spectrometry analysis to define the composition of IgG-associated glycans. Total IgG from the same individuals was similarly studied. Fourteen distinct glycan species were identified. Slight but significant increases in sialylation and galactosylation were found in the HPA-1a antibodies relative to total IgG. However, the most striking finding was a marked decrease in core fucosylation, which in some cases was as low as 10% of the value for total IgG. This difference persisted even in HPA-1a antibodies obtained several years after delivery. Similar studies of antibodies specific for class I HLA antigens present in 13 nonpregnant individuals who were refractory to platelet transfusions showed that the HLA antibodies did not differ from total IgG in the extent of core fucosylation. However, core fucosylation of an HLA antibody from one of the women sensitized to HPA-1a was significantly lower (43%) than that of total IgG (94%). In studies involving seven of the NAIT sera, it was found that decreased core fucosylation correlated with more effective phagocytosis of antibody-coated platelets by neutrophils. To evaluate the clinical significance of these findings, perinatal status of infants born to the women studied was evaluated retrospectively. A statistically significant correlation was found between decreased core fucosylation of maternal antibody and increased severity of NAIT. However, the data were widely scattered, making it uncertain whether measuring core fucosylation in a particular maternal antibody would be helpful in prenatal management of an infant at risk for NAIT.

The authors leave open the question of whether the anomalous properties of glycans identified in the HPA-1a antibodies reflects the fact that the original antigenic challenge occurred during pregnancy. It seems counterintuitive that this might be the case, because skewing of glycan synthesis to favor production of HPA antibodies lacking a core fucose could be deleterious to a fetus. On the other hand, production of such antibodies against a pathogen acquired during pregnancy could be a protective adaptation. Whatever the explanation, the interesting and provocative findings described by Kapur et al should stimulate further studies to characterize the effects of pregnancy on the properties of IgG glycans and the importance of IgG glycan variation in antibody-mediated human disease.

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

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● ● ● RED CELLS, IRON, & ERYTHROPOIESIS

Comment on Steinberg et al, page 481

"Packaging" of fetal hemoglobin in sickle cell anemia

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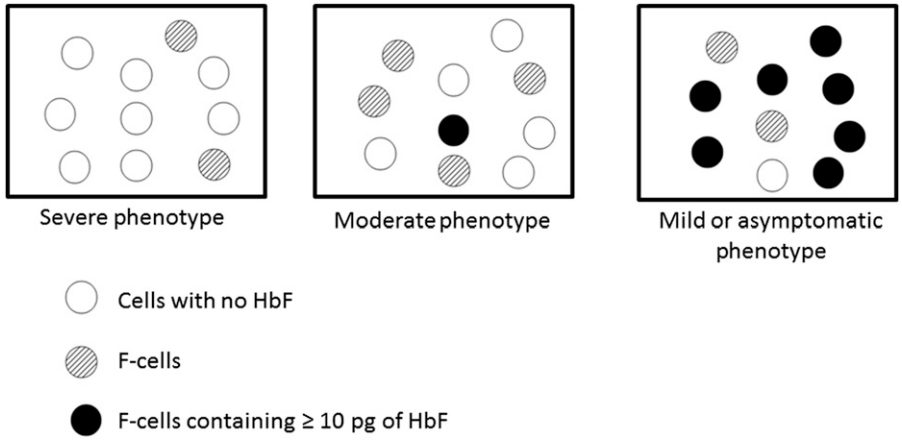
In this issue of *Blood*, Steinberg et al describe the clinical importance of the distribution or "packaging" of fetal hemoglobin (HbF) within erythrocytes of persons with sickle cell anemia.[1]

Ever since Janet Watson's astute observation in 1948,[2] the "protective" effect of HbF in persons with sickle cell anemia has been appreciated, and during the last several decades, increasing HbF levels by prescribing hydroxyurea has had salutary clinical effects. HbF has been measured by its overall concentration in the blood or by the percentage of erythrocytes containing fetal hemoglobin (F cells).[3] Now, Steinberg et al elegantly characterize a previously unappreciated third means of expressing the



Disease phenotype depends on how HbF is packaged in HbS-containing erythrocytes.

powerful ameliorative effects of HbF in patients with sickle cell anemia: ie, the percentage of erythrocytes containing ≥10 pg of HbF. This amount has been shown to inhibit deoxy sickle hemoglobin (HbS) polymer formation when the oxygen saturation is less than the 40% to 70% encountered in the microcirculation. By preventing polymerization, the beneficial effects for the patient include reduction in intravascular hemolysis, vaso-occlusion–induced pain and tissue damage, and endothelial injury.

