HLS

MODIFIED NO. 5

BIOCHEMISTRY

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Metabolism of iron

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Hematopoietic-lymphatic system

Color code
Slides
Doctor
Additional info
Important

We will cover the following aspects at this lec:

1. **Absorption**: How iron is absorbed in the body.
2. **Transport, Storage, and Elimination**
3. **Function**: The role of iron in the body.
4. **Regulation**: How these processes are controlled.
5. **Diseases Related to Iron**

Resources

Each resource of them talks about certain topic so the Dr collected them here

- 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

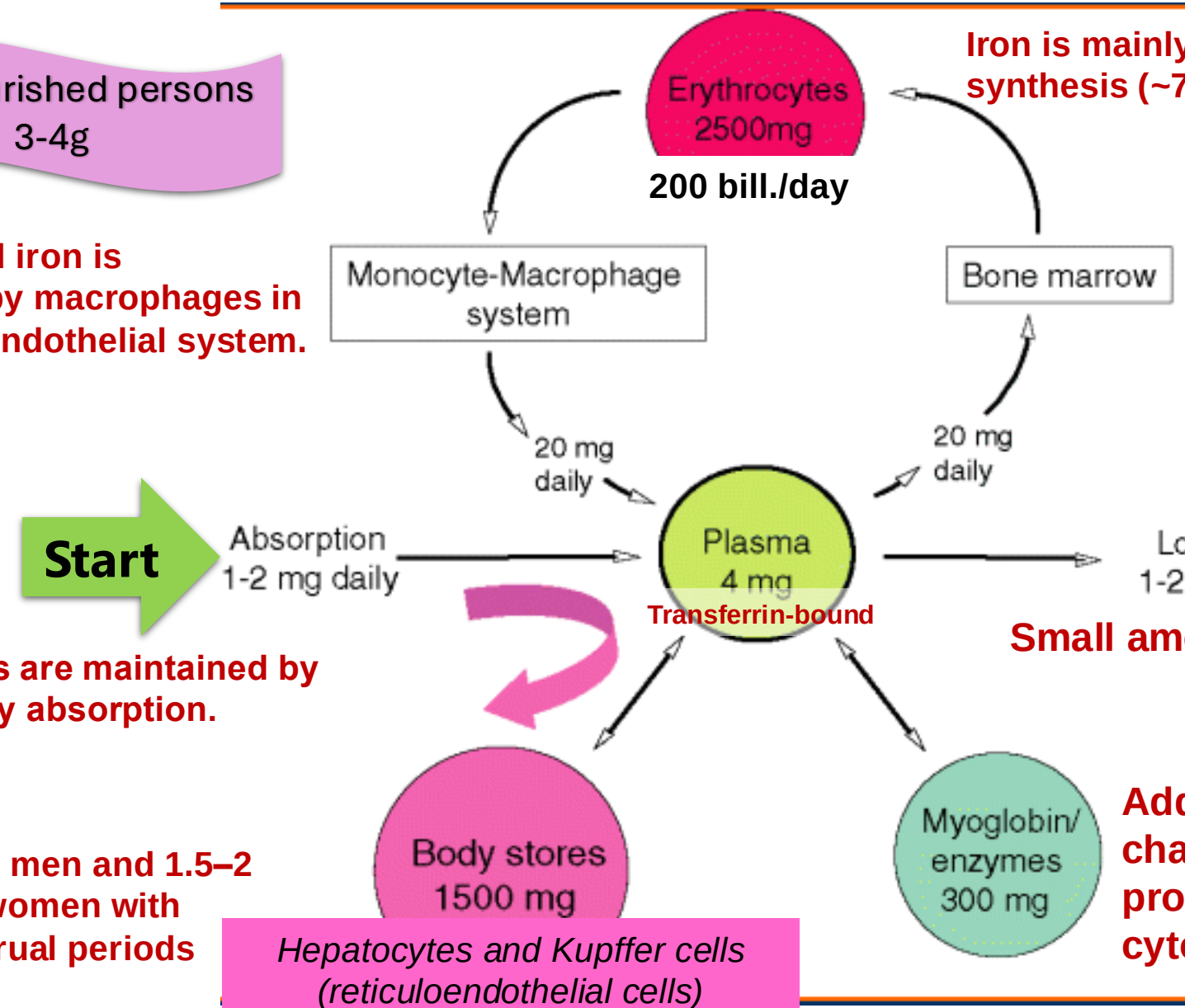
Importance of iron

- Within the body, iron exists in two oxidation states: ferrous (Fe^{2+}) or, the highly insoluble, ferric (Fe^{3+}) you will not see this form free in the body except bound to proteins such as transferrin or ferritin.
- Iron is an important element for metabolism because it is involved in oxygen storage (in muscles via myoglobin), and oxygen transport (via hemoglobin).
- It is also sreves as the prosthetic group of several enzymes such as redox cytochromes and the P450 class of detoxifying cytochromes.
- Yet…
- Iron can be potentially toxic due its ability to form free radicals.
- Solution: iron is not free.

⚠ However, iron can be toxic when free because it has the potential to produce free radicals. Therefore, it is usually bound to proteins to prevent toxicity.

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.

Small amounts are lost

Levels are maintained by dietary absorption.

