Metabolism of iron

Prof. Mamoun Ahram
Hematopoietic-lymphatic system

Resources

- This lecture
- Yiannikourides and Latunde-Dada. A Short Review of Iron Metabolism and Pathophysiology of Iron Disorders. Medicines 2019, 6, 85. https://www.mdpi.com/2305-6320/6/3/85
- Lippincott's Biochemistry, 7th edition

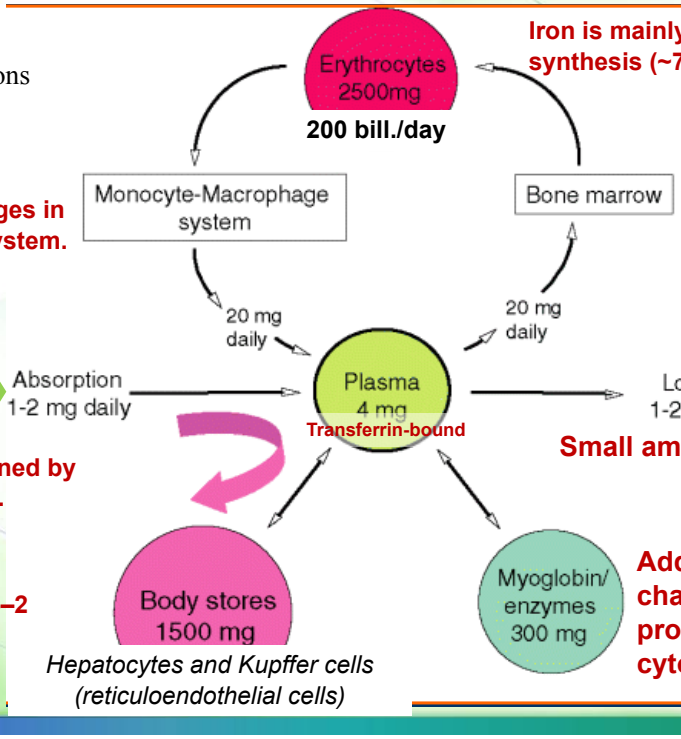
- The Medical Biochemistry page, Iron and Copper Metabolism https://themedicalbiochemistrypage.org/iron-and-copper-homeostasis/
- Fleming and Ponka, Iron Overload in Human Disease, N Engl J Med 2012;366:348-59, https://www.nejm.org/doi/full/10.1056/nejmra1004967
- Brissot and Loréal, Iron metabolism and related genetic diseases: A cleared land, keeping mysteries, Journal of Hepatology 2016 vol. 64 j 505–515, https://www.sciencedirect.com/science/article/pii/S0168827815007424?via%3Dihub

Importance of iron

- Within the body, iron exists in two oxidation states: ferrous (Fe2+) or, the highly insoluble, ferric (Fe3+).
- It is also the prosthetic group of several enzymes such as redox cytochromes and the P450 class of detoxifying cytochromes.
- Iron is important for metabolism and oxygen transport.
- Yet…
- Iron can be potentially toxic due its ability to form free radicals.
  - Solution: iron is not free.

What is life cycle of iron in the body?

Well-nourished persons
3-4g



Iron is mainly used for hemoglobin synthesis (~70% of all iron).

The released iron is scavenged by macrophages in the reticuloendothelial system.

Levels are maintained by dietary absorption.

Small amounts are lost

1 mg a day for men and 1.5–2 mg a day for women with regular menstrual periods

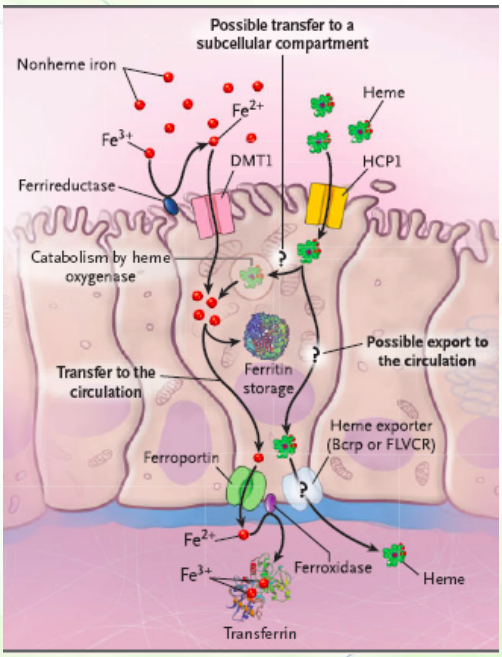
Hepatocytes and Kupffer cells (reticuloendothelial cells)

Additional iron (300 mg) is channeled to other cellular proteins (myoglobin and cytochromes).

