The Hepcidin Adventure Earns Rave Reviews at Plenary Session

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The appropriate regulation of total iron body stores is critical for the maintenance of erythropoiesis and for the prevention of tissue damage from excessive iron accumulation. Because humans lack mechanisms for efficient iron excretion, the maintenance of normal iron balance depends on an adequate control of intestinal absorption. Dietary absorption is, in turn, regulated by a network of proteins including the divalent metal transporter 1 (DMT1) and heme carrier protein 1 (HCP1) on the enterocyte apical membrane, the transferrin receptor and the cellular iron exporter ferroportin on the epithelial basolateral membrane, various cytochromes and ferroxidases, and numerous regulatory proteins including the human hemochromatosis protein (HFE), hemojuvelin, and the bone morphogenic proteins (BMPs). Despite this apparent complexity, recent research has demonstrated that the final common denominator in most of these pathways appears to be hepcidin, a key negative regulator of iron absorption. Hepcidin is a 25-amino-acid peptide synthesized in the liver that complexes with ferroportin and prevents iron egress from enterocytes and macrophages. Inappropriate hepcidin expression has been associated with several important human disease states, including most types of hereditary hemochromatosis, the iron overload seen in β-thalassemia major, and the anemia of chronic inflammation. Hepcidin levels are known to be inappropriately low in the setting of HFE and hemojuvelin mutations, and increased by inflammatory mediators such as interleukin-1 and interleukin-6. Also, anemia and hypoxia have been shown to result in decreased levels of hepcidin synthesis, although a mechanism for this negative regulation has not been previously elucidated.

Plenary abstract #3, presented on Sunday by co-author Dr. Bruce Beutler on behalf of his father, lead author Dr. Ernest Beutler, represents a major step forward in our understanding of iron metabolism. Through their groundbreaking work, Dr. Beutler's group described a key intermediate signaling molecule, TMPRSS6, which appears to be critical for the suppression of hepcidin synthesis. The initial steps in their project involved the generation of mutant mice using ethylnitrosourea (ENU) mutagenesis. This approach takes advantage of the strong mutagenic effect of the alkylating agent ENU on murine spermatogenesis and requires complex breeding practices over multiple generations, followed by rigorous phenotypic screening of the progeny to recognize potentially relevant genes. Dr. Beutler's group was able to identify a chronically iron deficient mouse with an unusual pattern of hair loss over the trunk but not the head (the *Mask* phenotype) due to a homozygous recessive genetic mutation. *Mask* mice were shown to express inappropriately high levels of hepcidin mRNA in the liver, even when fed an iron-deficient diet. Using positional cloning techniques, Dr. Beutler was able to ascribe the *Mask* phenotype to a splicing error in the *Tmprss6* gene, which encodes a membrane-bound serine protease. Importantly, when the wild-type *Tmprss6* gene was transfected into human hepatoma HepG2 cells, hepcidin induction by exogenous IL-6, IL-1, and hemojuvelin was greatly inhibited. When cells were transfected with mutated *Tmprss6*, however, a truncated copy of the protein lacking the serine protease domain was expressed that was much less effective in preventing hepcidin expression. This led the authors to conclude that the TMPRSS6 protein is a critical and non-redundant component of the hepcidin suppression pathway which is able to override several important hepcidin induction signals.

Dr. Beutler's work in the mouse has led to ongoing studies in chronically iron-deficient patients looking for *Tmprss6* loss of function mutations. If the dominant effect of the *Tmprss6* gene on hepcidin synthesis is confirmed in humans, the receptor could serve as a new therapeutic target for several hematologic disorders. In theory, inhibitors of the TMPRSS6 protein could be used to increase hepcidin levels and potentially relieve iron overload syndromes. Conversely, agonists might inhibit hepcidin production and potentially ameliorate the typically iron-refractory anemia of chronic inflammation. Future studies will hopefully allow for the ultimate translation of this important work from the bench to the bedside.