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).

🔴 Let's go over the **life cycle of iron**:

•The total amount of iron in the body of a well-nourished person ranges from **3 to 4 grams**, which is quite a lot. However, **only 1 to 2 milligrams** of iron are absorbed daily, which is relatively small compared to the total amount present in the body.

•The daily absorption is also **lower in men than in women** due to iron loss during the menstrual cycle in women.

•The amount which is lost daily also very little which means Iron is important so it will be preserved

•In the **plasma**, there is only a small amount of iron, around **4 milligrams**, which is mainly bound to a protein called **transferrin**. We will discuss transferrin in more detail shortly.

•Most of the iron in the body is directed to the **bone marrow**, where it is used to produce **erythrocytes**

•In total, about **2,500 milligrams (2.5 grams)** of iron is found within erythrocytes, accounting for about **70% of the body's iron**. This is a significant amount, considering there are approximately **200 billion erythrocytes** in the body.

•When erythrocytes undergo **hemolysis**, **macrophages** in the body will **phagocytose (engulf)** these dead cells. This process helps **preserve iron** and prevents potential toxicity.

•Besides erythrocytes, iron is stored in various body systems, mainly within **reticuloendothelial cells**, also known as **Kupffer cells** or **macrophages**, amounting to about **1.5 grams**.

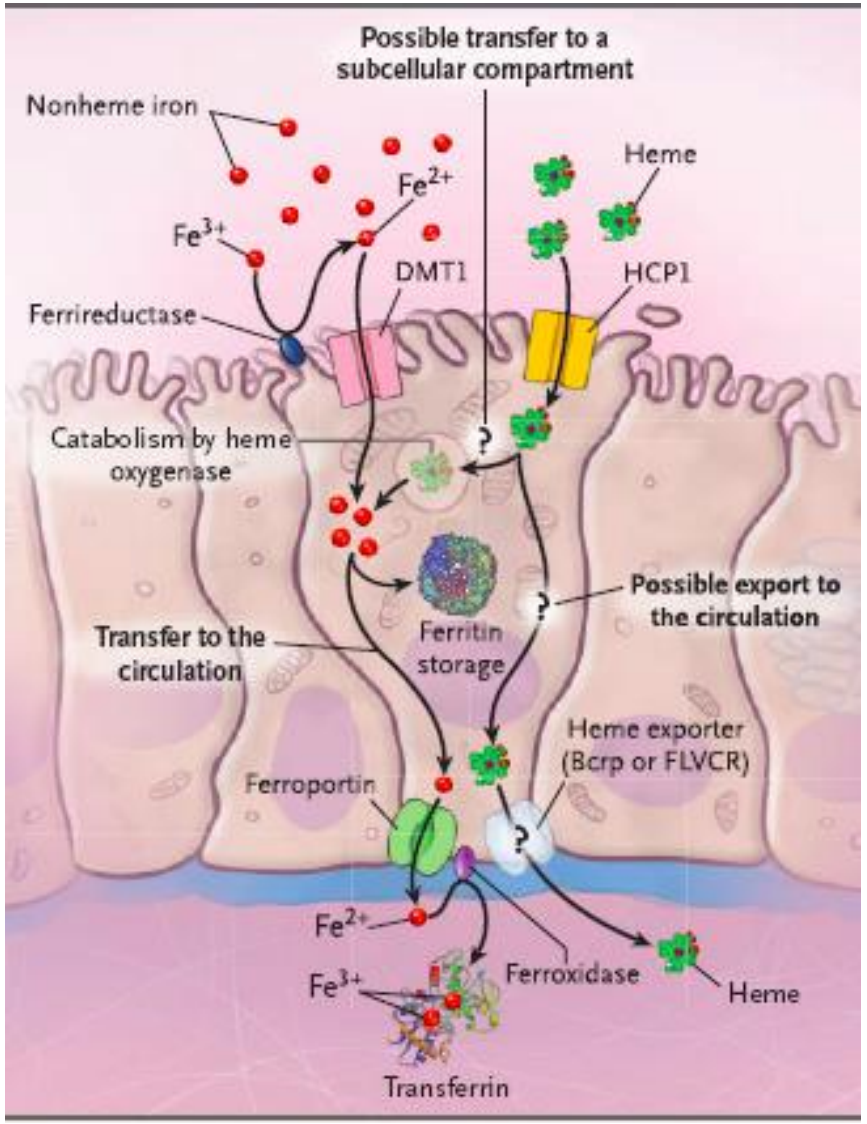
•Additionally, a good portion of iron is stored as **myoglobin in muscles**, serving as a reserve.