Iron absorption

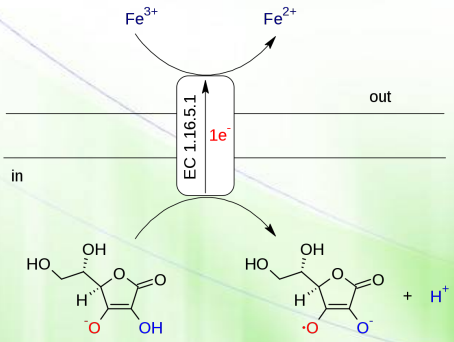
State of iron

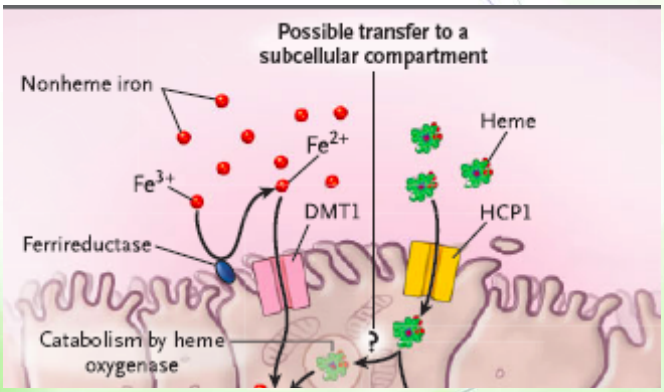
- Under conditions of neutral or alkaline pH, iron is found in the ferric Fe3+ state and, at acidic pH, in the ferrous Fe2+ state.
- In the stomach, iron will be in the ferrous state.
- In the duodenum, iron is in the ferric state.
- However, to be absorbed, dietary iron must be in its ferrous Fe2+ form.



Site of absorption

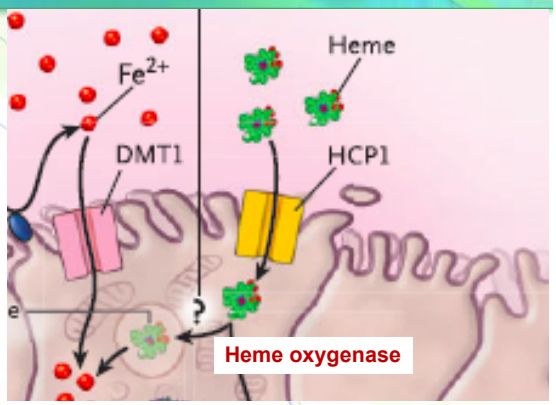
- Ferrireductase enzyme on the enterocytes' brush border reduces Fe3+ to Fe2+ in a vitamin C-dependent reaction.
- Divalent metal transporter 1 (DMT1) transports iron into the cell.
  - DMT-1 can transport other metal ions such as zinc, copper, cobalt, manganese, cadmium, and lead.

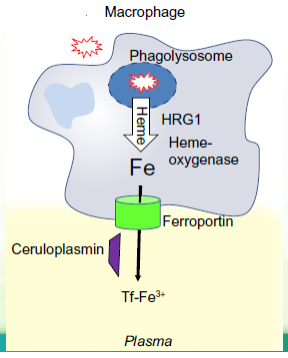




Heme as a source of iron

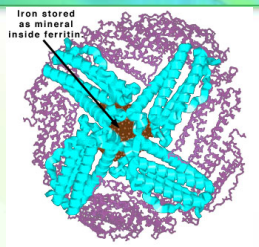
- Iron can also be obtained from ingested heme.
- Heme is absorbed by a receptor called heme-carrier protein 1 (HCP-1) and iron is released by heme oxygenase-1 (HO-1).
- In other cells such as macrophages, heme oxygenase also extracts iron from heme.





