in maintaining the CLL nodal malignant microenvironment, which sheds light on these clinical observations. Given the importance of BCR signaling in maintaining the CLL nodal malignant microenvironment, we have even more reason to pursue this pathway as a rational therapeutic target for this disease.

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Comment on Sachs et al, page 669

Is TRALI caused by HLA class II too?

Brian R. Curtis bloodcenter of Wisconsin

Donor leukocyte antibodies are most often implicated in transfusion-related acute lung injury (TRALI), including antibodies against class I and II human leukocyte antigens (HLA) and human neutrophil antigens (HNA). Mechanisms supporting a role for HLA class I and HNA antibodies have been described but not for HLA class II antibodies. In this issue of Blood, Sachs et al substantiate a possible mechanism involving activation of monocytes.1

TRALI continues to be the leading cause of transfusion-related mortality, and antibodies in donor blood targeting class I and II HLA and HNA are most often implicated in the pathogenesis. Favorable mechanisms for TRALI suggest that these antibodies bind to cognate antigens on primed neutrophils, which are sequestered in the lungs, and activate them leading to endothelial cell damage and pulmonary edema. Neutrophils express both class I HLA and HNA but not HLA class II, which begs the question, “How do HLA class II antibodies cause TRALI?”

Early studies by several groups reported individual cases of TRALI associated with HLA class II antibodies in donor plasma.2-4 Kopko and coworkers were the first to propose that, rather than affecting neutrophils, class II antibodies might target monocytes, which do express HLA class II. In subsequent studies,3 they provided in vitro evidence that plasma-containing HLA class II antibodies from donors implicated in TRALI can activate monocytes, but only if they express HLA class II antigens with which antibody reacts. In the same work, activated monocytes were shown to produce higher levels of intracellular cytokines, for example, interleukin-8 (IL-8) and tumor necrosis factor alpha (TNFalpha), which were postulated to activate primed neutrophils in the lung, resulting in TRALI.

In the current issue, Sachs et al extend these findings by showing that monocytes incubated with plasma-containing HLA class II antibodies (anti-DR52, anti-DR7) are stimulated to secrete high levels of cytokines (Groα, IL-8, TNFalpha) and leukotriene B4 (LTB4) only when they express the DR antigens for which the antibodies are specific, and that cytokine-rich supernatants from monocytes activated in this way, in turn, induce lipopolysaccharide (LPS)–primed human neutrophils to synthesize and release reactive oxygen species.1 In addition, in an ex vivo rat model, it was shown that changes typical of TRALI (increased lung endothelial permeability and weight) occur only when the combination of (1) specific HLA class II antibodies, (2) human monocytes expressing the cognate class II antigens, and (3) human neutrophils are simultaneously perfused through lungs of LPS-treated mice. It will be important to confirm these ex vivo findings in an in vivo animal model. Several animal models have been developed over the years to study mechanisms responsible for TRALI. Two recently reported models, one in mice,6 and another in rats,7 show particular promise, and have provided valuable information about the roles of class I HLA antibodies and lyso-phosphatidylcholine (lyso-PC) molecules in TRALI; these models or their equivalents will provide valuable tools with which to confirm these ex vivo results obtained by Sachs et al.

From what has been learned to date from animal models, the most probable mechanism responsible for TRALI appears to be the following: (1) a predisposing clinical condition (first event) in the patient (eg, infection, surgical trauma, hematologic disease, etc) results in sequestration of primed neutrophils in the lungs, (2) a biologic response modifier (eg, lyso-PCs, CD40L, or leukocyte antibodies in a transfused blood product [second event]) then induces neutrophil activation directly or indirectly through monocytes activated by class II HLA antibodies. Reactive oxygen species and other toxic substances released by neutrophils then cause acute lung injury, capillary leak, and pulmonary edema (TRALI).

Many US blood centers implemented transfusion of male-only plasma in the fall of 2007 and screening of blood donors for HLA antibodies in the fall of 2008 to reduce the transfusion of HLA antibodies. Recent Food and Drug Administration data show that TRALI fatalities have steadily decreased from 34 reports in 2007 to 16 reports in 2008 and 13 reports in 2009,8 indicating that these risk-reduction measures probably have been effective in reducing, but not eliminating, TRALI. Further reductions will require screening of blood donors for HLA antibodies, especially HNA-3a antibodies, which are the most commonly implicated HNA antibody, and the most frequent cause of fatal TRALI. Recent identification of the HNA-3a carrier protein and polymorphism that defines the HNA-3a and -3b antigens9,10 should make this possible.
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.

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Aptamer therapy for SCD?

David J. Anstee  BRISTOL INSTITUTE FOR TRANSFUSION SCIENCES

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, 3 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 protein:protein and protein:glycolipid interactions. 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 αvβ3. Monoclonal antibodies to αvβ3, cyclic pentapeptides containing the integrin recognition motif RGD, and synthetic peptides corresponding to the binding site for αvβ3 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. 9 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 al 10 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 PE-Glylated aptamer as other PE-Glylated 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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