•Iron is also found in **metabolic enzymes** such as **cytochrome P450 enzymes**, which are involved in important biochemical processes.

Iron absorption

State of iron

- Under conditions of neutral or alkaline pH, iron is found in the ferric Fe^{3+} state and, at acidic pH, in the ferrous Fe^{2+} 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 Fe^{2+} form.



•This explanation for the next 2 slides

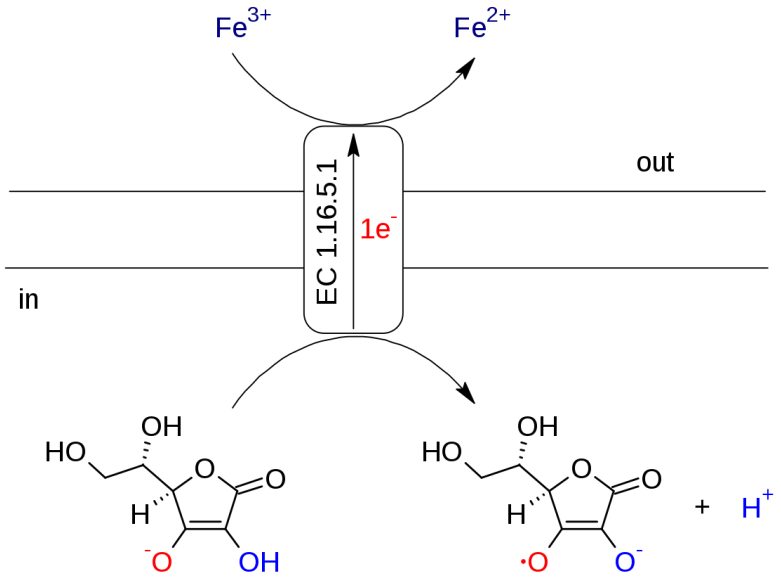
•🎯 In the **stomach**, iron is primarily in the **ferrous state (Fe^{2+})**. When iron passes into the **intestines**, particularly the duodenum, it is often found in the **ferric state (Fe^{3+})**. However, for iron to be effectively absorbed by intestinal cells, it must be in the **ferrous (Fe^{2+}) state**.