Proton pump-inhibiting drugs such as omeprazole greatly reduce iron absorption.

Fates of iron

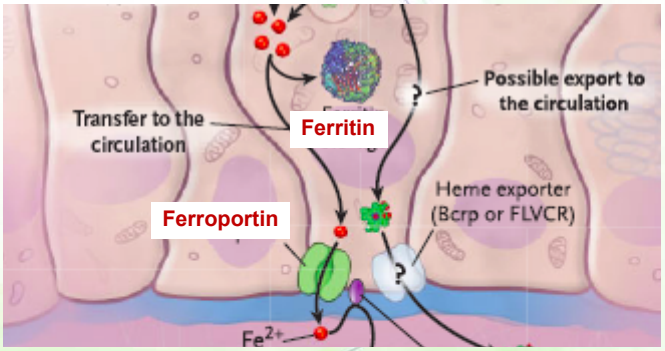


Fate 1: storage

- Cells can then store iron as ferritin.
  - Each Ferritin complex can store about 4500 iron (Fe3+) ions.
- But, if cells are sloughed off from the tip of the villus into feces before absorption, iron is eliminated from the body.

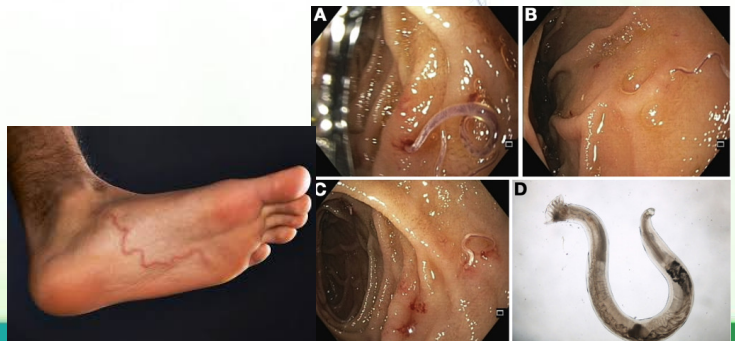
Fate 2: Transport

•Iron is transported out via a basolateral transporter known as ferroportin, which is distributed throughout the body on all cells.



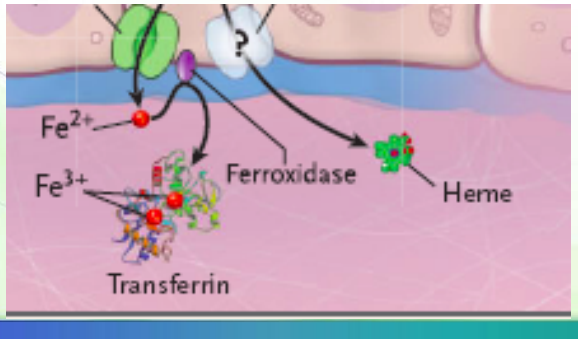
Intestine-related iron metabolism disorders

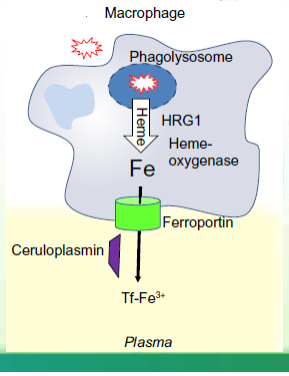
- Iron malabsorption
  - Gastrectomy (total or partial)
  - Celiac disease (villous atrophy)
  - Crohn's disease
  - Helicobacter pylori
- Intestinal hemorrhage (gastrointestinal-mediated iron loss)
  - Gastric cancer
  - Ulcers
  - Inflammatory bowl disease
  - Hookworm infection



Ferroxidase and transferrin

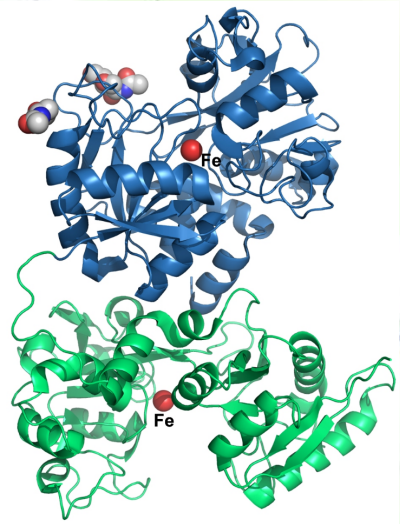
- Once iron leaves the intestinal cells, an iron oxidase, known as hephaestin or ferroxidase, converts iron from the ferrous state to the ferric state.
  - Nonintestinal cells use the plasma protein ceruloplasmin to oxidize iron.
- Iron is rapidly bound to transferrin, an iron-binding protein of the blood that delivers iron to liver cells and from liver cells for storage to other tissues via receptor-mediated endocytosis.





