IRON METABOLISM & DISORDERS

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Learning Objectives

- Students should be able to:
- To describe iron absorption and transport
- To identify iron storage and transport forms
- To differentiate between Iron defcy and overload in terms of causes, pathophysiology, lab investigations and treatment

Introduction

- Iron is a transition metal & one of the most essential trace elements,
- Iron ions readily form complexes with certain ligands, and are able to participate in the redox rxn $Fe^{2+} \rightarrow Fe^{3+}$ (due to ability to accept and donate electrons)
- This property allows Fe to perform many of its biochemical functions
- Free iron ions participate in ‘destructive’ chemistry; catalyzing formation of toxic free radicals
- Thus, very little free iron is normally found in the body
- Excess ferrous iron forms free hydroxyl radicals via the Fenton reaction that cause damage to tissues through oxidative reactions with lipids, proteins, and nucleic acids. Thus, dietary iron absorption and factors affecting bioavailability in the body are tightly regulated where possible.

Fenton Reaction

$$Fe^{2\oplus} + H_2O_2 \longrightarrow Fe^{3\oplus} + HO\cdot + OH^{\ominus}$$

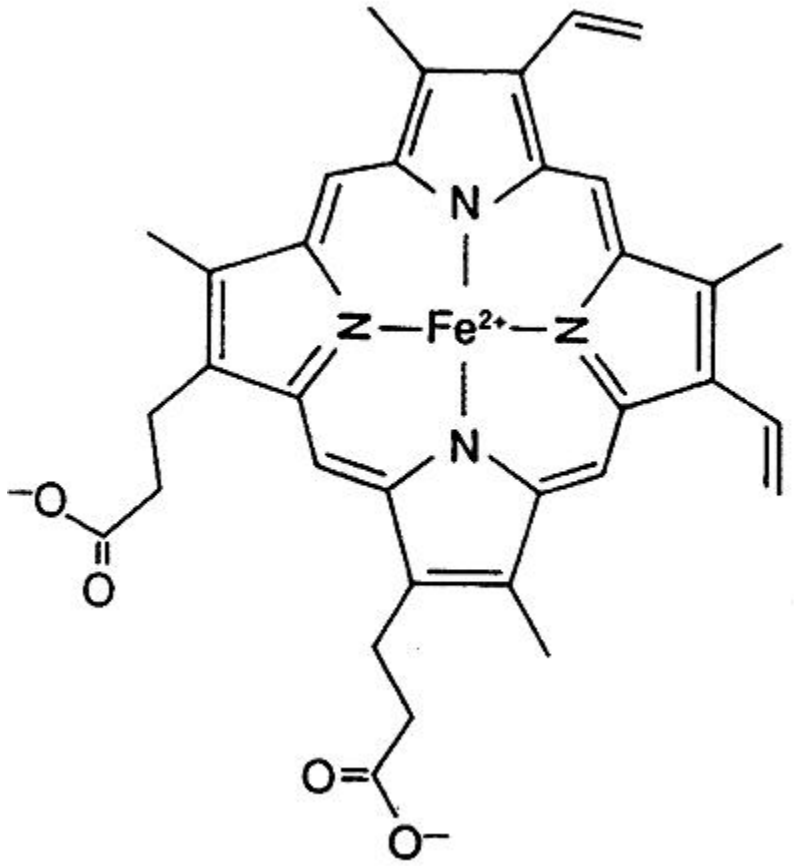
Ferrous | Hydrogen peroxide | Ferric | Hydroxyl radical | Hydroxyl

