Molecular mechanisms in iron metabolism

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seminar, pathophysiology

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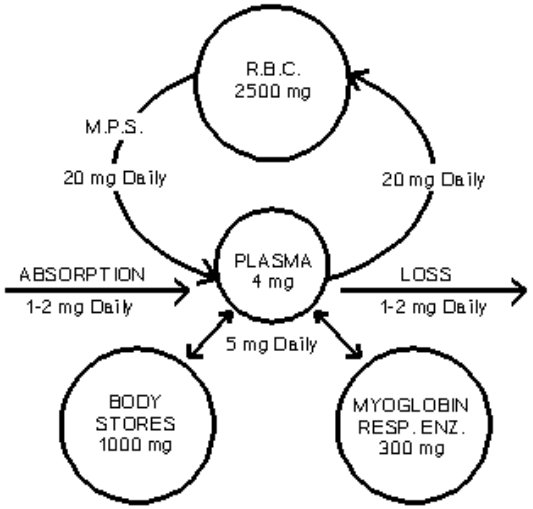
The ability of this transition metal to exist in ***2 redox states*** (Fe^{2+}, Fe^{3+}) makes it useful at the catalytic center of fundamental biochemical reactions.

During its transport/metabolism iron can be reduced by *ferrireductase* ($Fe^{3+} \Rightarrow Fe^{2+}$) or oxidized by *ferroxidase* ($Fe^{2+} \Rightarrow Fe^{3+}$)

Iron – kinetics



Iron - ***principle functions***

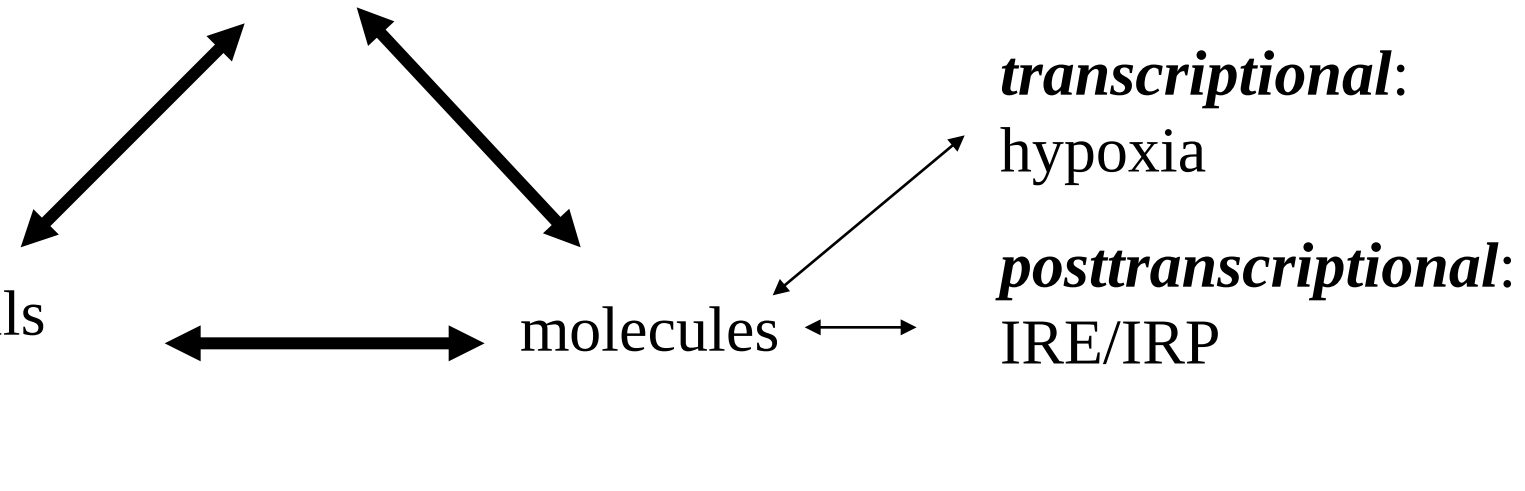
* transport of oxygen
* transport of electrons
* respiration
* DNA synthesis

The same properties that make iron useful in each of this reactions also make it ***toxic***.