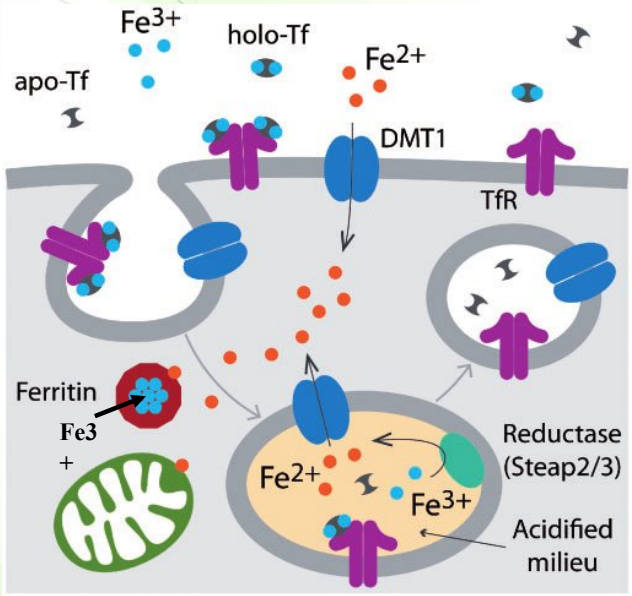
Properties of transferrin

- Apotransferrin can bind several metals, but ferric, not ferrous, iron has the highest affinity forming ferrotransferrin.
- Transferrin contains two sites that bind ferric irons:
  - *iron-binding sites of transferrin are normally only about 1/3 saturated with iron.*
- When iron exceeds normal levels, non-transferrin-bound iron (NTBI) appears.



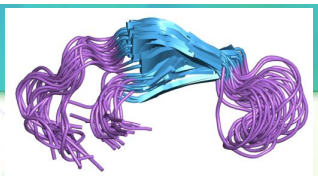
Receptor-mediated endocytosis

- Ferrotransferrin binds to a transferrin receptor (TfR) on the surface of cells triggering endocytosis into early endosomes (pH of 6.0).
- Early endosomes are transformed into late endosomes (pH of 5.0) where Fe3+ atoms dissociate, get reduced into Fe2+ by the ferrireductase STEAP3, and are transported into the cytosol via DMT1.
- STEAP3 depends on vitamin C.
- The apotransferrin-transferrin receptor complex is recycled back to the surface, apotransferrin dissociates, and the receptor binds another transferrin.
- Affinity of TfR to iron: diferric Tf (Fe2Tf) >monoferric Tf (Fe1Tf) >apo-Tf

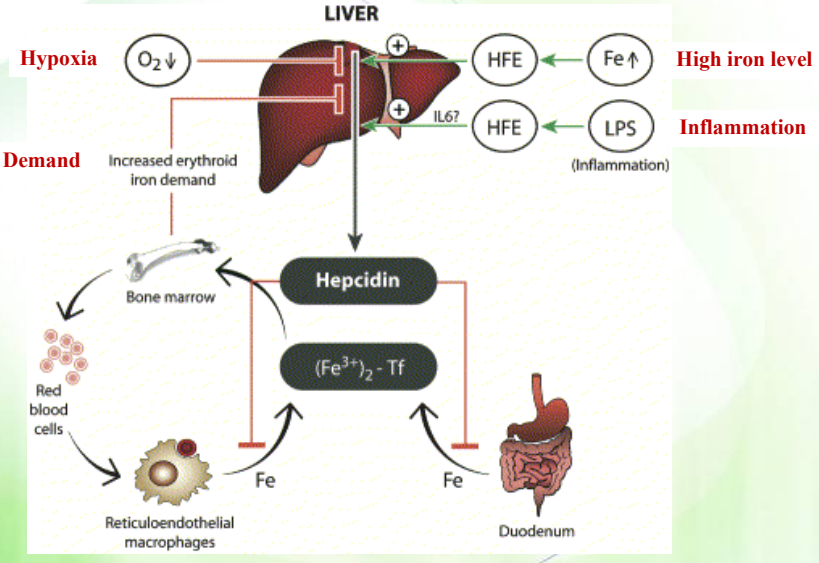


Regulation of protein function

Hepcidin (iron sensor)

