to eliminate the excess of α-chains, we can now address fascinating questions, both old and new. In β-thalassemia, the role of apoptosis has been well established as the main cause of reduced production of red cells. Formation of hemichromes (α-chain/heme aggregates) has been clearly associated with erythroid cell death. However, the extent of this phenomenon and whether the erythroid cells might be armed with additional tools to limit the damage associated with the excess of α-chains in the attempt to maximize red cell production is still debated. The data from Khandros et al suggest that these mechanisms play an important role in mitigating the phenotype of this disorder. Their results also suggest that these mechanisms are likely responsible for preventing any serious problem in β-thalassemia carriers. Furthermore, we can also speculate that the relative ability of these mechanisms to eliminate the excess of α-chains from the erythroid cells might also play an important role in the phenotypic variability observed in this disorder. β-thalassemia is another disorder in which these mechanisms likely play a major role. Additional studies will clarify these points.

The new observations from Khandros and colleagues also suggest a strong correlation between the excess of globin chains, their detoxification from the erythroid cells, and the degree of ineffective erythropoiesis. Therefore, it will be very interesting to investigate whether these responses modulate the phenotypic outcome in thalassemia disorders. If these mechanisms are shown to play a major role in limiting the effect of hemichromes on the ineffective erythropoiesis, new potential pharmacologic approaches might aim at increasing the elimination of these supernumerary molecules.

Recent data support the notion that modulation of the formation of hemichromes can profoundly alter ineffective erythropoiesis in β-thalassemia. Both administration of transferrin and increased expression of hepcidin can decrease erythroid iron intake, with subsequent reduction of hemichrome formation and amelioration of red cell morphology, production, and lifespan. In both cases, this was associated with increased hemoglobin levels. These observations support the data and the model proposed by Khandros and colleagues, in which elimination of some of the α-chains in excess allows production of better-quality red cells, while inhibition of the detoxification process increases the ineffective erythropoiesis. Interestingly, in animals in which transferrin or hepcidin were used as potential therapeutic tools, reduction of hemichrome formation was associated with diminished heme synthesis. This suggests that, potentially, the α-chains in excess might be disposed even more efficiently if they have fewer chances to aggregate with heme. Even this notion could be used to further enhance the ability of the detoxifying pathways to ameliorate the erythropoiesis in this disorder.

Moreover, the observation by Khandros et al might also prove useful in gene therapy for sickle cell anemia. It has been proposed that insertion of a normal β-globin gene into the hematopoietic stem cells of sickle cell patients might reduce the formation of the abnormal tetramers and reduce or prevent the formation of sickle red cells and the pathophysiologic sequelae associated with this phenomenon. However, the main concern associated with this approach is that, after gene transfer, the total amount of β-chains (sickle + normal) might exceed the amount of α-chains, leading to an α-thalassemia-like phenotype. The data from Khandros and colleagues suggest that a moderate excess of globin chains might be tolerated and eliminated efficiently by the erythroid cells. In conclusion, these novel findings will modify understanding of β-thalassemia and suggests new approaches to alleviate the symptoms of this disorder.

*** THROMBOSIS & HEMOSTASIS

Comment on Kasthuri et al, page 5285

**Monocytes in HIT: an evolving story**

**Steven E. McKenzie** THOMAS JEFFERSON UNIVERSITY

In this issue of Blood, Kasthuri and colleagues have examined the role of Fcγ receptors and signaling molecules in monocytes in HIT.1 Heparin-induced thrombocytopenia (HIT) is a paradoxical disorder. Patients with HIT develop thrombocytopenia while on heparin, yet the clinical manifestations are dominated by venous, arterial, and/or microvascular thrombosis. These thrombi are platelet- and fibrin-rich. However, the initiators of thrombosis have been poorly understood because clots develop in the presence of physically intact endothelium, that is, without exposure of blood to the subendothelial matrix. Initial progress in understanding fibrin...
Monocytes contribute to thrombosis in heparin-induced thrombocytopenia (HIT) by cell surface HIT immune complexes triggering the FcγRI receptor via erk1/2 to produce a TF+ surface and TF+ microparticles. Professional illustration by Paulette Dennis.

Monocytes express tissue factor (TF) when stimulated by the HIT immune complex, consisting of macromolecular heparin/PF4 in combination with anti-heparin/PF4 IgG antibodies. Now Kasthuri et al confirm and extend these findings, discovering that monocytes express TF and release TF/H11001 microparticles (MPs) on stimulation by HIT immune complexes.

The authors are to be commended for validating that both human HIT IgG and the HIT-like monoclonal antibody KKO act the same. As per the figure, they nicely demonstrate that the CD64 FcγRI receptor on monocytes, and not FcγRIIA (CD32a), transduces the signal to TF generation. Furthermore, they demonstrate that MEK and erk1/2 are involved. One more interesting note from these careful studies: their data are consistent with the localization of the stimulatory HIT immune complex on the neighboring cell surface, in keeping with the observations by Rauova and colleagues.

The generation of TF and TF+ MPs by monocytes likely plays a substantial role in the thrombosis of HIT. We can hope that this new knowledge of the effectors in this process enables targeted approaches that minimize hemorrhagic side effects in treating HIT.

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REFERENCES

SNPs and GVHD prediction: where to next?

Anne M. Dickinson

The article by Chien et al in this issue of Blood uses a novel approach to assess the role of single nucleotide polymorphisms (SNPs) in acute graft-versus-host disease (GVHD). Using a genome-wide association study (GWAS) employing an Affymetrix GeneChip Genome-Wide Human 500 000 SNP array, they screened 1298 allogeneic hematopoietic stem cell transplant donors and recipients and tested whether the results from 40 previously reported candidate SNPs could be replicated. They also used a novel approach to impute data using IMPUTE software (http://nathgen.stats-ox.ac.uk/impute/impute.html) where the genotyping data were not available.

Since the first publication describing a potential role of TNF and IL10 polymorphisms in predicting GVHD,2 a large number of reports have described a wide range of SNPs that are often also associated with inflammatory disease or autoimmune disease. Among the most studied but also with variable results have been IL10, TNF, and NOD2.

Of the 40 published candidates in the study by Chien et al, only 16 had usable data (genotype or imputed) for analysis. Interestingly, of all the SNPs analyzed, IL6 was the most consistent. The IL6G74 allele has also often been consistently associated with increased GVHD and increased serum levels of IL-6 that have also correlated with C reactive protein levels. Of the other SNPs that could be assessed by genotyping or imputation were those of CTLA4, MTHFR (5, 10-methylenetetrahydrofolate reductase), and
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