$$Fe^{3\oplus} + H_2O_2 \longrightarrow Fe^{2\oplus} + HOO\cdot + H^{\oplus}$$

Hydroperoxyl | Proton

$$2\,H_2O_2 \longrightarrow HO\cdot + HOO\cdot + H_2O$$

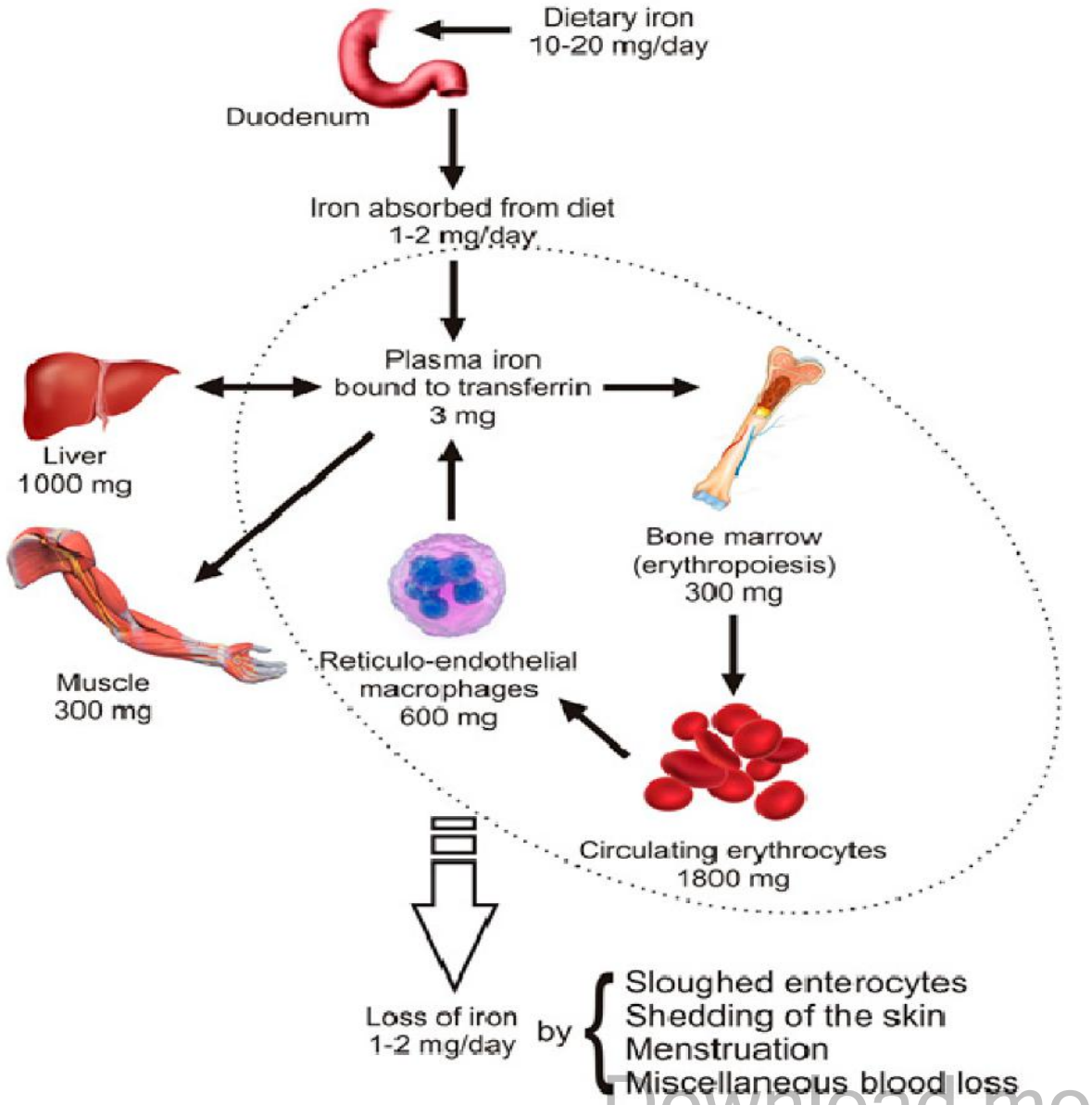
ChemistryLearner.com



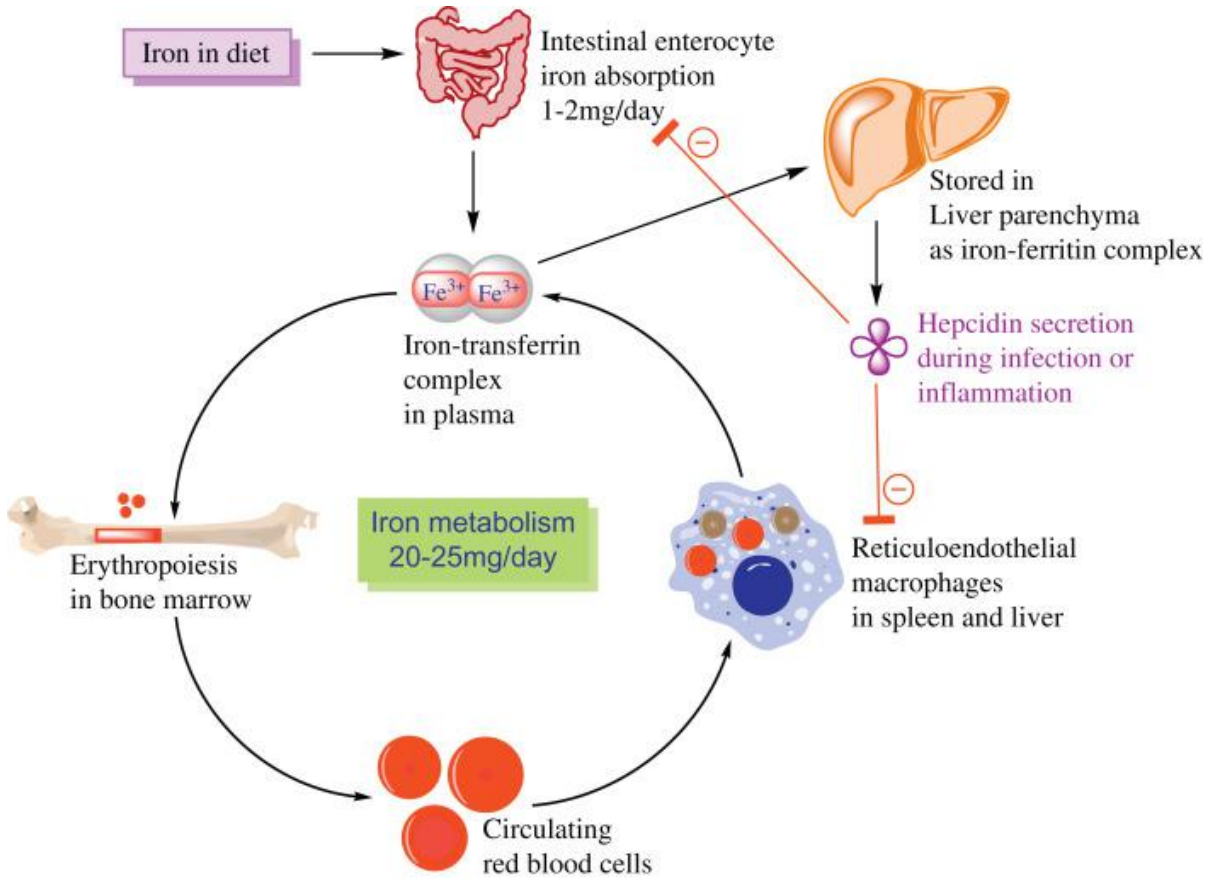
DISTRIBUTION OF IRON

- Total body iron content is 3 – 5g
- 65 - 75% in blood, rest in liver, bone marrow and muscles
- 65 - 75% of blood iron is hemoglobin (erythroid precursors and mature RBCs), Liver stores 10 - 20% in form of ferritin, 5% myoglobin
- Heme is the most predominant iron-containing molecule

Distribution of Iron



Distribution of Iron…



Recommended Dietary Allowance

- The **Recommended Dietary Allowance** (**RDA**) for all age groups of men and postmenopausal **women** is 8 mg/day; the **RDA** for premenopausal **women** is 18 mg/day

- Pregnant women: the **RDA** is 27 mg/day for **pregnant women**

- **NB:** Frequent blood donors and endurance athletes may need more iron.

Sources of iron

- Animal (heme iron) and Plant (non-heme) sources
- Heme iron is more readily absorbed than non-heme iron
- Heme iron; Liver, heart, kidney, red meat, poultry, oysters, clams, tuna, shrimps, eggs