Fenton's reakce: $Fe^{2+} + H_2O_2 \Rightarrow Fe^{3+} + OH^* + OH^-$

Iron – regulation

* iron ***amount***
* iron "***need***"
(e.g. hypoxia)



transferrin receptor (TfR)
ferritin
etc. (depending on cell type)

Iron – absorption

enterocytes in duodenum

3 “types” of iron + 3 ways of resorption

- ***ferrous*** iron nonheme
* DMT1
* ferrireductase (Dcytb)

- ***heme*** iron
?? (endosomal process)

- 1/3 of Fe in food but 2/3 of absorbed iron
- in the cell iron is released by heme oxygenase

- ***ferric*** iron
β_3 integrin-mobilferrin

- important part of food iron (up to 2/3), insoluble in pH>3
- influence of other dietary constituents on the solubility
- intracellular reduction in cytosol by paraferritin

DMT1 (*divalent metal transporter, also DCT1 or Nramp2*), can transport also other divalent cations (metals)
expression is induced by iron depletion – 3’IRE
intracellularly – endosomal transport
single chain transmembrane glycoprotein (90,000, 12q13)

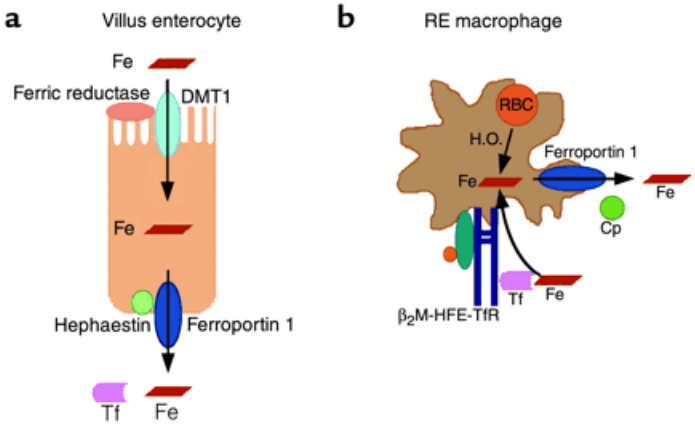
SFT (*stimulator of iron transport*) – transmembrane single chain protein (338 AA, 10q21) increases cellular uptake of iron, precise mechanism unknown

Ferrireductase (*Dcytb*) – reduces iron, in apical membrane of enterocytes, induced by hypoxia and iron depletion; similarity to duodenal cytochrome *b*, described in mouse (2001)

Mobilferrin – 56 kDa protein, occurs in enterocytes and nonintestinal cells (then used probably only if other mechanisms become saturated)

Paraferritin – complex (520 kDa) containing integrin, mobilferrin, flavin monooxygenase, β_2 microglobulin, DMT-1…(?)
intracellular ferrireductase

Export of iron from enterocytes/cells

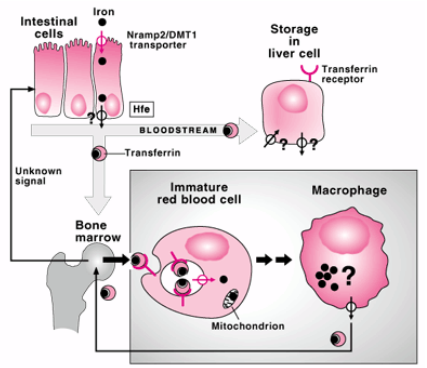


Ferroportin1 (Ireg1, MTP1) – protein transporting iron from the cells
(enterocytes, hepatocytes, macrophages, Kupffer cells etc.)
single chain transmembrane glycoprotein (62,000, chromosome 2),
regulated by 5'IRE and hypoxia

Hephaestin – transmembrane-bound ceruloplasmin homologue (155,000, Xq11-12),
possible intracellular ferroxidase

Ceruloplasmin – serum ferroxidase, single chain glycoprotein (132,000, 3q21-24)
that contains 6 copper atoms

Iron – transport



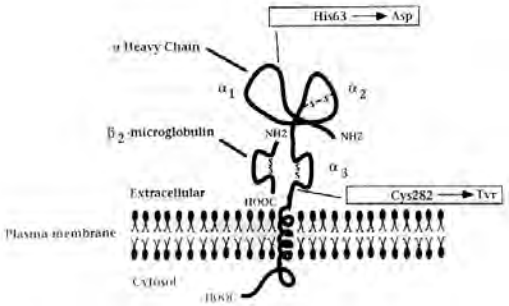
Transferin – single chain glycoprotein (79,500, β_1 globulin)
iron binding transport protein with homologous binding sites for iron (ferric form); under physiol. conditions saturated from about 30 %

