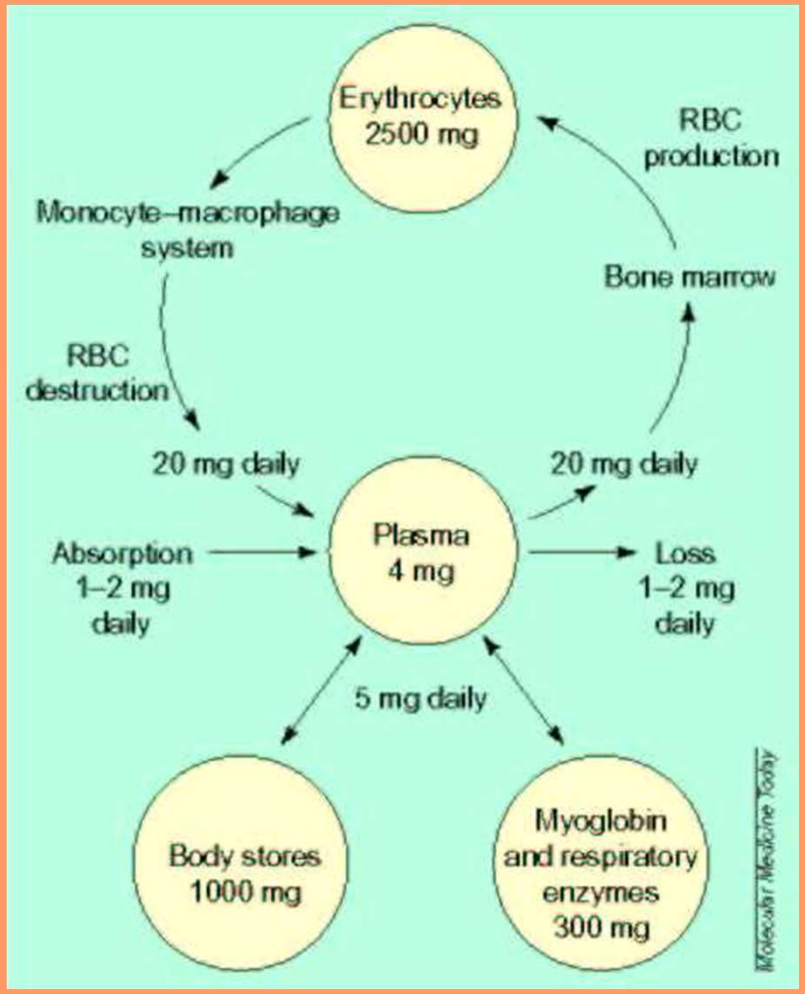
Iron metabolism and its disorders

Physiological functions of iron

- Iron is present in haem
  - haemoglobin/myoglobin
  - cytochromes
  - enzymes
    - e.g. catalase, peroxidase, ribonucleotide reductase, nitric oxide synthase
  - Fe is necessary for the cell cycle (transition from G1 → S phase)
  - ROS formation in white blood cells
- Free Fe is highly reactive – it catalyses Fenton reaction
    - $Fe^{2+} + H_2O^2 \rightarrow Fe^{3+} + OH\bullet + OH^-$
  - most iron is in the complex form to minimize negative effects
  - with organic anions
  - with ferroproteins
  - stored bound to ferritin (or hemosiderin)
- As no specific excretory mechanism exists, the absorption of Fe is tightly regulated