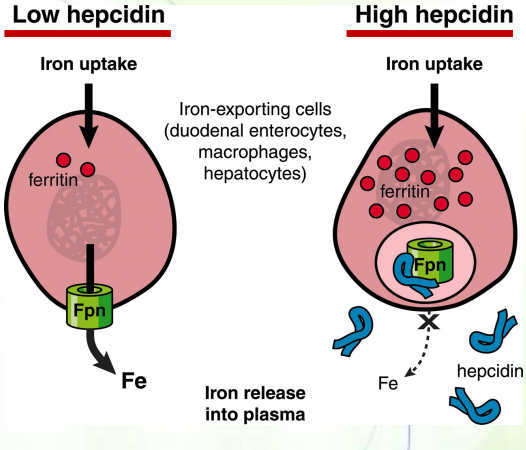


- Hepcidin is a peptide hormone (25 amino acids) secreted by the liver and it **reduces** iron levels.
- When iron level increases and in cases of inflammation, hepcidin secretion increases.
- When iron levels are low, there is high iron demand, or hypoxia, its release is suppressed.

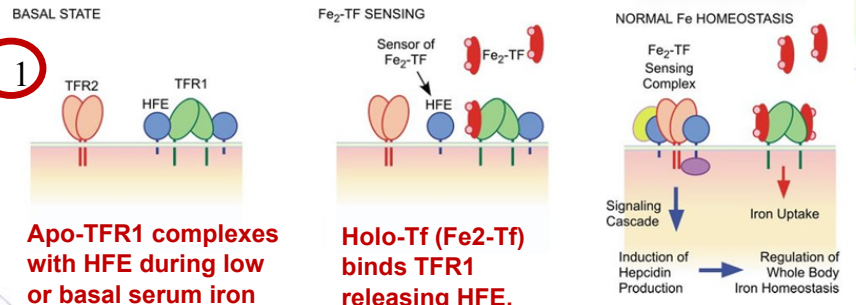


How does hepcidin reduce iron levels in the body?

- Hepcidin binds to the basolateral iron transporter ferroportin inducing ferroportin internalization and degradation.
  - This results in higher iron storage.
    - Iron is eliminated in sloughed off intestinal cells.
    - Iron is not released from macrophages.
- Hepcidin also inhibits the presentation of the iron transporters (e.g. DMT1) in intestinal membranes decreasing iron absorption.



Regulation of hepcidin



1

Apo-TFR1 complexes with HFE during low or basal serum iron conditions.

Holo-Tf (Fe2-Tf) binds TFR1 releasing HFE.

HFE binds TFR2 and induces an intracellular signal that stimulates hepcidin production.

2

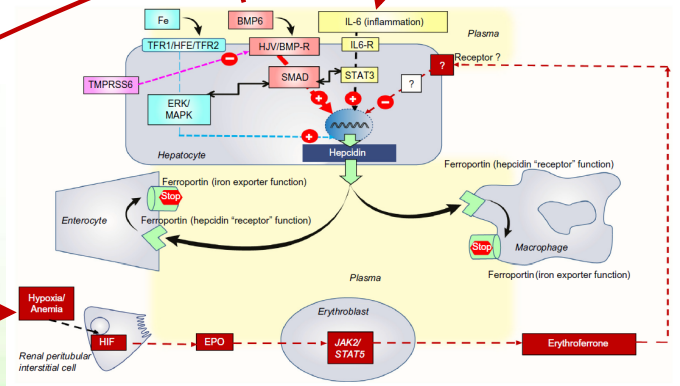
Inflammatory cytokine, IL6, induces the expression of hepcidin

3

Release of bone morphogenic protein 6 (BMP6) is induced by intracellular iron, which binds to its receptor (BMPR). BMPR is bound to hemojuvelin (HJV) protein stimulating the synthesis of hepcidin.