The authors note the experiment of nature exemplified by the phenotype resulting from the compound heterozygous state of HbS and pancellular hereditary persistence of fetal hemoglobin (S-HPFH).[4] In this condition, every erythrocyte remarkably contains not only HbS but also approximately 10 pg of HbF. The result is nearly complete inhibition of deoxyHbS polymerization so that such individuals have a normal phenotype or only very minimal hemolysis. The authors thus posit that a therapeutic goal of achieving 10 pg of HbF per cell in persons with sickle cell anemia could represent a pharmacologic cure.

Hydroxyurea therapy is often beneficial (and correlates roughly with the percentage rise in HbF), but unfortunately the deleterious clinical manifestations of intravascular hemolysis and vaso-occlusion frequently continue.[5] In this article, the authors describe examples from the clinical sickle cell literature of diverse β globin haplotypes that are associated with widely ranging HbF values and clinical sequelae. Yet, because it is uncommon for HbF levels to exceed 20% to 25% (with or without hydroxyurea), most persons with sickle cell anemia have pain, organ damage, and a shortened lifespan. Nevertheless, the authors depict in various hypothetical examples how persons with specific concentrations of HbF or percentages of F cells can have widely differing percentages of circulating erythrocytes that exceed the protective threshold of 10 pg/cell, ranging from virtually none to 70% or more (see figure).

A clinical correlate of the observation by Steinberg et al is the use of a chronic hypertransfusion program for primary or secondary stroke prevention or as a means of reducing the frequency or severity of vaso-occlusive crisis and acute chest syndrome. Suppressing the proportion of cells containing HbS to <30%, a common goal of chronic transfusions, assures that sickle cell–related complications are reduced or prevented.[6] The result would be similar when 70% HbS-containing cells also have >10 pg of HbF/cell (as in persons with HbS-HPFH).

So how do we achieve the postulated objective of increasing HbF to >10 pg in most or nearly all of these patients' cells? Clearly hydroxyurea alone is not capable of that goal without risks of excessive toxicity. The authors point out that even the promising approach of blocking the BCL11A pathway[7] may not result in the desired pharmacologic cure unless the result is a pancellular increase in HbF as observed in compound heterozygotes with HbS-HPFH.

The authors' characterization of packaging HbF in the majority of cells to achieve a 10-pg level and render them incapable of sickling is an admirable goal. What an achievement it would be if each individual in the world with sickle cell anemia could someday be presented with such a therapeutic package as a gift of life.

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● ● ● RED CELLS, IRON, & ERYTHROPOIESIS

Comment on Alvarez-Dominguez et al, page 570

Long noncoding RNAs in erythropoiesis

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In this issue of *Blood*, Alvarez-Dominguez et al use a combination of genomics technology, bioinformatics, and functional analyses to provide new insights into our understanding of the role of long noncoding RNAs (lncRNAs) in erythropoiesis.[1] This is an initial step forward in our understanding of the many roles of lncRNAs in normal and perturbed erythropoiesis. lncRNAs have recently emerged as critical, multifunctional regulators of cellular gene expression.

Traditionally, the regulatory functions of RNA have been thought to be limited to their roles as ribosomal, messenger, and transfer RNAs. Development of high-throughput sequencing methodology and its application to transcriptome analyses has led to the realization that there are many more RNAs, termed noncoding RNAs (ncRNA), produced within the cell.[2] We now know that the majority of the mammalian genome (~2/3) is transcribed, with <2% of the genome yielding transcripts with protein coding potential.[3] Thus, huge amounts of ncRNA are produced within the cell. ncRNAs have been classified as housekeeping RNAs, microRNAs, small interfering RNAs, PIWI-interacting RNAs, small ncRNAs (<200 nucleotides [nt] in length), and long ncRNAs (lncRNAs, >200 nt in length).

The focus of the report by Alvarez-Dominguez et al is on lncRNAs in erythropoiesis. Defined as RNA transcripts >200 nt in length that lack coding potential, lncRNAs are a large and diverse group of transcripts.[3] Thousands and thousands of lncRNAs have been identified in cells from diverse organisms. Although the role of most lncRNAs is unknown, functions of several lncRNAs have been identified, including regulation of cellular processes such as