and other developments like modifications to prolong half-life are more likely to attract investment and effort. Meanwhile, clinicians may wonder whether there is a case for treating PUPs with lower purity plasma-derived factor VIII after all. ■

REFERENCES

1. White GC, Kempton CL, Grimsley B, Nielson B, Roberts HR. Cellular immune responses in hemophilia: why do inhibitors develop in some, but not all hemophiliacs? J Thromb Haemost. 2005;3:1676-1681.
2. Guérois C, Laurian Y, Rothschild C, et al. Incidence of factor VIII inhibitor development in severe haemophilia A patients treated only with one brand of highly purified plasma-derived concentrate. Thromb Haemost. 1995; 73:215-218.
3. Rothschild C, Laurian Y, Satre EP, et al. French previously untreated patients with severe haemophilia A after exposure to recombinant factor VIII: incidence of inhibitor and evaluation of immune tolerance. Thromb Haemost. 1998;80:779-783.
4. Aledort LM, DiMichele DM. Inhibitors occur more frequently in Africo-American and Latino haemophiliacs. Haemophilia. 1998;4:68.
5. Goodeve A. The incidence of inhibitor development according to specific mutations—and treatment. Blood Coagul Fibrinolysis. 2003;14:S17-S21.
6. Schwaab R, Brackmann HH, Meyer C, et al. Haemophilia A: mutation type determines risk of inhibitor formation. Thromb Haemost. 1995;74:1402-1406.

HEMATOPOIESIS

Comment on Zhang et al, page 73

The erythropoietin receptor lends a Friendly hand

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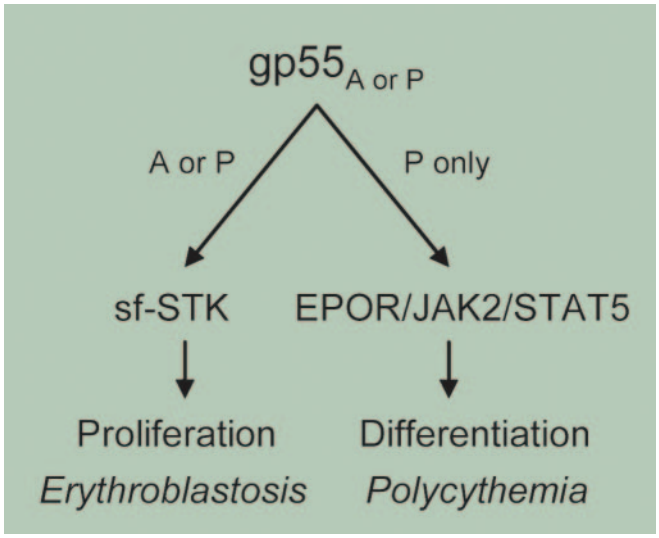
An elegant genetic study clarifies the role of the erythropoietin receptor in the pathogenesis of erythroblastosis and polycythemia induced by Friend virus.

In 1957, Charlotte Friend described erythroleukemia in mice that was transmissible by a cell-free filtrate.[1] The retrovirus and disease that bear her name have proven to be a powerful model system for studying erythropoiesis, erythropoietin signaling, leukemogenesis, and retroviral pathogenesis.[2] Friend virus, a complex of replication-competent helper virus and replication-defective spleen focus-forming virus (SFFV), induces disease in susceptible mice in 2 distinct stages. The initial premalignant phase is characterized by splenomegaly due to polyclonal expansion of nontransformed erythroblasts. Two different variants of SFFV ($SFFV_P$ and $SFFV_A$) cause either polycythemia or anemia, respectively, during this period. Subsequently, clonal erythroleukemia emerges with loss of p53 and frequent activation of the Ets family transcription factor PU.1 through proviral insertion. The genetic basis of the first stage of Friend disease was clarified by 2 important observations. The first was the discovery by Li, D'Andrea, and coworkers[3] that the envelope glycoprotein of $SFFV_P$, $gp55_P$, interacted with and activated the erythropoietin receptor (EpoR). The related envelope protein from $SFFV_A$ does not activate EpoR, although both forms of SFFV can induce erythroid burst-forming units (BFU-Es) in the absence of Epo. The second finding was the positional cloning by Ney and Correll's group of the Friend disease susceptibility locus *Fv2*, a mouse gene that encodes a naturally occurring truncated form of the receptor tyrosine kinase STK (sf-STK).[4] Mice lacking sf-STK do not develop either erythroblastosis or erythroleukemia after Friend virus infection.