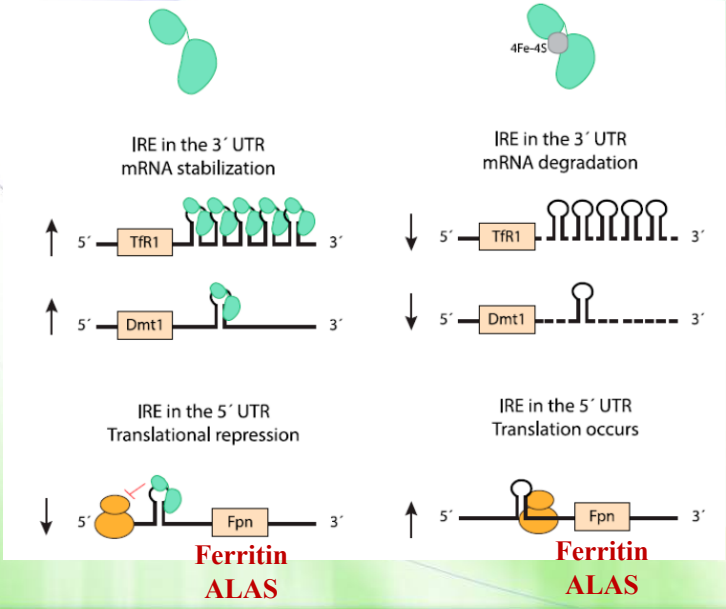
4

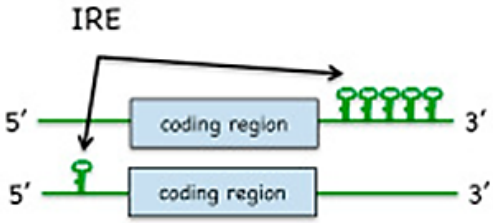
The expression of hepcidin is negatively regulated by anemia and hypoxia, which induce the synthesis of EPO (erythropoietin) by the kidney. EPO stimulates the synthesis of erythroferrone, which inhibits the synthesis of hepcidin.

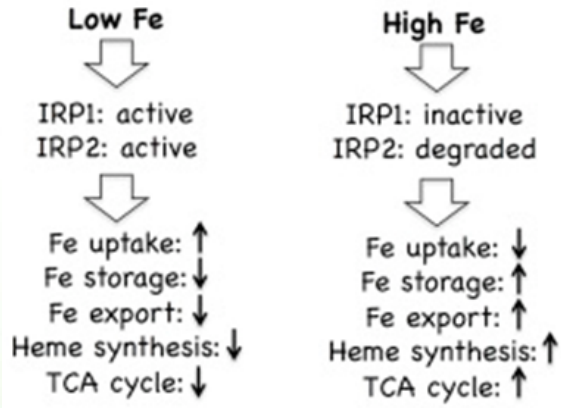


Post-transcriptionl regulation of expression

Iron-response element
Iron regulatory protein







Iron-related diseases

Hereditary hemochromatosis (HH)
Iron-deficiency anemia

Hereditary hemochromatosis

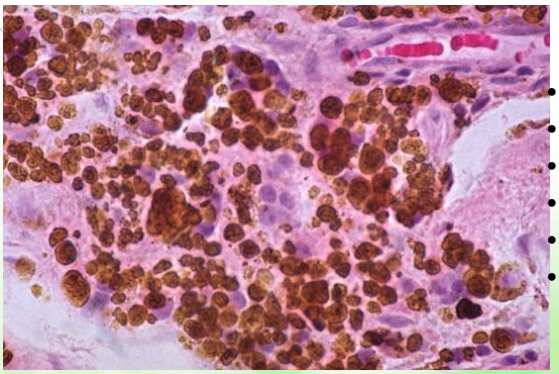
- It is a group of disorders in iron metabolism that is characterized by excess iron absorption, saturation of iron-binding proteins and deposition of hemosiderin in the tissues.
  - more commonly in males than in females (why?)
- The primary cause of hemochromatosis is the inheritance of an autosomal recessive allele designated as HFE (type I or primary HH) , but four other genes that regulate the hepcidin–ferroportin axis can also be involved.

