HFE is the Key (to Iron Regulation)
BROOKFIELD CENTRAL HIGH SCHOOL
Yuhan Chen, Bryan Dongre, Justin Fu, Zach Gerner, Nick Nabar, Vick Nabar, Nikil Prasad, Josh Speagle, Sai Vangala
Advisor: Mrs. Louise Thompson  Mentor: Andrea Ferrante, MD - Blood Center of Wisconsin

Abstract

Accumulation of excess iron commonly causes Hereditary Haemochromatosis. Various genetic mutations lead to different forms of the disease, which have distinct clinical presentations. Hereditary Haemochromatosis is a form in which iron accumulates in hepatocytes and intestinal epithelial cells due to a mutation in the HFE gene located on chromosome 6. The HFE gene encodes for a non-classical MHC class I protein. In physiological conditions, the HFE molecule is expressed and translated to the cell surface where it may interact with transferrin receptor (TfR) (Figure 1). The binding of the α1/α2 domains of HFE to the transferrin receptor allows for controlled release of iron bound to Tf-TR complex (Figure 2). A mutation (845G>A) causes the replacement of a cysteine with a tyrosine (C282Y). This replacement prevents the α3 subunit of HFE from folding properly and interacting with β2 microglobulin, preventing the translocation of the HFE-β2 microglobulin complex to the cell membrane and promoting its rapid degradation (Figure 1). This defect hinders the regulatory capability of HFE (Figure 2). Current treatments of affected patients include phlebotomy to prevent organ damage from accumulated iron. Further study to increase understanding of the regulatory mechanism may lead to improved treatment design.

Clinical Aspects of Iron Accumulation

One of the causes of hereditary hemochromatosis (HH) is a mutation affecting the HFE (High iron) molecule. HH is the clinical manifestation of iron release deregulation. Unregulated release of iron is caused by a mutation in the gene coding for the HFE protein, leading to an accumulation of iron in hepatocytes and intestinal epithelial cells. Symptoms are abdominal pain, fatigue, darkening of skin, and joint pain. Hemochromatosis can lead to liver and other types of cancer. If diagnosed early, treatment can be started and organ damage can be halted. The most common treatment is phlebotomy, in which blood is removed from the body, taking with it the accumulated iron.

Ferritin

Ferritin is a ubiquitous protein that stores iron in a non-toxic, ionic form. Iron atoms are catalysts in the formation of free radicals from oxygen species, whereas the iron ion in the ferric state does not. Ferritin controls the release of iron when it is needed and transports the iron to where it is needed within the cell.

HFE molecule (PDB file 1a6z) showing α1, α2, α3 subunits and β microglobulin. The 845G>A mutation disrupts the disulfide bond in the α3 subunit (red) by replacing the cysteine 260 with a tyrosine. A second mutation results in the replacement of histidine 41 to aspartate, disrupting the salt bridge seen in the α1 α2 subunits (yellow) and the groove (blue). Research on the HFE molecule reveals that it is almost identical in structure to a molecule with a completely different function involved in the immune system: the HLA molecule.

Endocytosis brings Tf-TfR complex into cell

Regulated iron is released and stored in complex with Ferritin

Ferritin Complex

HFE interacts with Tf-TfR complex

HFE degrades in the cytoplasm

Iron accumulates inside target cells

Degraded HFE fails to bind to Tf-TfR complex

The Tf-TfR complex releases iron in excess

A magnified view of the disulfide bond (A) and salt bridge (B) described above.

The presence of HFE dramatically reduces cell-associated transferrin, supporting the inverse relationship between HFE and the regulation of iron released into target cells.

Figure 1: (A)(C) precipitation of HFE antibodies with the Tf-TfR complex supports the proposed binding of HFE to the Tf-TfR complex. (B)(D) show the existence of HFE and the Tf-TfR complex within the cell.

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Figure 2: The presence of HFE dramatically reduces cell-associated transferrin, supporting the inverse relationship between HFE and the regulation of iron released into target cells.


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