How these 3 transmembrane proteins might function in erythroid progenitors is a mystery. In one model, gp55 mediates a functional interaction between EpoR and sf-STK, analogous to that demonstrated for EpoR and another receptor tyrosine kinase, c-Kit.[5] In the current issue of *Blood*, however, Zhang and colleagues use a genetic approach to demonstrate that gp55 must interact separately with Epo-R and sf-STK. Balb/c mice (sensitive, expressing sf-STK) engineered to express a murine EpoR mutant lacking cytoplasmic tyrosines required for Stat5 activation were nonetheless susceptible to Friend virus–induced erythroblastosis and splenomegaly, as were mice lacking both Stat5a and 5b. Friend virus induced small splenic foci of erythroblasts but not overt erythroblastosis after infection of Balb/c fetal liver cells lacking EpoR, whereas erythroblastosis and splenomegaly were restored by transgenic expression of human EpoR, which is not activated by gp55, at least in cell lines.[6] By contrast, polycythemia induced by $SFFV_P$ did require EpoR and Stat5. These studies, together with recent observations that gp55 can also bind and activate sf-STK,[7] suggest a model where gp55 from either SFFV strain can activate sf-STK and induce erythroblastosis, whereas $gp55_P$ causes Epo-independent terminal erythroid differentiation and polycythemia through EpoR and Stat5 (see figure). These results do not exclude possible indirect interactions between sf-STK and EpoR (for example, through JAK2). The reported resistance of human EpoR to activation by $gp55_P$



Model of erythroblastosis and polycythemia induced by Friend virus. The envelope glycoprotein (gp55) of both the anemia (A)– and polycythemia (P)–inducing strains of SFFV induces erythroblastosis and splenomegaly that requires sf-STK. Only $gp55_P$ induces Epo-independent terminal erythroid differentiation, through EpoR and Stat5. For details, see the complete figure in the article beginning on page 73.

also deserves a second look, particularly in primary cells. Surprises will no doubt continue to emerge from the rich pathobiology of Friend virus. ■

REFERENCES

1. Friend C. Cell-free transmission in adult Swiss mice of a disease having the character of a leukemia. J Exp Med. 1956;105:307-318.
2. Ney PA, D'Andrea AD. Friend erythroleukemia revisited. Blood. 2000;96:3675-3680.
3. Li JP, D'Andrea AD, Lodish HF, Baltimore D. Activation of cell growth by binding of Friend spleen focus-forming virus gp55 glycoprotein to the erythropoietin receptor. Nature. 1990;343:762-764.
4. Persons DA, Paulson RF, Loyd MR, et al. Fv2 encodes a truncated form of the Stk receptor tyrosine kinase. Nat Genet. 1999;23:159-165.
5. Wu H, Klingmuller U, Besmer P, Lodish HF. Interaction of the erythropoietin and stem-cell-factor receptors. Nature. 1995;377:242-246.
6. Showers MO, DeMartino JC, Saito Y, D'Andrea AD. Fusion of the erythropoietin receptor and the Friend spleen focus-forming virus gp55 glycoprotein transforms a factor-dependent hematopoietic cell line. Mol Cell Biol. 1993;13:739-748.
7. Nishigaki K, Thompson D, Hanson C, Yugawa T, Ruscetti S. The envelope glycoprotein of Friend spleen focus-forming virus covalently interacts with and constitutively activates a truncated form of the receptor tyrosine kinase Stk. J Virol. 2001;75:7893-7903.