- Non-heme iron; Bran, instant oatmeal, cereals, beans, tofu, spinach, brown rice, whole wheat bread, iron-fortified foods
- Vit. C (Eg orange juice) increases iron absorption

NB: In premature infants, early start of cereals is recommended (~4 months)

Functions of Iron

- Exerts its functions through biomolecules in which it is present
- Hemoglobin & Myoglobin – transport of oxygen & CO_2
- Cytochromes – Electron Transport Chain & oxidative phosphorylation
- Peroxidase (lysosomal enzyme) – phagocytosis & killing of bacteria by neutrophils
- Immune competence (immune cell proliferation and maturation)
- Iron cofactors in enzymes; Succinate dehydrogenase, isocitrate dehydrogenase (TCA cycle); catalase (breakdown of H2O2), myeloperoxidase, ribonuclease reductase, xanthine oxidase etc

Factors affecting plasma Iron concn

Physiological Factors

- Sex and age
- Pregnancy and oral contraceptives
- Circadian rhythm
- Monthly variations in females

Pathological factors

- Iron defcy (enhance) and iron overload
- Acute or chronic illness
- Hypoplastic marrow
- Heamolytic anaemia
- Liver disease
- Impaired iron absorption in malabsorption syndrome eg steatorrhea
- Impaired absorption in total or partial surgical resection of stomach or intestines.