Groups/classes of hereditary hemochromatosis

- Type 1 (hemochromatosis protein, HFE-dependent)
  - Most common
- Type 2A (HJV-dependent)
- Type 2B (hepcidin-dependent)
- Type 3 (TfR2-dependent)
- Type 4 (ferroportin-dependent)
  - Autosomal dominant disorder

Hemosiderin

- The normal total body iron stores may range from 2 to 6 gm, but persons with hemochromatosis have much greater stores exceeding 50 gm.
- If the capacity for storage of iron in ferritin is over-saturated, iron is stored as water-insoluble deposits known as hemosiderin, mainly in macrophages.
- Excess hemosiderin leads to cellular dysfunction and damage.

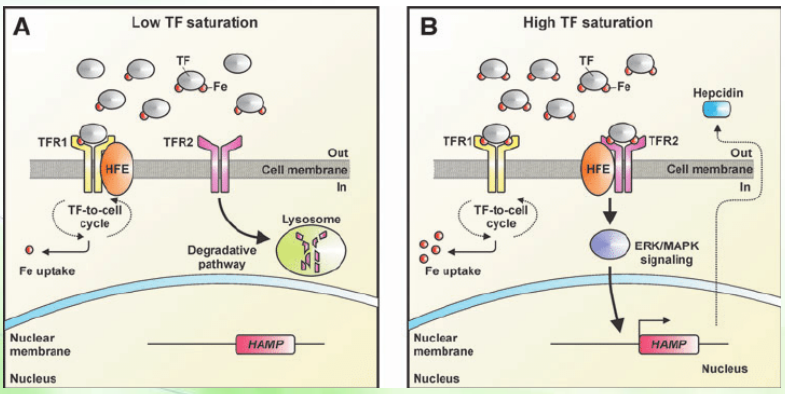


Affected organs and conditions

- Liver (hepatic fibrosis)
- Pancreas (diabetes mellitus)
- Joints (arthropathy)
- Skin (pigmentation)
- Heart (cardiomyopathy)
- Gonadotrophin-secreting cells (hypogonadotrophic hypogonadism)

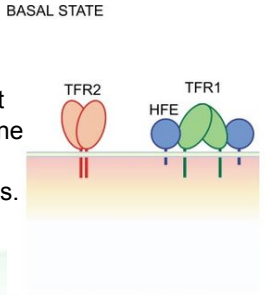
Regulation of transferrin receptor

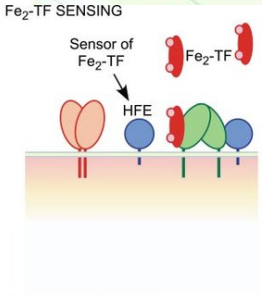
- HFE is a major histocompatibility complex (MHC) class-1 gene.
- Normal HFE complexes with TfR1 reducing iron transfer into cells.
- Mutated HFE has a reduced presence on membrane and/or lack of interaction with Tfr1, leading to the loss of inhibition of transferrin receptor, and, therefore, increased iron uptake and storage.



Mechanism of action

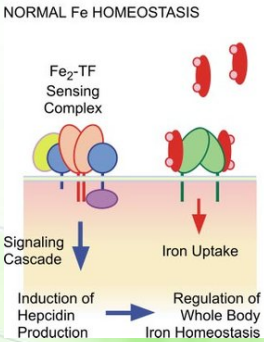
TFR1 exists as a complex with HFE at the plasma membrane during low or basal serum iron conditions.

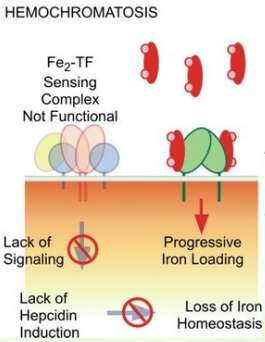




Serum Fe2 -TF competes with HFE for binding to TFR1. Increased serum transferrin saturation results in the dissociation of HFE from TFR1.

HFE binds TFR2 and induces a intracellular signaling that stimulates hepcidin production.