Fe balance

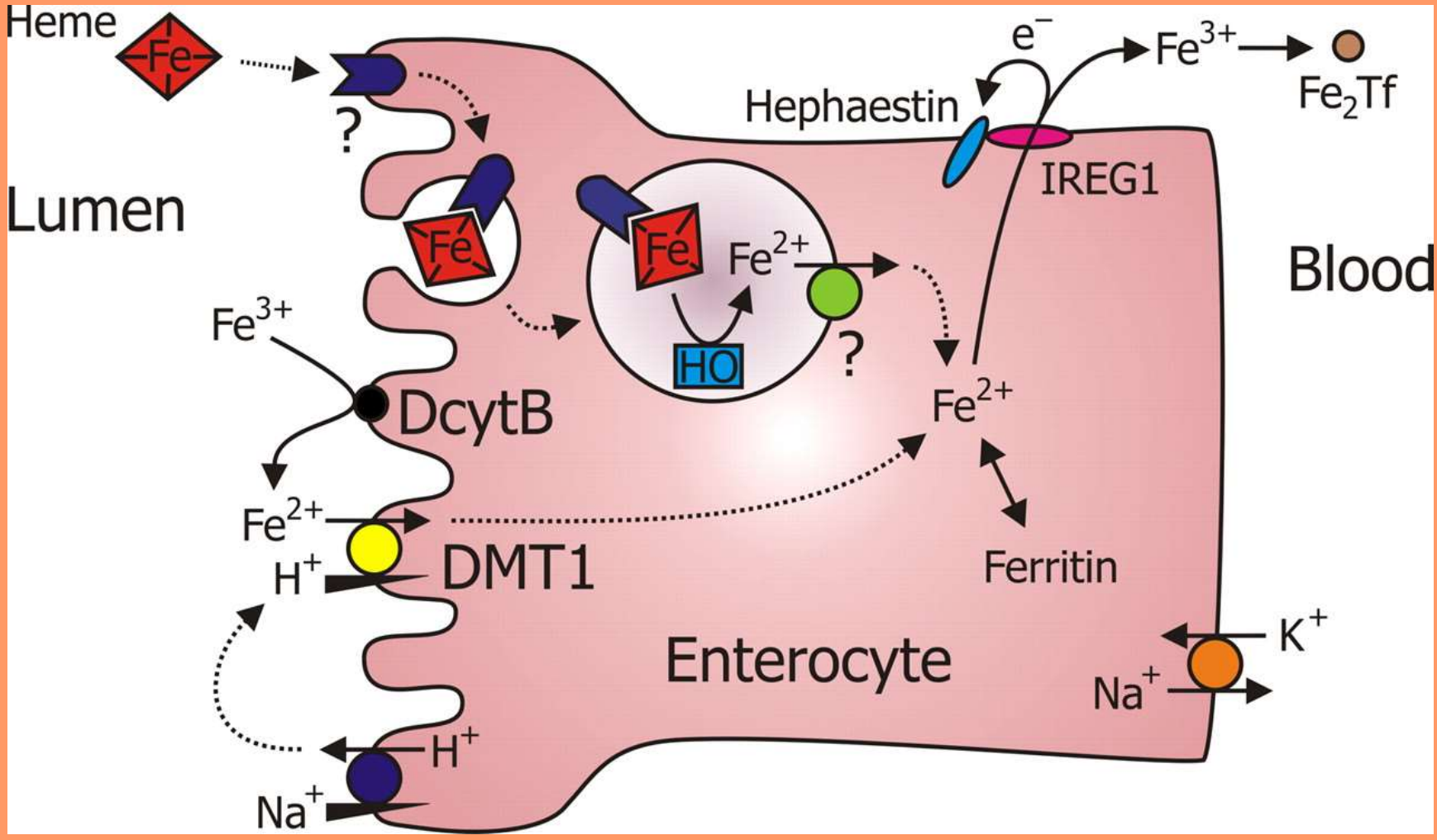
- 35 – 45mg of Fe per 1 kg of body weight in an adult
  - 60 – 70% is part of Hb in erythrocytes
  - 10% is contained in myoglobin, cytochromes and iron-containing enzymes
  - 20 – 30% is stored bound to ferritin and hemosiderin in hepatocytes and macrophages
- The total amount of Fe is constant in an adult, there is a balance between the intake and the losses
  - the daily supply of food contains approximately 10 - 20mg of iron
  - only 5 – 10% of iron gets to organism
  - average daily losses are 0.5-1mg in men 1-2mg in women of fertile age
- Intake of iron occurs in the duodenum and proximal jejunum

