in the future. Steps to reduce or eliminate bioactive lipids, for example, lyso-PCs, and other substances that accumulate in stored blood products should also be helpful. Stay tuned as the quest for an ultra-safe blood supply continues.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


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Aptamer therapy for SCD?

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In this issue of Blood, Gutsaeva et al describe an aptamer with high affinity for murine P-selectin and its efficacy in preventing vaso-occlusion in a mouse sickle cell disease (SCD) model.1

Each year, more than 200,000 children are born with SCD,2 yet there is a paucity of treatment options available for sufferers.3 The disease is caused by homozygous expression of a mutation in the beta globin gene which changes a single amino acid (Glu6Val) in the translated protein resulting in assembly of Hemoglobin S (HbS). HbS polymerizes upon deoxygenation giving rise to sickle red cells which are more adhesive than normal red blood cells. The increased adhesive property of sickle red cells causes recurrent vaso-occlusion events in patients and these are associated with increased morbidity and mortality after irreversible organ damage and/or stroke.

A major focus of research in this field has been the use of drugs to stimulate increased expression of Hemoglobin F (HbF) because HbF interferes with HbS polymerization, and patients with high levels of HbF have a milder disease. Most notable among these drugs is hydroxyurea. However, there are concerns about potential side effects of this chemotherapeutic agent and approximately 25% of patients are poor or nonresponders to treatment.3

An alternative strategy is to target vaso-occlusive episodes. Vaso-occlusion caused by sickle red cells is a complex process involving leukocytes, platelets, and endothelial cells and multiple proteins: protein/glycolipid interactions.4 However, inhibitors of some of these interactions cause a major reduction in vaso-occlusion when it is experimentally induced in animal models, suggesting that it may be feasible to develop a single drug capable of preventing and/or reversing vaso-occlusion. One key interaction involves the endothelial integrin αβ3. Monoclonal antibodies to αβ3, cyclic pentapeptides containing the integrin recognition motif RGD, and synthetic peptides corresponding to the binding site for αβ3 on ICAM-4 are very effective inhibitors of vaso-occlusion.5-7 Another key interaction involves endothelial selectins. Sickle red cells adhere to P-selectin on thrombin-treated vascular endothelium and this adhesion is inhibited by heparin.8 A synthetic pan-selectin inhibitor, GMI-1070, with a predominant specificity for E-selectin in vitro, inhibited sickle red cell–leukocyte interactions and improved blood flow and survival of SCD mice.9 Chang et al show that the pan-selectin inhibitor GMI-1070 reduces the number of sickle red cells interacting with adherent leukocytes and consider that E-selectin–induced neutrophil activation is critical for neutrophil-sickle red cell interaction.9

Gutsaeva et al provide evidence that aptamer ARC5690 directly inhibits endothelial adhesion of both sickle red cells and leukocytes and suggest sickle red cells have an as-yet-unidentified ligand for P-selectin.1 Selectins bind diverse acidic oligosaccharide structures. The sulfated glycolipid isolated from red cells by Hillery et al10 might therefore be a candidate for such a ligand.

Aptamers are single-stranded oligonucleotides isolated by selection for binding to target proteins. Therapeutic efficacy of aptamers has been demonstrated in humans for diseases other than SCD.11 In the Gutsaeva et al study, the 33-mer oligonucleotide (ARC5690) was coupled to a 40-kDa branched polyethylene glycol group to inhibit renal filtration and prolong the plasma half-life.1 It will be important to assess the effect of repeated exposure to a PEGylated aptamer as other PEGylated products have proved to be immunogenic. Nevertheless, these results represent an exciting development offering the possibility of a much-needed, novel, targeted therapy for patients with SCD.

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