ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Red Cell Membrane, Part 2: Disorders of the Red Cell Membrane

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This is part 2 of a 3-part series on the red cell membrane.

H&O How common are red cell abnormalities?

XA Anemia, which is the most common symptom of red cell abnormalities, affects approximately one-quarter of people globally. In a report from the Global Burden of Disease Study 2010, which was published in the *Lancet* in 2012, anemia was the most important disorder in terms of its overall contribution to global years lived with disability (YLDs). The overall burden of anemia was large—68.2 million YLDs, or almost one-tenth (8.8%) of all YLDs worldwide—reflecting both the high prevalence of anemia and the moderately severe disability it produces, especially in cases of severe anemia. By far the most important contributor to this health loss was iron-deficiency anemia, which accounted for 62.2% of anemia YLDs globally. The second-leading specific cause of anemia YLDs was thalassemia (6.7% of total anemia YLDs), which was followed by malaria (4.9%). Hookworm and sickle cell anemia together accounted for a further 7.2%.

H&O Why are so many people affected?

XA The high incidence of malaria is the main reason why so many people are affected with a variety of red cell disorders. Malaria infects approximately 400 million people each year, of whom 2 to 3 million die of the illness. In evolutionary terms, the interactions between the malaria parasite and the human erythrocyte altered the characteristics of hemoglobin and the red cell membrane in areas of malaria epidemics. This leads to many red cell diseases, including sickle cell disease, thalassemia, red cell membrane abnormalities, and enzyme-deficiency diseases such as pyruvate kinase deficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

H&O Could you discuss these diseases in greater detail?

XA Regarding sickle cell disease, people whose red cells exhibit the sickle trait have a survival advantage over those with normal red cells in regions where malaria is endemic. Sickle cell trait is the genetic condition selected for in regions of endemic malaria. Sickle cell disease is a necessary consequence of the existence of the trait condition because of the genetics of reproduction.

As for thalassemia, this condition also has reached levels of expression in human populations because it protects against malaria. The imbalance in globin chain production that is characteristic of thalassemia produces membrane oxidation by hemichromes and other molecules that generate reactive oxygen species. Reactive oxygen species also injure and kill malaria parasites.

As far as enzyme-deficiency diseases are concerned, the high frequency of alleles that produce red cells with G6PD deficiency is one of the most dramatic examples of the selective pressure of malaria on humankind. G6PD prevents oxidation of the heme group. In its absence, hemichromes and other species that generate reactive oxygen species accumulate in erythrocytes. *Plasmodium falciparum* parasites grow poorly in erythrocytes that are deficient in

G6PD. Also, the discovery that pyruvate kinase–deficient human erythrocytes are resistant to malaria has again highlighted the host-parasite relationship.

H&O What are the various disorders in which the red cell membrane plays a role?

XA The red cell membrane disorders include alterations in both membrane structural organization and membrane transport function. The membrane structural organization disorders are hereditary spherocytosis, hereditary elliptocytosis, and hereditary ovalocytosis; the primary membrane transport function disorder is hereditary stomatocytosis. Altered function also can be caused by secondary effects on the membrane resulting from mutations in globin genes: sickle cell disease, sickle cell-hemoglobin C disease (Hb SC), homozygous hemoglobin C disease (Hb CC), unstable hemoglobins, and thalassemias.

H&O What are the characteristics of each of these disorders?

XA All of these disorders are characterized by anemia, of course. Beyond that, a common feature of all forms of hereditary spherocytosis is loss of membrane surface area and resultant change in cell shape, from discocytes to stomatocytes to spherocytes. Typical hereditary spherocytosis consists of evidence of hemolysis with anemia, jaundice, reticulocytosis, gallstones, and splenomegaly, as well as spherocytes with reduced membrane surface area on peripheral blood smear.

Regarding hereditary elliptocytosis, a common feature of all forms of this condition is a mechanically unstable membrane. This mechanical instability results in progressive transformation of cell shape during circulation from discocytes to elliptocytes, and—in severe cases—to membrane fragmentation and generation of cells with reduced membrane surface area and abnormal morphology. Splenectomy significantly reduces the severity of the anemia by increasing the circulatory life span of fragmented red cells.