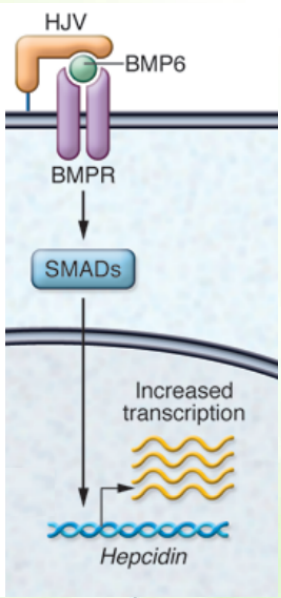


Mutation or absence of HFE or TFR2 prevents formation of a functional iron sensor and signal transduction effector complex leading to dysregulation of systemic iron homeostasis

Juvenile hemochromatosis

- Type 2A hereditary hemochromatosis
  - *AKA* HFE2 (HJV)-dependent hereditary hemochromatosis
- Mutations in HJV gene, which encodes the protein "hemojuvelin", account for the majority of JH.
- Normal HJV upregulates expression of hepcidin.

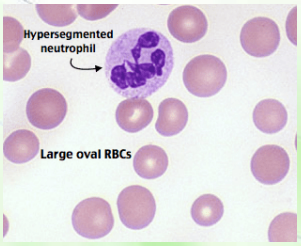
- Type 2B is also juvenile hemochromatosis but is caused by mutations in hepcidin gene.

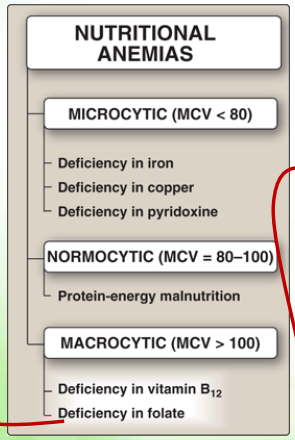


Iron-deficiency anemia

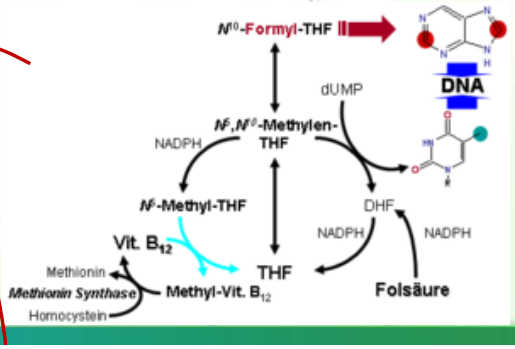
- Anemias are characterized by a deficiency in the number of mature erythrocytes in the circulation, lowering the oxygen-carrying capacity of the blood, causing tissue hypoxia, and clinical symptoms such as fatigue, weakness, increased cardiac output, as well as increased morbidity and mortality.

Cells cannot synthesize DNA and, hence, cannot divide and megaloblasts accumulate.



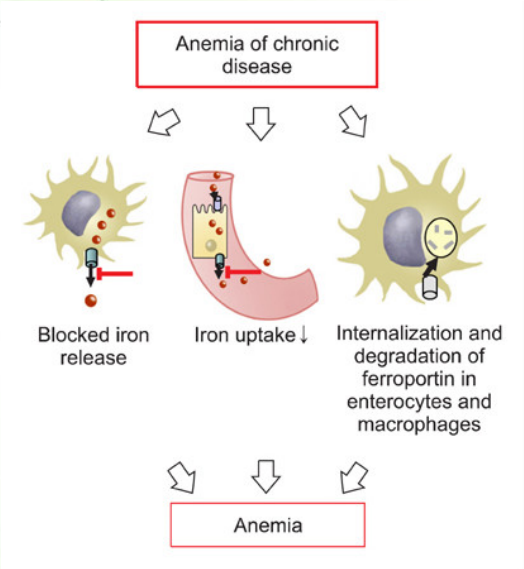


Folate is not regenerated



Anemia of chronic disease

- Causes: chronic kidney disease, chronic infections and chronic inflammatory diseases
- Inflammatory cytokines increased hepcidin production by hepatocytes downregulation of ferroportin expression in major iron-exporting cells such as macrophages, duodenal enterocytes, and hepatocytes decreased enteric iron absorption and, perhaps more importantly, to increased iron retention within splenic macrophages and hepatocytes.



Additional molecular consequences of chronic inflammation