IMMUNOBIOLOGY

Comment on Zimring et al, page 187

Transfusion tickles T cells through cross-priming

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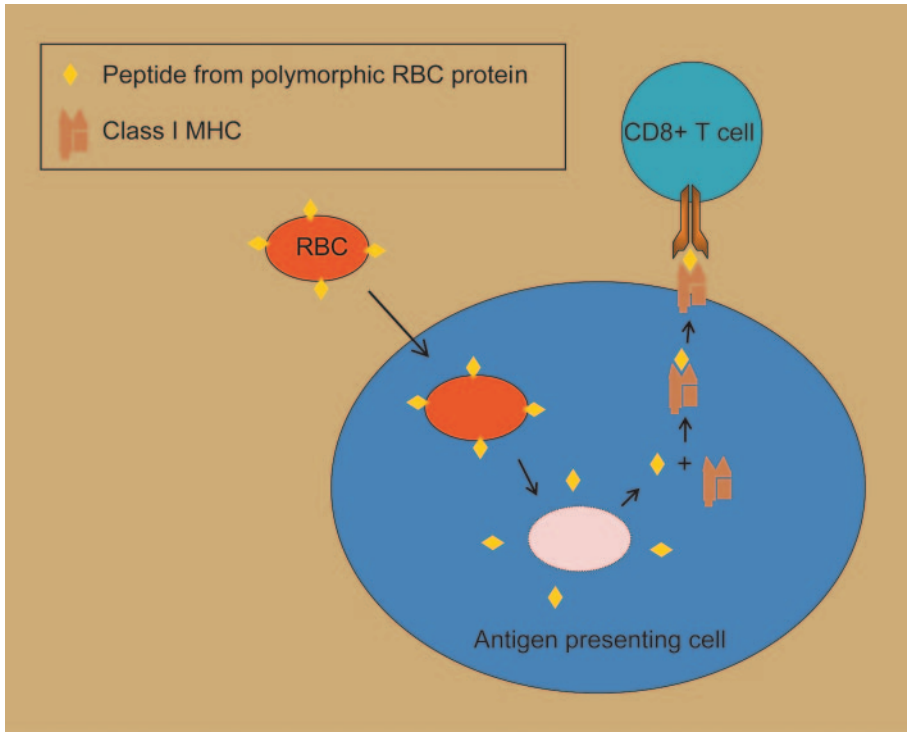
A mouse model is used to show that RBC surface proteins recognized as foreign can trigger recipient CD8$^+$ T-cell responses even in the absence of donor leukocytes.

Blood transfusion is not an immunologically inert event. In a relatively short time frame, the recipient is exposed to a large quantity of polymorphic antigens, and antigen-specific immune responses can and do develop. The most well-recognized of these is the development of alloantibodies against polymorphic epitopes located on red blood cell (RBC) surface proteins. Alloantibodies are responsible for delayed hemolytic transfusion reactions, but when alloantibodies are detected, clinical problems are, for the most part, fairly easily avoided through the selection of appropriate, cross-match compatible units.

A less well appreciated immunologic effect of blood transfusion is the development of cell-mediated immunity and the induction of CD8$^+$ cytotoxic T lymphocytes (CTLs) with specificity against polymorphic peptides derived from allelic variants of normal proteins, also known as minor histocompatibility antigens (MiHAs). This type of immune response may contribute to the unusually high rates of rejection of allogeneic bone marrow observed among patients with sickle cell disease who undergo HLA-matched bone marrow transplantation (BMT).[1] Such patients typically have received previously numerous blood transfusions, and may therefore have developed CTLs with specificity to MiHAs.

The mechanisms involved in the development of anti-MiHA CTLs following transfusion are not well understood, but it has been generally assumed that donor white cells are important. This belief stems in part from the demonstrated beneficial effects of leukoreduction in preventing humoral alloimmune responses in other transfusion situations,[2] as well as from the ameliorating effects of leukoreduction in transfusion-associated BMT graft rejection in experimental dog models.[3]

The current study by Zimring and colleagues challenges the assumption that a CD8$^+$ T-cell response to RBC-associated MiHAs cannot occur in the absence of donor leukocytes. The authors use a well-characterized mouse model in which both the antigen and the responding T cells are known in advance. The authors prepared highly leukoreduced mouse RBCs and then chemically modified them to express on their cell surface a xenoantigen—chick ovalbumin (OVA). These modified RBCs (now expressing a "MiHA" in the form of the cross-linked OVA) were transfused into mice that had been preloaded with CD8$^+$ T cells capable of recognizing a peptide from OVA. In response, this T-cell population greatly expanded. The transfusion of RBCs modified with an irrelevant



Cross-priming of CD8$^+$ T-cell responses to RBC surface antigens. In this highly schematized model, a transfused RBC expressing a polymorphic variant of a cell-surface protein is taken up by a recipient antigen presenting cell. Peptides derived from RBC proteins are loaded onto class I MHC molecules, then shuttled to the cell surface, where they can stimulate responses in recipient cognate CD8$^+$ T cells.

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