Cellular Adhesion and the Endothelium

E-Selectin, L-Selectin, and Pan-Selectin Inhibitors

Marilyn J. Telen, MD

KEYWORDS

• Adhesion • Sickle cell disease • Endothelium • Selectins • Integrins

KEY POINTS

- Adhesion of sickle red blood cells (RBCs) and leukocytes to endothelium, as well as to each other, is critical to the process of vasoocclusion in sickle cell disease (SCD).
- Selectins mediate rapidly reversible adhesive interactions, leading to rolling and tethering of cells under conditions of shear stress. This type of transient slowing or immobilization can lead to integrin activation and firm integrin-mediated adhesion.
- Both in vitro and in vivo preclinical studies support the hypothesis that E-selectin-mediated interactions have a critical role in vasoocclusion in SCD.
- Early-phase clinical studies suggest that an investigational drug, GMI-1070, which is a pan-selectin inhibitor with most activity against E-selectin, may be an effective intervention capable of shortening time to resolution of vasoocclusion in SCD.

INTRODUCTION

Sickle cell disease is characterized by episodic, acutely painful vasoocclusive episodes. The pathophysiology of vasoocclusion is thought to involve a wide variety of adhesive interactions involving erythrocytes (RBCs), the endothelium, and leukocytes, including neutrophils, monocytes, and lymphocytes. Platelets likely also contribute to the vasoocclusive process that characterizes SCD (**Fig. 1**).

All hematopoietic cells, as well as endothelial cells, express multiple adhesion molecules, and many of these have been demonstrated in a variety of in vitro, in vivo, and ex vivo model systems to play a role in adhesive interactions that occur as a result of the presence of sickle RBCs (SS RBCs). Because such adhesive events are believed to be critical to the vasoocclusive process, they are a particularly attractive therapeutic

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Division of Hematology, Department of Medicine and Duke Comprehensive Sickle Cell Center, Duke University Medical Center, Box 2615, Durham, NC 27710, USA
E-mail address: marilyn.telen@duke.edu

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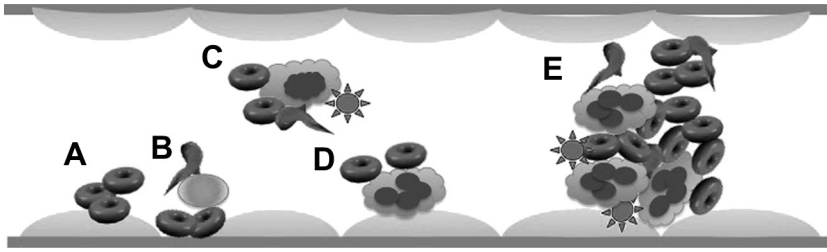

Fig. 1. Interactions between blood cells and the endothelium in sickle cell disease. (*A*) Red cells containing primarily HbS (SS RBCs) adhere directly to the endothelium, a process that initially involves tethering via endothelial P-selectin and then results in firm adhesion via red cell ICAM-4 (LW blood group antigen protein) and endothelial $\alpha V\beta 3$ integrin. (*B*) SS RBCs can activate endothelial cells, causing them to retract as well as to upregulate adhesion molecule expression. Retraction exposes subendothelial matrix, which contains both thrombospondin and laminin, for which RBCs express specific receptors. The laminin receptor is BCAM/Lu, the protein that bears Lutheran blood group antigens. Mature SS RBCs bind to thrombospondin via CD47; CD36 expressed by reticulocytes can also bind to thrombospondin. (*C*) SS RBCs can interact with leukocytes during low shear stress conditions and directly activate their ability to adhere to endothelial cells. Monocytes in the circulation can form circulating aggregates with both RBCs and platelets. (*D*) Neutrophils can roll and tether to endothelial cells via P- and E-selectins, after which they bind more firmly to endothelial integrins. Adherent neutrophils "capture" SS RBCs. (*E*) Adherent neutrophils and SS RBCs, or circulating multicellular aggregates, can form large adherent cellular masses that grow to obstruct or nearly obstruct postcapillary venules. Slow blood flow promotes sickling of already deoxygenated SS RBCs.

target by which to address the cause of greater than 90% of health care required by patients with SCD. Most patients with SCD experience at least one such acutely painful episode annually, and many experience multiple events each year. Each event typically requires parenteral opioid therapy, often during a hospital stay of many days. However, identifying the most important adhesion receptors to target with potentially therapeutic drugs has been challenging.

SELECTINS AND SELECTIN-MEDIATED ADHESION

Among the adhesion receptors expressed by both hematopoietic and endothelial cells are the 3 known types of selectins: P-selectin, E-selectin, and L-selectin. Selectin ligands comprise a variety of sialylated and fucosylated carbohydrates containing an epitope common to both sialyl-Lewis a (sialyl-Le^a) and sialyl-Lewis X (sialyl-Le^x).[1–3] Selectins contribute to a wide variety of physiologically important processes, including interactions of hematopoietic stem cells with the bone marrow microenvironment, homing of lymphocytes to high endothelial venules, migration of leukocytes to areas of inflammation,[4] and metastasis of cancer cells.[5]

In general, selectins mediate rapid on-off interactions, whereas integrins, another class of ubiquitous adhesion receptors, mediate high-affinity, stable adhesion. Selectins are therefore thought to provide the initial interaction between hematopoietic cells in motion and other cells, which may be stationary (such as endothelial cells) or also in motion, such as other circulating blood cells.[6] Shear stress may be critical to the activation of at least some selectin-mediated events, which then lead to "tethering," or short-lived adhesion of one cell to another. In interactions involving endothelial cells, "rolling" is then observed,[6] consisting of repeated short-lived interactions of