Comment on Chang et al, page 1779

Mightier than the sickle cell

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In this issue of Blood, Chang and colleagues demonstrate that a synthetic small molecule inhibitor designed to displace ligand binding to E-selectin disrupts key signaling and activation events leading to vaso-oclusion in SCD.1

The age-old adage “the pen is mightier than the sword” reminds us that creativity and innovation eventually triumph over brute force in solving difficult challenges. Case in point, sickle cell disease (SCD) is a prevalent genetic disorder that poses a significant clinical challenge as it manifests as recurrent vaso-occlusion and chronic organ damage that results in significant morbidity and mortality. The report by Chang et al demonstrates the efficacy of a novel synthetic small molecule pan-selectin inhibitor denoted GMI-1070 in reversing vascular occlusions observed in a mouse model expressing defective human hemoglobin.1 GMI-1070, under development by GlycoMimetics Inc to treat SCD, is designed to occupy the carbohydrate docking domain of selectin receptors and thereby block the heterotypic adhesive interactions supported by the binding of sialyl Lewis-x decorated glycoproteins presented on an adjacent cell membrane. One such interaction is the capture of red blood cells (RBCs) by neutrophils as they roll on inflamed endothelium via membrane-expressed E-selectin. Indeed, the Frenette laboratory recently reported that E-selectin is predominant over P-selectin in activating integrins that capture sickle RBCs at the leading edge of a rolling neutrophil during inflammation in mice.2 In human SCD, there is evidence that neutrophils in blood express constitutively active β₂-integrins and respond with enhanced sensitivity to chemokine activation of adhesion.3 Thus, the genetic advantage afforded by the sickle cell allele that provides RBC resistance to malaria infection also promotes their abnormal adhesion to neutrophils. It is reasonable to ask why nature selected such an impractical process by which the clustering of E-selectin ligands on neutrophils dynamically signals activation of β₂-integrins and adhesion leading to vaso-occlusion.

Leukocyte lore has it that the primary activation signal received by a neutrophil as it recruits to an inflamed venule is via engagement of G-protein-coupled chemokine receptors that in turn trigger integrin activation and cell arrest. However, this mechanism does not completely account for the efficiency by which neutrophils navigate the repulsive forces of flowing blood to efficiently survey miles of microvasculature and arrest only at appropriate sites of inflammation. Recent studies have revealed that clustering of E-selectin ligands during neutrophil rolling in shear flow functions to amplify up to 100-fold the sensitivity to subsequent chemokine activation via a mechanism that involves cytoplasmic calcium flux within the region of adhesive contact.4,5 Additional evidence of the potential importance of E-selectin in SCD comes from the studies of Kato and colleagues at the National Institutes of Health who measured the level of adhesion molecules in the plasma of 160 sickle cell patients over a 4-year period and found a strong correlation of soluble E-selectin with mortality.6 Considering the wide expression of E-selectin in skin microvasculature and its rapid inflammatory induction in most organs, the challenging nature of medical management of SCD becomes apparent.7 Hydroxyurea, which increases fetal hemoglobin thereby inhibiting polymerization of sickle RBC hemoglobin, also lowers the blood neutrophil count and is the only drug demonstrated to decrease morbidity and perhaps mortality in SCD.8 However, there is currently no therapy available that specifically targets the adhesion molecules responsible for triggering vascular occlusions. But there is hope on the horizon as GlycoMimetics moves into phase 2 clinical trials with their antagonist GMI-1070. To date, this drug appears to be well tolerated and indeed inhibits neutrophil activation based on ex vivo functional assessment of neutrophils from blood samples of these subjects. Whether Chang’s observations of GMI-1070’s efficacy in improving blood flow and survival of SCD mice will translate to ameliorating vaso-occlusive crisis in human disease remains to be determined.

Conflict-of-interest disclosure: The authors disclose that there is one of several sites enrolled in clinical trials with GlycoMimetics Inc, but they do not have any financial interest in nor receive financial compensation from the company.

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