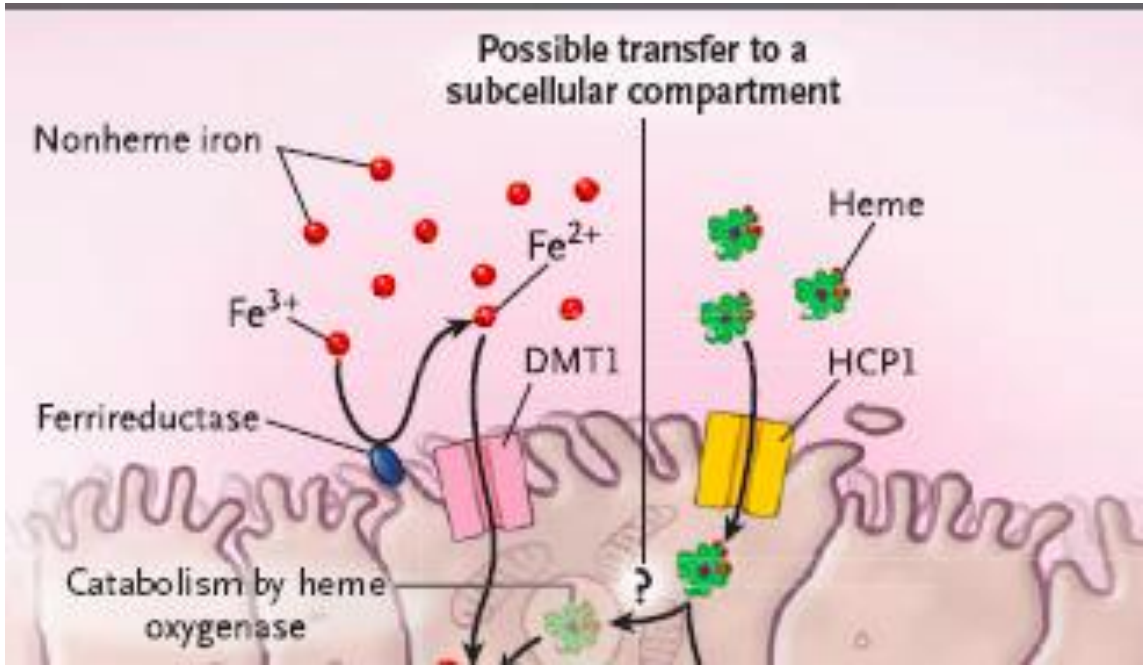
•As iron moves from the stomach to the intestines, enzymes known as **ferrireductases** on the surface of the intestinal cells play a critical role. These enzymes convert **Fe^{3+} to Fe^{2+}**, allowing it to be absorbed. This reduction process depends on **Vitamin C** as a cofactor.
•The **divalent metal transporter 1 (DMT1)** then transports the ferrous iron (Fe^{2+}) into the intestinal cells.

•In addition to non-heme iron(which we talked about its absorption mechanism above), **heme iron** can be absorbed through a different mechanism. Heme, derived from animal sources, is absorbed by a receptor called the **heme carrier protein 1 (HCP1)**. Once heme enters the cells, the iron is extracted by an enzyme known as **heme oxygenase-1 (HO-1)**.

Site of absorption

- Ferrireductase enzyme on the enterocytes' brush border reduces Fe^{3+} to Fe^{2+} 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.