Other factors affecting Iron concn

- Ferrous (Fe2+) absorbed, Ferric (Fe3+) not absorbed in human body
- Acidity, HCL, Vit C, Cysteine, SH grp of proteins facilitates Fe3+ → Fe2+ (conversion by ferric reductase) which is easily absorbed
- Alkali decreases absorption
- Calcium, copper, zinc, lead inhibit absorption
- Phytic acid and oxalic acid decrease absorption
- Polyphenols found in black and herbal tea, coffee, wine, legumes, cereals, fruit, and vegetables inhibit **iron absorption**
- High phosphate dietary content decreases absorption, low PO4 enhances

NB: Frequent blood donors and endurance athletes may need more

Iron compartments

- 3 major iron compartments in the body
- 1) Functional iron: Haemoglobin, myoglobin, iron-containing enzymes
- 2) Storage iron: Ferritin, hemosiderin
- 3) Transport/Circulating iron: Found in transferrin

Iron absorption & Transport

- Dietary Fe absorption occurs in duodenum and proximal jejunum
- Heme Fe is absorbed via Heme transporter
- At physiological pH, iron exists in the oxidized, ferric (Fe3+) state. To be absorbed, iron must be in the ferrous (Fe2+) state or bound by a protein such as heme.
- In the proximal duodenum, a **ferric reductase** enzyme, duodenal cytochrome B (Dcytb), on the brush border of the enterocytes converts the insoluble ferric (Fe3+) to absorbable ferrous (Fe2+) ions.
- **Divalent metal cation transporter 1** (**DMT1**) transports iron across the apical membrane and into the cell.
- Once inside the enterocyte, iron can be stored as **ferritin** or transported through the basolateral membrane and into circulation bound to **ferroportin**

Iron absorption & Transport…..

- The transmembrane protein ferroportin is the only efflux route of cellular iron and is regulated almost exclusively by **hepcidin** levels.
- Hepcidin: It is a liver derived protein that has pro-homonal signaling activity. **It is a key regulator of iron absorption**
- Hepcidin binds ferroportin causing its degradation
- Genlly, any signal that ↑ hepcidin levels ↓ Fe absorption into the blood
- Multicopper ferroxidases, **ceruloplasmin** (plasma) and **hephaestin** on the basolateral membrane of the enterocyte catalyze oxidation of Fe^{2+} → Fe^{3+} and subsequent binding of Fe^{3+} to transferrin in the plasma.

Iron absorption & Transport…..

Both DMT1 and Ferroportin 1 are widely distributed throughout the body and are involved in iron transport in other tissues as well.

