the crypt cell hypothesis has been effectively knocked out of contention, it will be informative to see the effect of targeted disruption of *Hfe* in specific hepatocellular populations.

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

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HEMATOPOIESIS

Comment on Zohn et al, page 4174

Of mice and iron: ferroportin disease

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In this issue of *Blood*, Zohn and colleagues describe a novel mouse mutant that bears a striking similarity to the most enigmatic of human hemochromatosis disorders, ferroportin disease.

Patients present with either of 2 clinical scenarios when they carry mutations in the gene encoding the iron exporter ferroportin. Rarely, they have tissue iron overload that is indistinguishable from classical HFE hemochromatosis. The majority of patients, however, have macrophage-predominant iron accumulation, with or without systemic iron overload. In contrast to other hemochromatosis disorders, patients with this second form of ferroportin disease often have iron-deficient erythropoiesis and mild anemia.

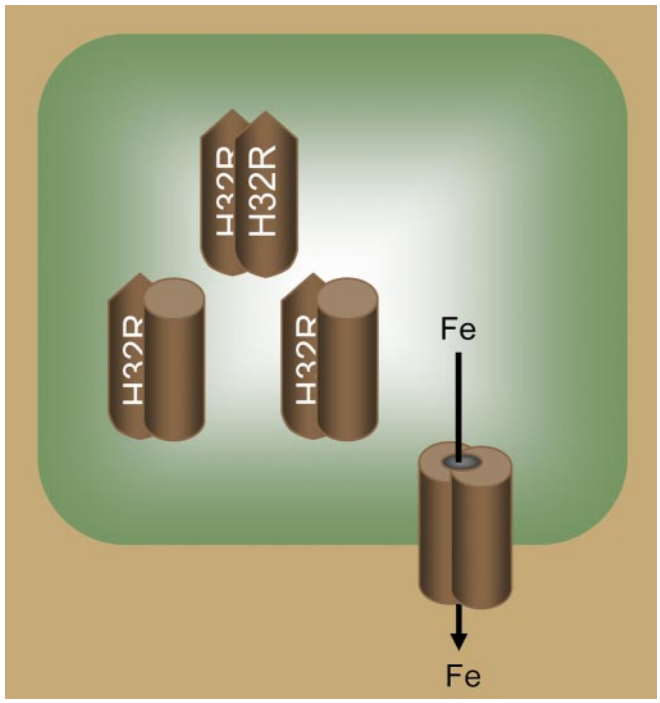
In vitro studies of mutant ferroportin proteins provided a possible explanation for these different presentations. Normally, ferroportin activity is controlled by hepcidin, a peptide hormone that attaches to ferroportin to trigger its degradation. Mutations that render ferroportin resistant to hepcidin are associated with the hemochromatosis phenotype because unchecked ferroportin activity leads to increased intestinal iron absorption and increased release of iron stores. In contrast, mutations that perturb ferroportin trafficking or function are associated with macrophage iron loading.

Both forms of ferroportin disease are autosomal dominant. This makes sense for gain-of-function mutations that render ferroportin resistant to hepcidin regulation. But simple loss-of-function mutations are often silent in the heterozygous state and, importantly, mice carrying one inactivated ferroportin gene appear normal. The *flatiron (ffe)* mouse, characterized in this report, is an informative animal model that provides an explanation for ferroportin disease—disease-associated mutations do more than simply interrupt protein function.

The *ffe* mouse develops a disorder similar in all regards to the macrophage-predominant ferroportin disease. Zohn and colleagues determined that it carries a missense mutation that substitutes a large, charged arginine residue for a histidine residue (H32R) in the first putative transmembrane segment of ferroportin. As might be expected for this type of mutation, the H32R mutant protein cannot traffic to the cell surface. Animals homozygous for the mutation die early in gestation. Importantly, in vitro studies showed that the H32R mutant form of ferroportin actively inhibits the function of normal ferroportin protein, acting as a "dominant negative."

These observations strongly support the idea that functional ferroportin is a dimeric or multimeric protein, and that the mutant form interacts with the wild-type form to interfere with its localization (see figure). In this way, the *ffe* mouse settles a recent dispute over the native structure of the ferroportin transporter by confirming that it must self-associate to be active. Thus, this paper offers a satisfying explanation for why both forms of ferroportin disease are inherited in an autosomal dominant pattern. In the rare event that an individual inherits 2 loss-of-function alleles, the likely outcome is prenatal demise.

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



Normal ferroportin protein must form multimers (shown here as dimers) to localize properly to the cell surface for cellular iron export. Ferroportin protein carrying the H32R mutation does not traffic to the cell surface. Multimers containing both normal ferroportin polypeptide and mutant ferroportin polypeptide are similarly retained within the cell. Thus, a missense mutation in one allele results in substantial loss of ferroportin activity and clinical disease.