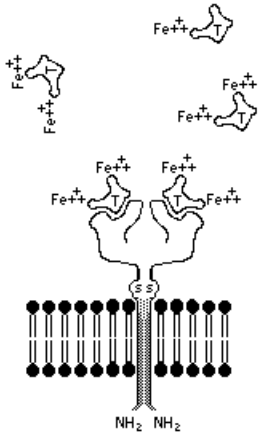
Iron – entry to cells

Transferrin receptor (TfR) – receptor-mediated endocytosis of Tf
TfR1 (CD71, 3q21) more abundant in organs except of liver, regulated by IRE at 3' end, transmembrane glycoprotein, made of 2 identical chains; 185,000
TfR2 (7q22) more abundant in liver, no IRE, its precise regulation unknown; 215,000

HFE – MHC class 1-like membrane glycoprotein (orig. HLA-H), 6p21, binds β_2-microglobulin. Binds TfR, reduces its affinity for Tf. In enterocytes participates in regulation of iron absorption.

TRIP – TfR independent pathway





Iron – intracellular storage/function

DMT1 – transport from endosom to cytoplasm

Feritin – spherical protein shell of 24 subunits (440,000) of 2 types – H a L with different chromosomal localization, binds and stores ferric iron (up to 4500 atoms), H subunit oxidizes iron, regulated by 5' IRE

Frataxin – mitochondrial protein, entry of iron to mitochondria, hydrophilic protein 210 AA (18,000, 9q13), precise function unknown

Ferrochelatáza – mitochondrial enzyme, insertion of Fe^{2+} into tetrapyrrole – protoporphyrin IX (heme formation)

Iron – regulation of absorption

The most important checkpoint of iron homeostasis in higher organisms is
contained in the epithelial cell layer of the duodenum.

The precursor cell acts as a sensor of body iron needs, upon differentiation
the enterocyte is capable of iron transport.
It receives signal about the iron stores in the organismand adapts the expression
of respective molecules.

Theories

- iron content in the precursor cell –
labile iron pool – influences expression (IRE) of DMT1 and ferroportin 1 in mature enterocyte

- ***hepcidin***: putative iron-regulatory hormon, could reflect the iron stores and transport such information to the duodenal crypts

HFE in connection with TfR1 in the precursor cells controls the iron uptake from plasma (iron sensing)

According to the iron content in the precursors the expression of DMT1 and ferroportin (i. e. the transport capacity) is set up in the fully
differentiated enterocytes

The information about the serum (body) iron (stores) is thus separated from the information about iron in intestine (external iron)

Hepcidin

- hepatic bactericidal protein from the group of cysteine-rich, cationic, antimicrobial peptides
- expression stimulated by LPS
- mRNA does not have IRE
- its expression might be connected to iron stores in hepatocytes (through TfR2)
- serum hepcidin by interaction with the HFE-β_2M-TfR1 complex increases iron uptake by duodenal crypt cells
- crypt cells differentiate into daughter enterocytes programmed to have decreased expression of iron transport proteins

This could explain also the iron kinetics during infections.

Summary

* Iron content in the ***precursor cells in duodenal crypts*** is important for the regulation of iron absorption.

* This is controlled by the ***plasma iron resorption*** on the basolateral membrane.

* The iron resorption on the basolateral membrane is facilitated by the complex ***TfR1-HFE-β_2M***.

* A ***solubile*** factor physiologically controling this resorption might exist (hepcidin ?).

* Disorders in orchestration of these factors can lead to disorders in iron resorption.

* The most important disorder is increased resorption – ***hereditary hemochromatosis*** (HH).

Hereditary hemochromatosis
is iron overloading disorder with increased resorption of iron by enterocytes.

The molecules (mutations of them) causing the HH phenotype are known.

Absolutelly the most frequent is the mutation of ***HFE*** (over 80 %).
Such disease is transmitted in autosomal recessive way.

Considerably uncertainty exists in the mechanism by which the normal gene product, HFE, regulates iron homeostasis.

Other molecules can rarely cause HH, the transmission can be different.

- *ferroportin 1*
- *TfR2*
- *β_2M*
- *hepcidin*

Friedreich's ataxia
hereditary ataxia, in youth the neurological manifestations, heart problems etc.

Genetics
mutation of *frataxin* (9q13-q21), expanded GAA triplets

Atransferinemia
very rare transferrin missing, symptoms in infants, microcytary hypochromic anemia and hemosiderosis