12

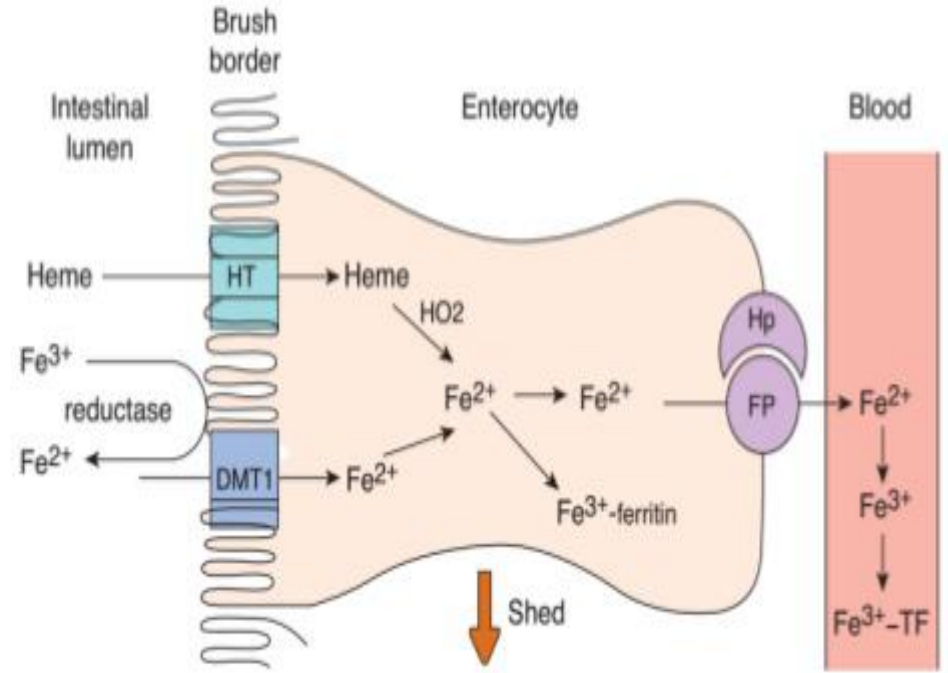
Iron absorption

DMT 1: Divalent Metal Transporter 1

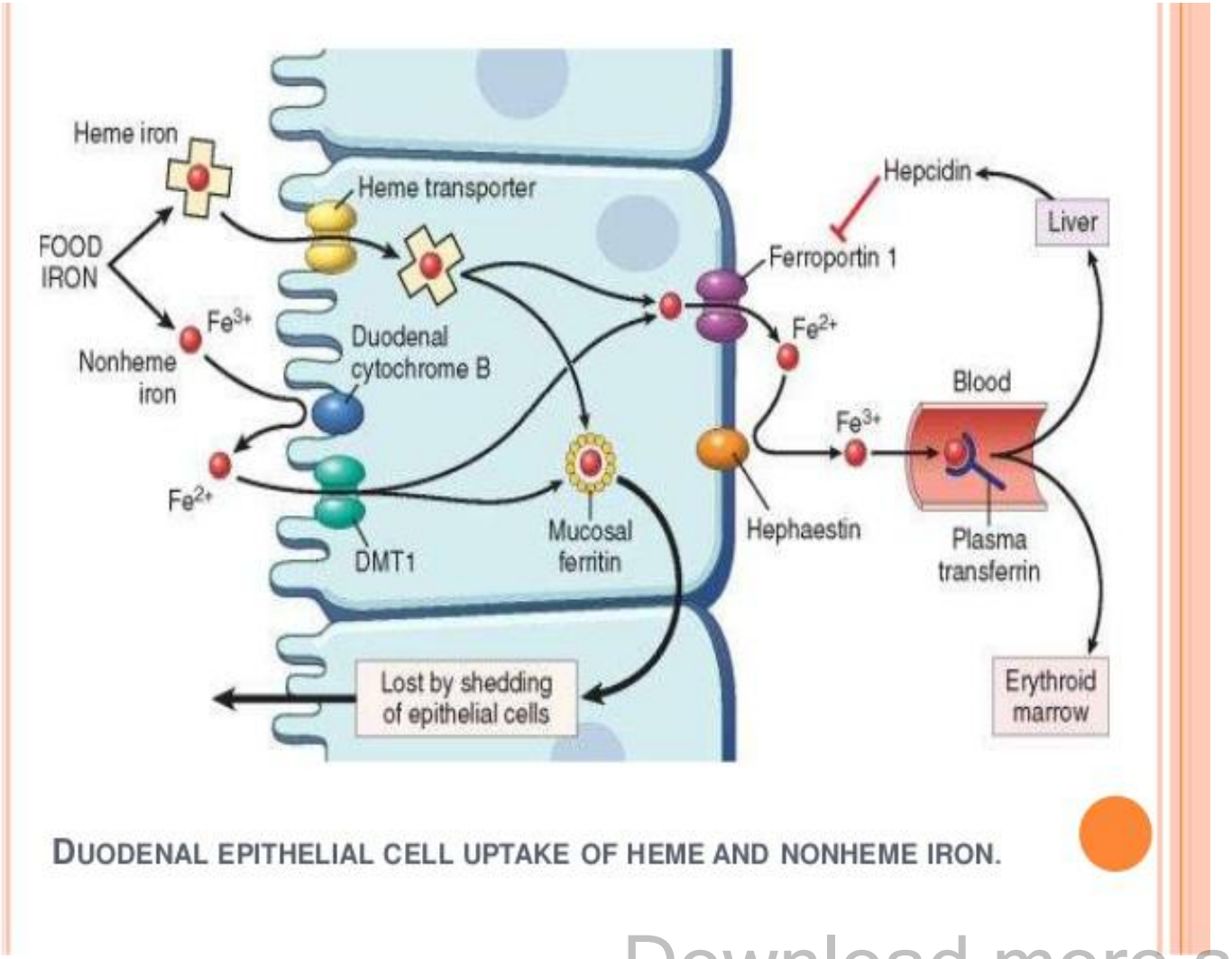
HT: Heme Transporter

FP: Ferroportin 1

HP: Hephaestin



Iron absorption & Transport…..



DUODENAL EPITHELIAL CELL UPTAKE OF HEME AND NONHEME IRON.