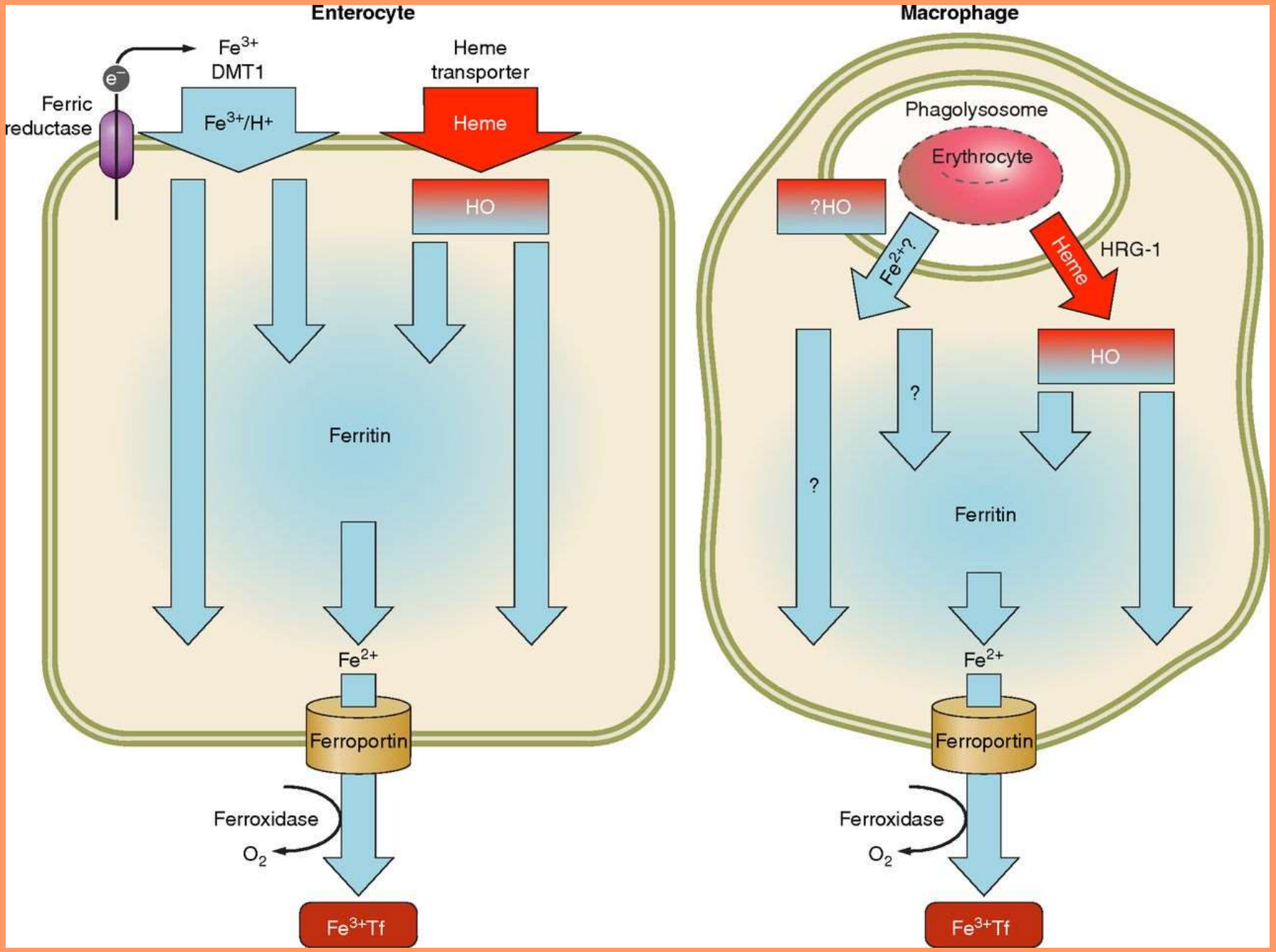


Distribution of iron in the organism

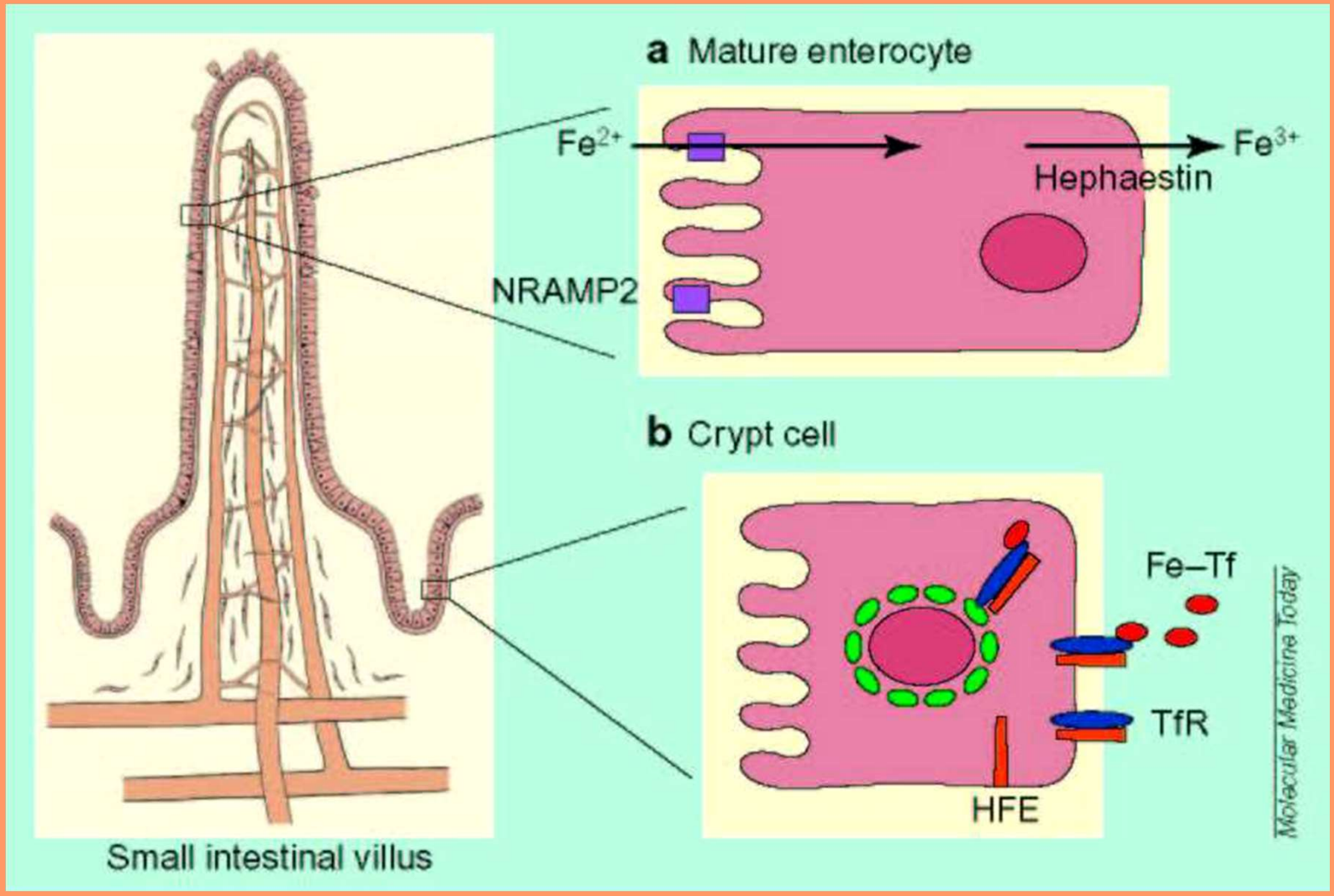
- circulation of Fe and its cellular uptake
  - transferrin – liver-produced protein with 2 binding sites for Fe^{3+}
  - the ratio of monoferric to diferric transferrin is normally approx. 2:1 (30% saturation)
  - transferrin receptors (TfR1 and 2) at cellular membrane enables the cellular uptake of Fe driven by momentary needs
    - It is most abundant in the membrane of erythroblasts, but not mature erythrocytes
- storage and recycling of Fe
    - In the liver (hepatocytes) and in macrophages
      - Fe is bound to cellular or serum ferritin (up to 4000 Fe atoms)
      - hemosiderin (aggregated molecules of of ferritin)
- excretion
  - There is no specific mechanism of iron excretion
    - desquamation of cells (GIT, skin)
    - menstruation in women

