Ironing out the Wrinkles of Fe Metabolism

By Robert L. Redner, MD, and Vida Almario Passero, MD

Lee Trevino once said, "During a [lightning] storm hold up a 1-iron. Not even God can hit a 1-iron." Proper iron play is critical — on and off the golf course. Iron, man, and metabolism were the subjects of yesterday's and today's session on the physiology of iron recycling and its disorders, organized by Chair Mario Cazzola, MD, and the Scientific Committee on Iron and Heme.

Carole Beaumont, PhD, discussed the role of erythrophagocytosis in iron homeostasis. Red-cell iron accounts for the majority of body iron, and recycling of heme iron provides most of the iron required for erythropoiesis. Peroxidation of lipoproteins, loss of sialic acid residues, and formation of senescence neoantigens act as signals to identify aging red cells to liver and spleen macrophages. After recognition, red cells are internalized by phagocytosis. The phagosome ultimately degrades red cells. Heme is catabolized to release free iron, which is secreted back into the plasma by ferroportin or retained intracellularly within ferritin. This process is accompanied by changes in the macrophages: heme itself activates transcription of heme oxygenase, whereas iron modulates ferroportin and ferritin mRNA translation. As in other organs of the body, hepcidin ultimately regulates the amount of iron that is released from macrophages, through interaction with ferroportin.

Elizabeta Nemeth, PhD, continued the discussion of ferroportin, the only known cellular iron exporter, and outlined the steps to "ferroportin disease." Ferroportin is a transmembrane protein expressed in all cells involved in iron metabolism: macrophages, hepatocytes, enterocytes, and placental trophoblasts. In these cells, ferroportin is primarily regulated by the hepatic hormone hepcidin. Hepcidin binds to ferroportin extracellularly and causes its internalization and degradation. By shutting down iron export, hepcidin acts as the major regulator of iron absorption and metabolism. (The regulation of hepcidin expression will be un-*Mask*ed in Plenary abstract #3 this afternoon.) Hepcidin-ferroportin interaction is critical for normal iron homeostasis. Conditions that alter the interaction lead to disease states, including anemia of chronic disease, iron-loading anemias, and hemochromatosis. While the majority of patients with hemochromatosis display abnormalities in hepcidin, mutations of ferroportin can also cause hemochromatosis. Indeed, missense mutations have been identified that alter ferroportin sensitivity to degradation, alter its ability to bind hepcidin, or bind other ferroportin molecules (ferroportin is a multimer) to prevent their degradation.

Intracellularly, most of the enzymes that metabolize iron are located in the mitochondrion. Clara Camaschella, MD, detailed an analysis of defective mitochondrial iron metabolism in disease. It is known that mutations of the mitochondrial enzyme aminolevulinic acid synthase 2(ALAS2) can lead to X-linked sideroblastic anemia, as can defects in the mitochondrial exporter of iron sulfur clusters ABCB7. Dr. Camaschella identified an unusual patient with microcytic-hypochromic anemia, few ringed sideroblasts, and iron overload. She found in this individual a mutation of glutaredoxin-5, an enzyme previously shown in mutant zebrafish to disrupt iron-sulfur clusters, thereby affecting aconitase, upregulating Iron-Regulatory–Protein 1 (IRP1), and inhibiting ALAS through its iron responsive element. Dr. Camaschella's patient, remarkably, normalized his anemia after iron chelation. Dr. Camaschella hypothesized that the patient's anemia ultimately relates to altered levels of IRPs, and that chelation, intefering with this mechanism, relieves IRP excess to improve heme synthesis and anemia.

In the Tuesday Late-Breaking Abstract Session, Melanie Percy, PhD, will present her research to identify hypoxia inducible factor 2 as the complex that controls erythropoietin expression in humans. She will discuss the mechanism by which oxygen – or the lack of it – regulates gene expression and erythropoietin production.