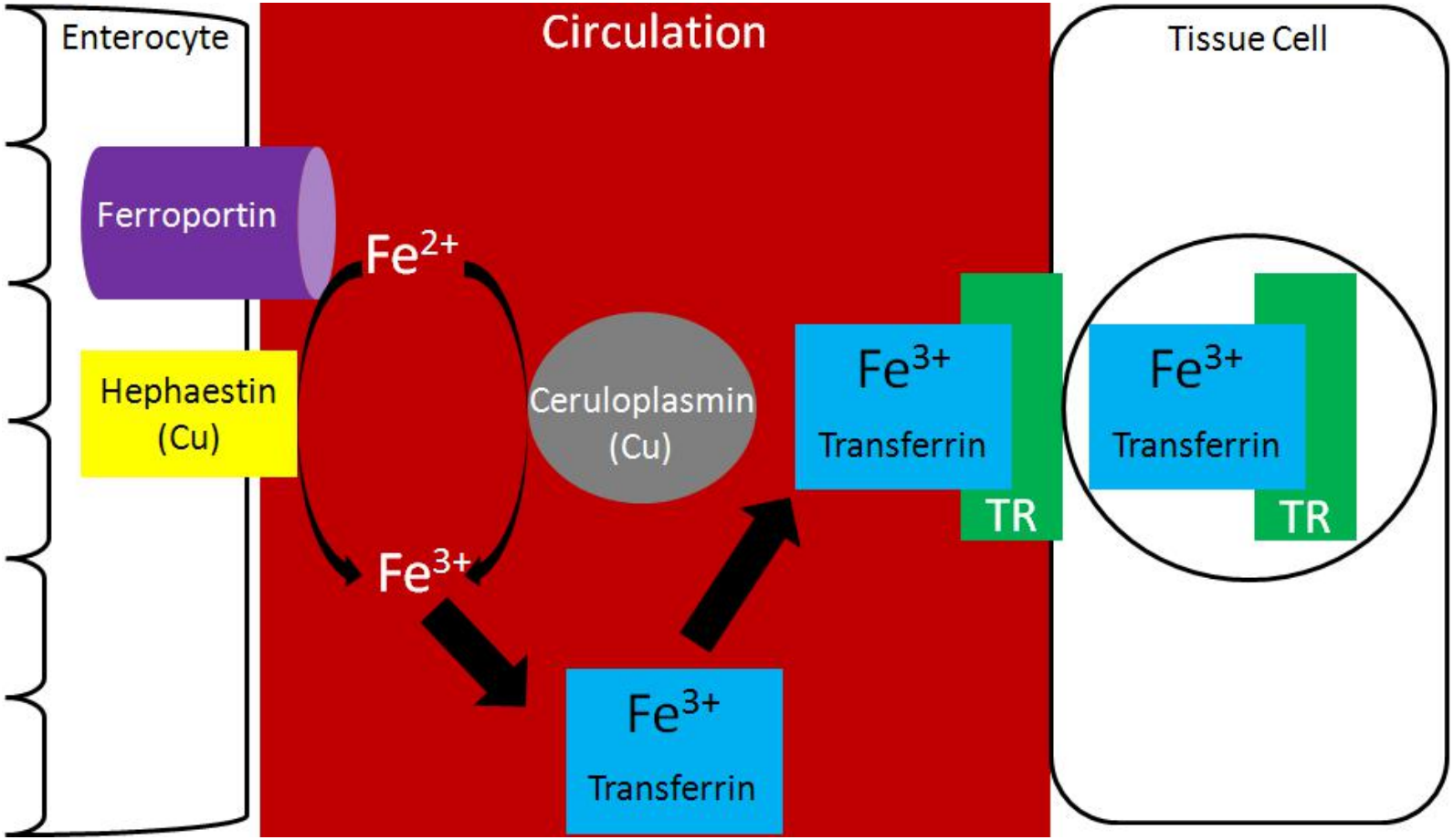
Iron Transport

- Transferrin is the major protein responsible for transporting iron in the body.
- Transferrin receptors, located in almost all cells of the body, can bind two molecules of transferrin.
- The principal role of **transferrin** is

  - to chelate iron so that it can be rendered soluble,

  - prevent the formation of reactive oxygen species (ROS),

  - and facilitate its transport into cells.
- Both transferrin concentration & transferrin receptors are important in assessing iron status.