Absorption of Fe and its release into the circulation

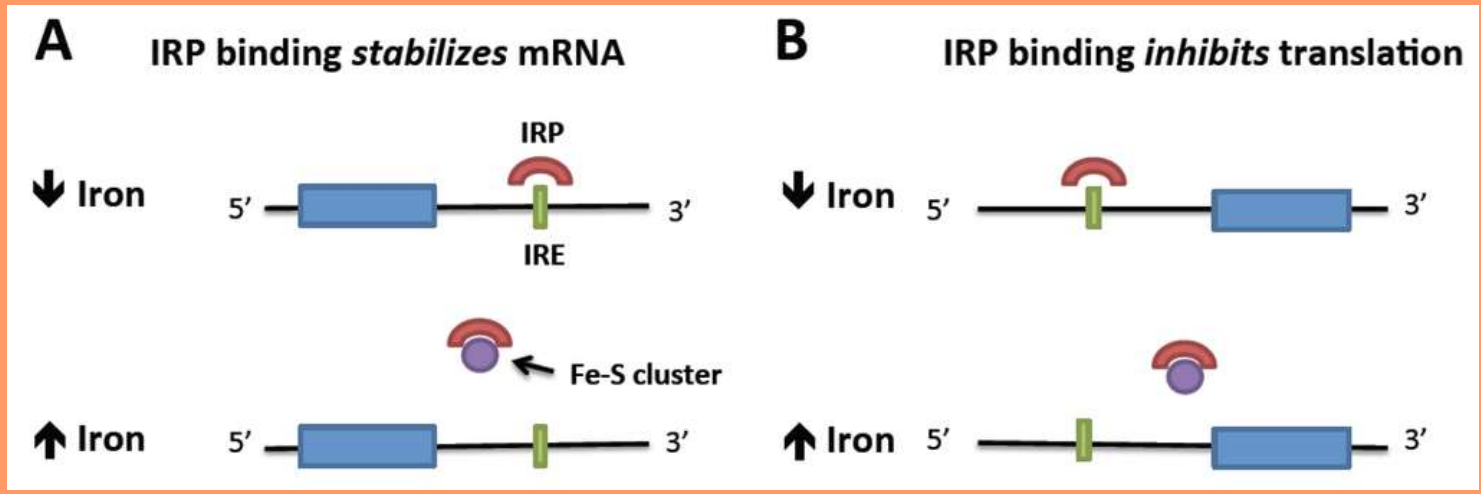



Enterocyte
Macrophage
Fe3+
DMT1
Heme
transporter
e−
Ferric
reductase
Fe3+/H+
Heme
HO
Ferritin
Fe2+
Ferroportin
Ferroxidase
O2
Fe3+Tf
Phagolysosome
Erythrocyte
?HO
Fe2+?
Heme
HRG-1
HO
?
?
Ferritin
Fe2+
Ferroportin
Ferroxidase
O2
Fe3+Tf