As for hereditary ovalocytosis, a distinguishing feature of ovalocytes is that their red cell membrane is very rigid and mechanically more stable. Ovalocytosis is characterized by the presence of oval-shaped red cells with 1 or 2 transverse ridges or a longitudinal slit on blood smears.

Hereditary stomatocytosis is a rare red cell disorder that is divided into 2 different entities: dehydrated hereditary stomatocytosis (also called xerocytosis) and overhydrated hereditary stomatocytosis. Both forms of stomatocytosis exhibit a cation leak to the univalent cations Na+ and K+, resulting in altered intracellular cation content and cell volume alterations. The distinctive feature of dehydrated hereditary stomatocytosis is cell dehydration, with a resultant increase in mean corpuscular hemoglobin concentration and decreased osmotic resistance. The distinctive feature of overhydrated hereditary stomatocytosis is increased cell hydration with resultant increase in mean corpuscular volume, a decreased mean corpuscular hemoglobin concentration, and an increased osmotic fragility. The increased osmotic fragility is not the result of reduced cell surface area, but of increased cell volume with normal surface area. Although splenectomy is highly beneficial in the management of hereditary stomatocytosis and hereditary elliptocytosis patents with moderately severe to severe anemia, it is contraindicated in hereditary stomatocytosis owing to membrane transport defects, because venous thromboembolic complications occur following splenectomy.

Finally, the inability to regulate cell volume has long been recognized to be a feature of a number of hemoglobinopathies, including sickle cell disease, Hb SC disease, Hb CC disease, unstable hemoglobins, and thalassemias. Increased cell volume is a feature of hemoglobin H (α-thalassemia), whereas cell dehydration is a feature of β-thalassemia intermedia and major. The SK1-Gardos channel and the Na+-K+ cotransporter have been implicated in dehydration of sickle red cells.

H&O What is the molecular and genetic basis for these disorders?

XA The molecular basis for membrane loss in hereditary spherocytosis is the result of the defective anchoring of the skeletal network to the membrane as a result of defects in several proteins (ankyrin, spectrin, band 3, and Rh complex). Hereditary spherocytosis is the result of defects in any of the protein components involved in vertical linkages between skeletal network and the membrane.

The molecular basis for decreased membrane mechanical stability in hereditary elliptocytosis is weakened lateral linkages in membrane skeleton due to either a defective spectrin dimer-dimer interaction or a defective spectrin-actin-protein 4.1R junctional complex. Reduced avidity of lateral interactions due to defects in α-spectrin, β-spectrin, or protein 4.1R lead to decreased membrane mechanical stability. Thus, hereditary elliptocytosis is the result of defects in any of the protein components that are involved in lateral linkages in the skeletal network.

As for hereditary ovalocytosis, inheritance of ovalocytosis is autosomal dominant. Only heterozygotes have been identified in regions of high prevalence, implying that homozygosity may lead to embryonic or fetal lethality. Hereditary ovalocytosis appears to provide some protection against all forms of malaria. In all cases of ovalocytosis studied to date, only 1 mutation has been

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identified: a genomic deletion of 27 base pairs in codons 400 to 408, located at the boundary of the cytoplasmic and first transmembrane domain of band 3. Thus, hereditary ovalocytosis is unique among red cell membrane disorders in that the identical mutation in a single gene is responsible for the morphologic phenotype.

Regarding hereditary stomatocytosis, both the dehydrated and overhydrated forms exhibit a cation leak to the univalent cations Na+ and K+ that results in altered intracellular cation content and cell volume alterations. Several recent studies, including one by Dr Ryan Zarychanski and colleagues at the University of Manitoba, have shown that dehydrated hereditary stomatocytosis is associated with mutations in PIEZO1. However, the molecular basis for overhydrated hereditary stomatocytosis has not yet been defined.

Suggested Readings

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