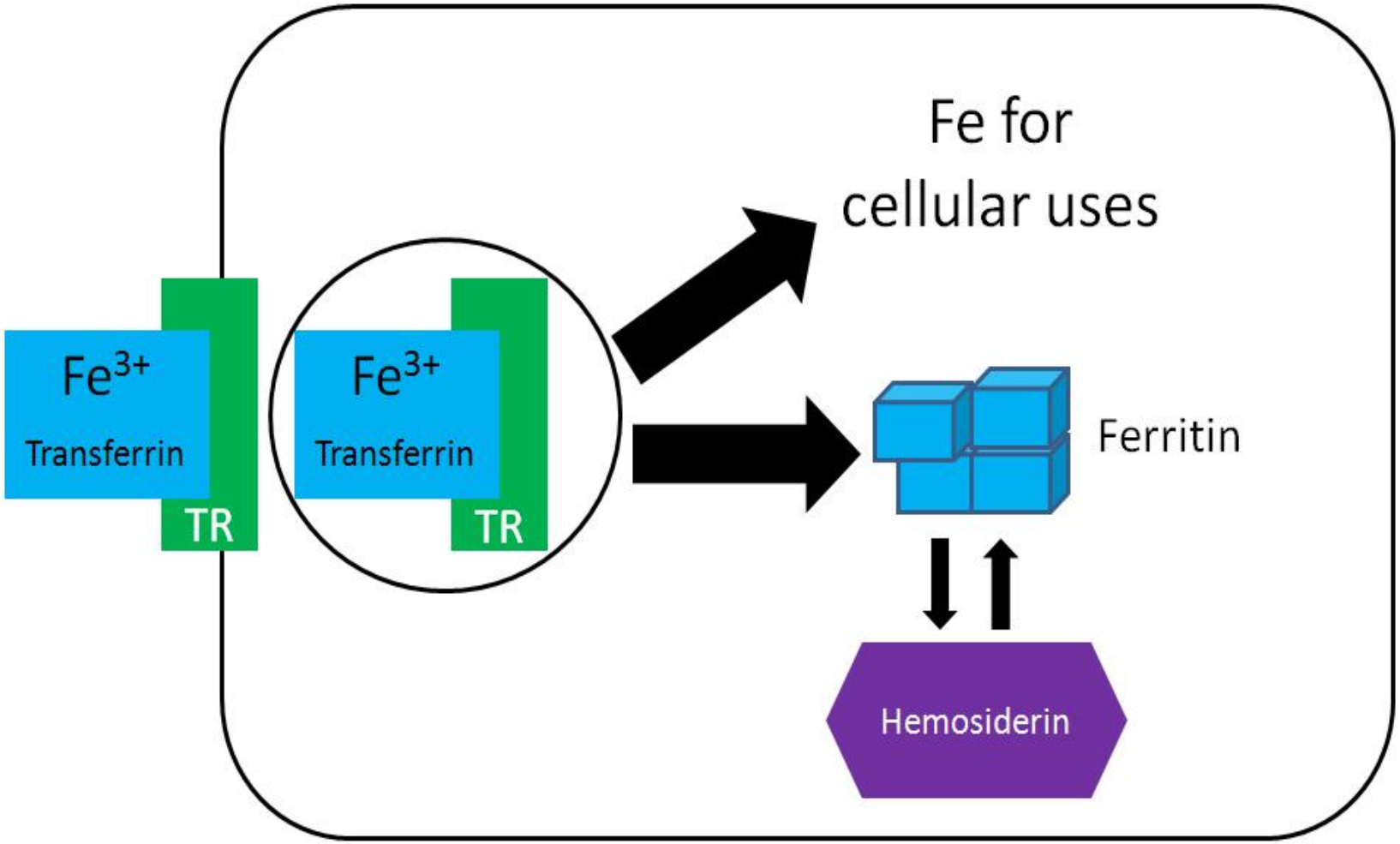


Iron storage

- Fe is stored as ferritin, hemosiderin
- The liver is the primary storage site in the body, with the spleen and bone marrow being the other major storage sites.
- This critical pool may be the first to diminish in iron defcy state
- Ferritin is a protein with a capacity of about 4500 Fe^{3+} (Ferric iron) per protein molecule, thus is the primary **iron storage** protein, but at higher concentrations, iron is also stored in **hemosiderin**.
- The amount of Fe in the storage compartment depends on Fe balance (positive or negative)

NB: Ferritin is a positive acute phase responder

Iron storage……



Disorders of Iron Metabolism; Defcy & Excess

Iron deficiency Anaemia (IDA)

- Fe defcy is the most common micronutrient defcy
- Affects about 15% of world population
- Those with higher than average risk; pregnant women, young children and adolescents, women of reproductive age
- Type is usually microcytic hypochromic anaemia

Signs/Symptoms

- Fatigue, dizziness, palpitations
- Pallor, smooth tongue, koilonychia, splenomegaly, dysphagia

Causes

- Increased blood loss;
  - Hookworm infestation- 0.3 ml/day blood loss
  - Repeated pregnancies- 1g loss /pregnancy
  - Chronic blood loss- hemorrhoids, melaena, menorrhagia, colon cancers, stomach ulcers, any GI bleeding
- Inadequate intake of iron and high intake of inhibitors of Fe absorption
- Decreased release from ferritin ???