Maturation of the enterocyte

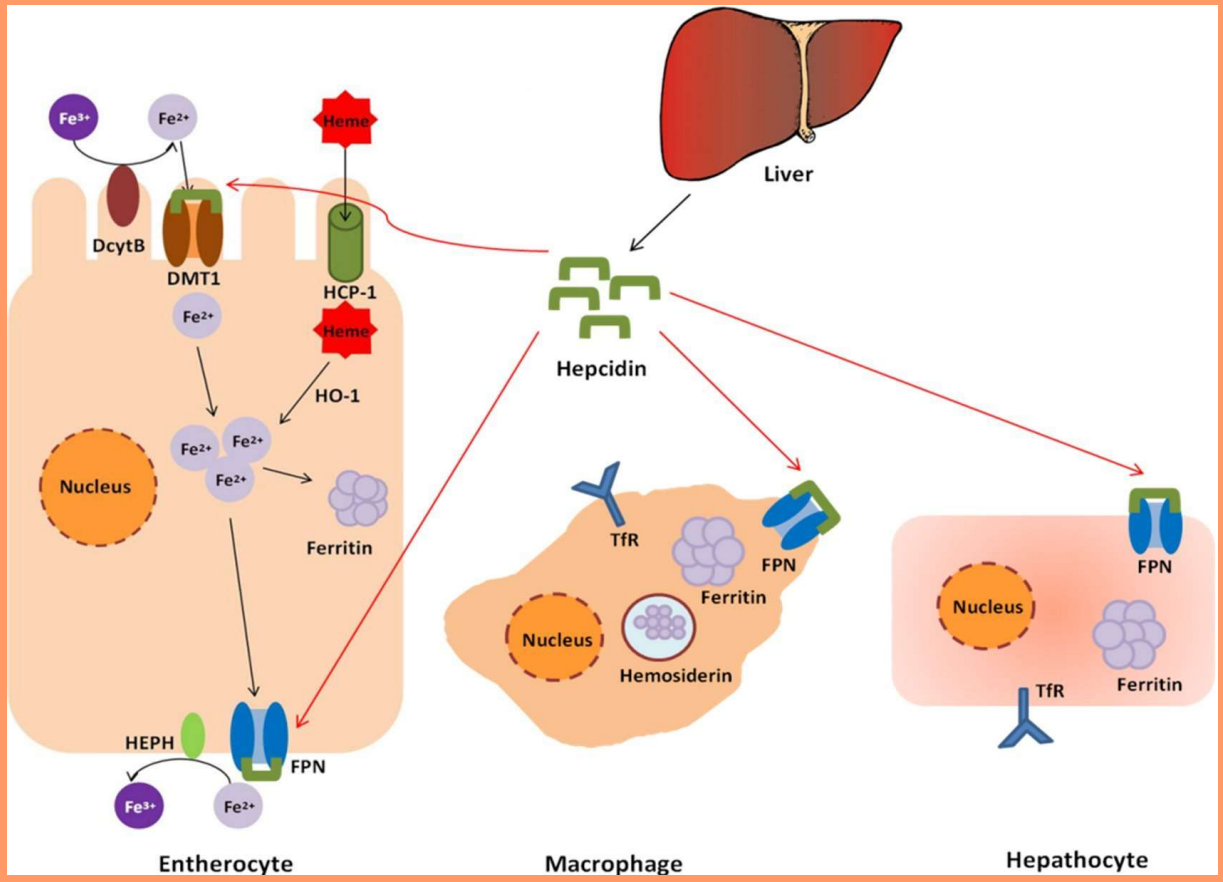


Post-transcriptional regulation of gene expression by Fe



- Fe binds to IRP (iron-responsive proteins) and deactivates them by changing their conformation
- When intracelular levels of iron are low, IRP bind to IRE (iron-responsive elements) at 5’ or 3’ untranslated region of mRNA
  - 5’ IRE (low translation)
    - e.g. ferritin
  - 3’ IRE (inhibits mRNA degradation → high translation)
    - e.g. DMT1 or TfR

Iron metabolism regulation



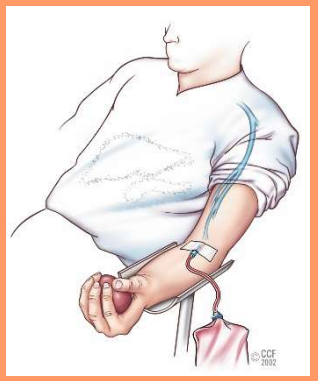
Hepcidin – blocks the transport of Fe from enterocyte

Disorders of iron metabolism

- Iron deficiency anemia (IDA)
  - decreased absorption / increased losses
  - ↓ ferritin, ↑ transferrin, ↓ transferrin saturation, ↑ sTfR
- Anemia of chronic diseases (ACD)
  - normal total amount of Fe in organism, but Fe is stored in macrophages instead of being part of haem
  - ↑ ferritin, ↓ transferrin, ~/↓ transferrin saturation, ↓ sTfR

Hemochromatosis

- Acquired
  - increased parenteral intake
    - repeated transfusions
    - excessive supplementation - rare
  - excessive hemolysis
    - hemolytic anemias – often treated by transfusions



- Hereditary
  - excessive absorption
    - autosomal recessive monogenic disorder (1:200 – 400 in northern Europeans)
    - mutation in the HFE gene (6^{th} chromosome) – inducer of hepcidin expression
      - mostly C282Y or H63D mutations

- Clinical presentation
  - iron deposits in various organs (liver, heart, pancreas, joints) and their dysfunction
  - ↑ ferritin, ↓ transferrin, ↑ transferrin saturation, ↓ sTfR, ↑ non-transferrin bound iron (reactive)
  - skin pigmentation („bronze diabetes“)
  - in most cases, non-specific symptoms are present (tiredness, hepatopathy, endokrinopathy, diabetes, artralgias…)
  - treatment - phlebotomy