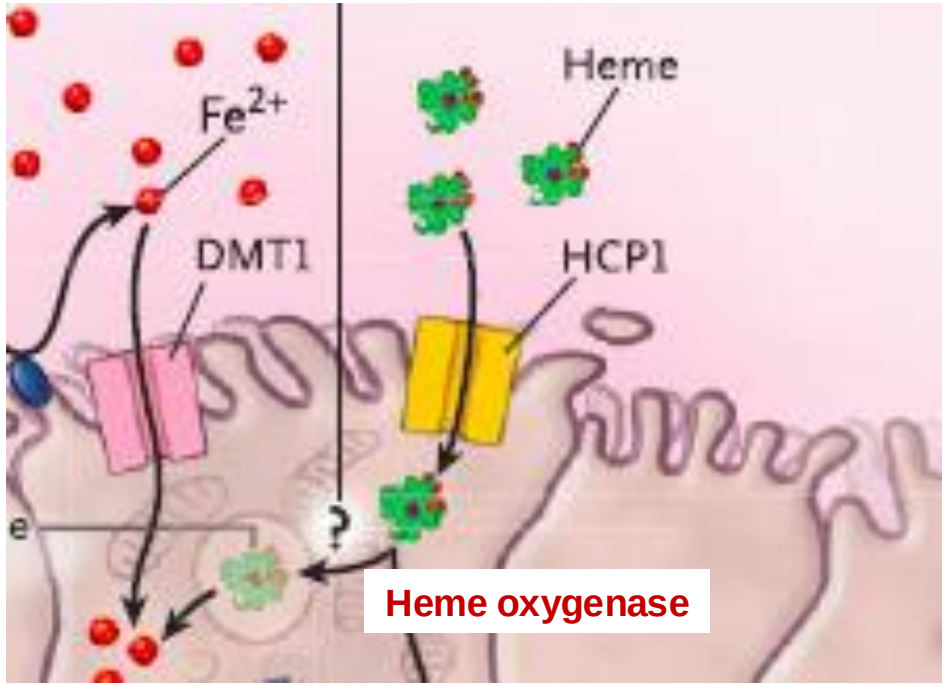


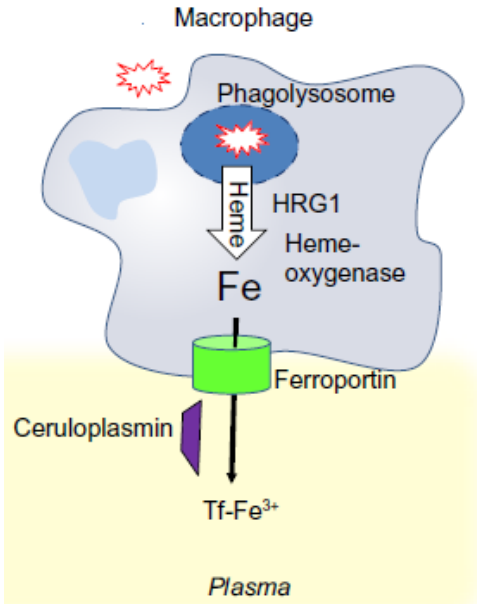


Heme as a source of iron

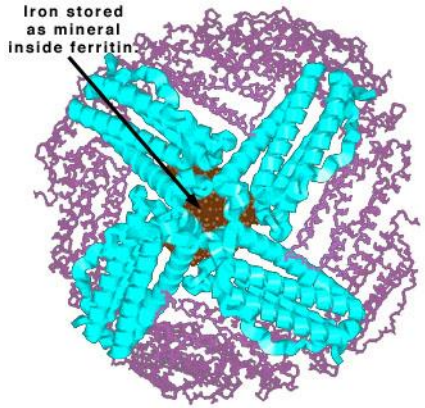
- Iron can also be obtained from ingested heme.
- Heme is absorbed by a receptor called heme-carrier protein 1 (HCP-1) and iron is released by heme oxygenase-1 (HO-1).
- In other cells such as macrophages, heme oxygenase also extracts iron from heme. When iron is absorbed as **heme**, similar extraction processes occur within **macrophages** (phagocytic cells).
- The **heme carrier protein (HCP)** transports heme into the **macrophages**, where iron is extracted, just like in the intestines.

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





Fates of iron

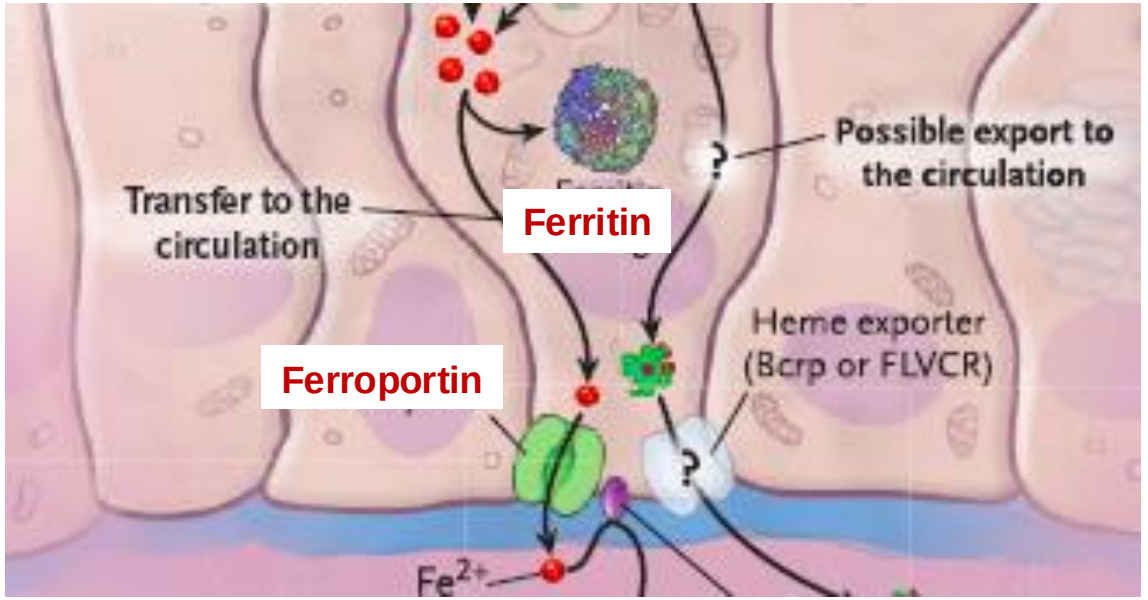


Fate 1: storage

- Cells can then store iron as ferritin.
  - Each Ferritin complex can store about 4500 iron (Fe^{3+}) 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.