Lab findings in IDA

- Microcytic hypochromic anaemia
- Low Hb level (< 11.0 g/dL)
- Low serum iron
- Low MCV, MCH, MCHC
- Low serum ferritin
- Low transferrin saturation
- High Red Cell Distribution Width (RDW)
- High Total iron binding capacity (TIBC)

Treatment of IDA

- Oral iron 3 – 5 mg Fe/kg/day
- IV or IM iron
- Blood transfusion if heart failure is imminent
- Treat underlying cause
- Dietary education

Anaemia of Chronic disorder

- Diagnosis reqs the presence of chronic inflammatory condition
- Eg infection, autoimmune disease, kidney disease, cancer etc
- Pathophysiol mechanisms:

- Slightly shortened RBC survival
- Impaired erythropoiesis due to decreases in both erythropoietin (EPO) production and marrow responsiveness to EPO
- Altered Fe metabolism due to an increase in hepcidin, which inhibits iron absorption and recycling, leading to iron sequestration.

Lab findings & Treatment

Lab findings:

- normocytic (initially) or microcytic anaemia
- Low reticulocyte count
- Serum iron: Low to normal
- Ferritin: Normal to increased

Treatment

- Treat underlying disorder
- Give erythropoietin, iron supplements
- Anaemia is generally mild, transfusions are rarely reqd

Iron Overload

- Iron overload states are collectively referred to as hemochromatosis, whether or not tissue damage is present
- Primary Fe overload: most freqtly assoced with Hereditary Hemochromatosis (a homozygous recessive disorder leading to abnormally high Fe absorption)
- Secondary Fe overload: may result from excessive dietary, medicinal, or transfusional Fe intake.
- HH causes tissue accumulation of iron, affects liver function, and often leads to

Hereditary Hemochromatosis

- Hereditary hemochromatosis is present at birth. But, most people don't experience signs and symptoms until later in life — usually after the age of 40 in men and after age 60 in women.
- Women are more likely to develop symptoms after menopause, when they no longer lose iron with menstruation and pregnancy.
- The most common cause of severe iron overload → Fe deposits in organs
- a defect in the hemochromatosis gene (HFE), most commonly C282Y or H63D gene mutation → abnormally high Fe absorption

Signs & Symptoms of HH

- Asymptomatic (75%)
- Liver dz (hepatomegaly, cirrhosis late in the dz)
- Skin bronzing/hyperpigmentation due to melanin
- Diabetes mellitus, (bronze diabetes)
- Arthropathy,
- Amenorrhea, impotence, hypogonadism
- Cardiomyopathy
- Osteopenia and osteoporosis
- Hair loss

Lab investigations & Treatment

- Genetic testing: pivotal for diagnosis of hemochromatosis
- Transferrin saturation levels >50%
- Increased Serum/Plasma ferritin
- Increased Serum/Plasma iron
- TIBC saturation of > 50%
- Hepatic iron quantification with MRI might be helpful.
- Liver biopsy & histologic evaluation with iron staining (Perls Prussian blue)

- Treatment
- Venesection; each 500ml of blood removes ~ 250mg of Fe
- Chelators eg deferoxamine, Deferasirox, Deferiprone, Iron-binding dendrimers

Secondary Iron Overload

- Repeated blood transfusions (each unit of blood provides about 250 mg of iron; tissue deposition becomes significant when more than about 40 units of blood are transfused)
- Exogenous iron given to treat anemia
- Increased iron absorption; in patients with ineffective erythropoiesis may be partly due to the secretion, by erythroid precursors, of erythroferrone (ERFE), which suppresses hepcidin.
- Seen in hemoglobinopathies and congenital hemolytic anemias

Signs & Symptoms

- The clinical consequences of iron overload are the same regardless of the etiology and pathophysiology of the overload.
- Liver disease is the most common cause of death. Followed by Cardiomyopathy with heart failure

Treatment

- Usually iron chelation with deferasirox or deferoxamine, or sometimes deferiprone
- Goal of Tx; transferrin saturation of < 50%.

Case study

- A 65 year old woman with a hx of diabetes was seen by her physician for weight loss, anorexia and general fatigue. As part of the phy exam, both ‘bronze’ skin pigmentation and enlarged liver were noted. Her initial chemistry investigations showed;
- ALP 180 U/L (30 – 135)
- ALT 200 U/L (10 – 60)
- Total bilirubin 2.5mg/dL (0.2 – 1.2)
- Serum iron 180 µg/dL (45 – 150)

Further testing for the elevated iron showed;

- Transferrin 210 mg/dL (200 – 380)
- Ferritin 300 µg/L (10 – 250)
- % Transferrin saturation 80

Questions

1) What is your diagnosis?

2) What happens to serum ferritin in this condition?

3) What are your treatment options?

THANKS FOR LISTENING