The cumulative effects of these processes contribute to the emergence of vasculopathy, affecting blood vessels, and a range of other complications. While recent research has elucidated the pivotal role of the innate immune system in SCD pathogenesis, insights into the involvement of the adaptive immune system remain limited. This comprehensive review delves into the intricate interplay among the immune system, inflammation, oxidative stress, blood transfusion, and their collective impact on the progression of sickle cell anemia.

Keywords: Sickle cell anaemia • Chronic inflammation • Immune system

Introduction

SCD poses a global health challenge, impacting a substantial population. The highest prevalence is observed in Africa, particularly Nigeria, which is identified as the epicenter with 4 to 6 million affected individuals. A study reported a staggering annual count of around 150,000 SCD-afflicted children born in Nigeria, of whom 70-90% succumb before reaching five years of age. Sickle Cell Disease (SCD) is an inherited genetic disorder linked to abnormal hemoglobin [1]. The most severe form is Hemoglobin SS [2]. Beyond its rheological aspects, SCD is marked by chronic inflammation and oxidative stress, culminating in vasculopathy and diverse chronic complications. The condition arises from a specific mutation in the gene responsible for the β-globin chain, leading to a substitution of glutamic acid with valine. This genetic alteration results in the synthesis of abnormal hemoglobin (HbS) that polymerizes under low oxygen conditions, distorting red blood cells into characteristic sickle shapes [3].

The polymerization of hemoglobin initiates a cascade of complications, including vascular-endothelial dysfunction, deficiency in anti-inflammatory agents like nitric oxide, inflammation, oxidative stress, hypercoagulability, and recurrent immune cell activation. These events release free radicals via liberated hemoglobin and heme, along with activation of pro-oxidant enzymes. Excessive free radicals contribute to heightened oxidative stress, fostering chronic inflammation and diminishing life expectancy. Patients with SCD necessitate regular blood transfusions, which heighten exposure to foreign antigens and the risk of generating alloantibodies, potentially leading to delayed hemolytic responses and challenges in finding suitable blood matches. Additionally, multiple transfusions are linked to infection transmission, inflammation, and iron buildup. These factors collectively impact the progression of SCD, with the intricacies of immune system dysregulation warranting further exploration [4].

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Literature Review

Both the innate and adaptive immune responses in SCD are compromised, rendering individuals susceptible to infections. Researchers suggest that chronic activation of the innate immune system results in an excess of Reactive Oxygen Species (ROS). Elevated ROS levels, lead to oxidative stress and tissue damage. Furthermore, studies highlight dysfunction in adaptive immune cells, manifested by decreased antibody levels compared to healthy counterparts. Emerging evidence also indicates impairment in the quantity and function of T and B cells. In light of these inquiries, this review aims to dissect current literature, offering an updated comprehension of the interplay between immune response, inflammation, oxidative stress, blood transfusion, and the pathogenesis of SCD.

Various types of leukocytes, including neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets, have been implicated in the progression of SCD, as indicated by several research studies. These cells are reported to contribute to inflammation, adhesion, and the characteristic painful crises of SCD. Remarkably, even without infection, there is a prevalent occurrence of leukocytosis and immune activation. Flow cytometry studies were utilized to investigate the expression of CD18 on peripheral blood neutrophils-a molecule upregulated during inflammation that binds to endothelial adhesion molecules ICAM-1 and ICAM-4, leading to activation and inflammation. These investigations revealed elevated CD18 expression in SCD patients, resulting in heightened neutrophil affinity for the vascular endothelium and increased adherence. Consequently, sickled red cells were recruited, elevating the risk of vaso-occlusive crises (VOC).

Discussion

Further contributions have shown that polymorphonuclear leukocytes (PMNs) exhibit substantial CD64 expression along with elevated levels of

L-selectin, SCD 16, and elastase, all amplifying adhesion to the endothelium [5]. The higher leukocyte counts in both male and female SCD patients experiencing complications compared to their healthy counterparts. Clinicians often employ white blood cell counts to predict stroke and acute chest syndrome. The release of free haemoglobin and heme during hemolysis emerges as critical triggers for both innate and adaptive immune responses, with indications that patients with higher hemolysis rates face elevated risks of premature mortality. The continuous breakdown of red blood cells leads to persistent activation of innate immune cells, fostering a state of chronic inflammation [6].

Endothelial cells, as one of the initial responders to heme presence, undergo activation. Heme prompts endothelial cells to express adhesion molecules (E-selectin, intercellular P-selectin, vascular cell adhesion molecule 1), initiating the activation and recruitment of other immune cells like macrophages, neutrophils, mast cells, and platelets. Activated macrophages secrete pro-inflammatory cytokines, including IL-1β, through NLRP3 inflammasome stimulation, contributing to a pro-inflammatory and pro-coagulant environment. Consequently, this sustained inflammation leads to VOC, a phenomenon commonly observed in SCD patients.

Heme also directly links to neutrophil activation by functioning as a prototypical pro-inflammatory molecule, drawing neutrophils to injury sites via protein kinase C stimulation and ROS generation. Additionally, heme inhibits neutrophil apoptosis by modulating phosphoinositide 3-kinase and NF-κB signaling, further fueling chronic inflammation. Neutrophils play a significant role in VOC development, with elevated counts tied to clinical complications such as earlier mortality and haemorrhagic stroke.

Conclusion

Sickle cell disease characterizes as a hemolytic anemia wherein red blood cells experience a shortened lifespan. Patients endure recurring hemolytic episodes, causing the release of heme and hemoglobin into the bloodstream. This diminishes the presence of anti-inflammatory molecules, thereby triggering a cascade of reactions involving immune cell activation and oxidative stress. These mechanisms are frequently intensified due to repeated transfusions and the emergence of autoantibodies. The repetitive occurrence of these events culminates in the establishment of an environment that is both pro-inflammatory and pro-coagulant, rendering patients prone to complications like stroke.

Acknowledgment

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Conflict of Interest

None.

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