Once iron enters the intestinal cells, it can take one of two fates:

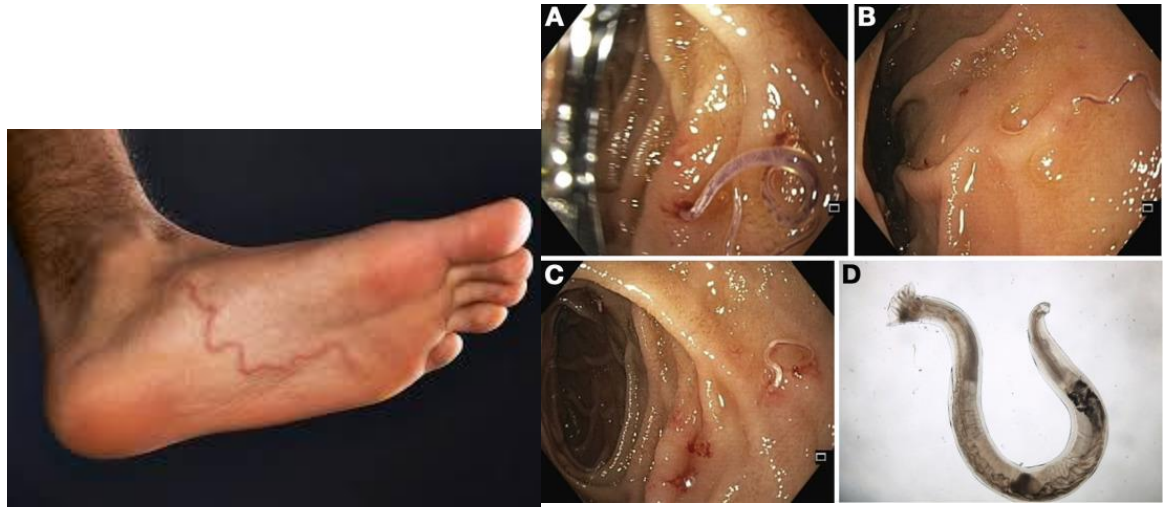
1. Storage: Iron can be stored in a protein called ferritin, which can hold up to 4,500 iron atoms. This makes ferritin a critical storage protein. When the intestinal cells undergo apoptosis and are sloughed off, the iron stored within them is also lost from the body.
2. Transport: Iron can be transported out of the cells via a protein known as ferroportin. This protein is also found in macrophages, where it helps in the release of iron.

It's important to note that iron can be lost when the intestinal cells die and are shed, leading to iron loss in the process. This is a natural way the body regulates iron levels.

Intestine-related iron metabolism disorders

Iron loss in the intestines can occur through two mechanisms:

- Iron malabsorption
  - Gastrectomy (total or partial)
  - Celiac disease (villous atrophy)
  - Crohn's disease
  - Helicobacter pylori
- Intestinal hemorrhage (gastrointestinal-mediated iron loss)= loss of iron by bleeding
  - Gastric cancer
  - Ulcers
  - Inflammatory bowl disease
  - Hookworm infection as u see in pics



📌 All written here is additional for ur better understanding

Iron Malabsorption: Disorders affecting the duodenum and jejunum can impair iron absorption, leading to deficiency.

Gastrectomy: Reduced stomach acid after surgery hinders iron conversion and absorption

Celiac Disease: Damage to the small intestine from villous atrophy reduces iron absorption.

Crohn's Disease: Inflammation and scarring disrupt iron absorption in the intestines.

H. pylori: Infection affects stomach acid production and competes for iron, leading to deficiency.

Intestinal Hemorrhage: Chronic bleeding from the gut causes iron loss, leading to deficiency.

Gastric Cancer: Alters stomach function and can cause bleeding, impairing iron absorption.

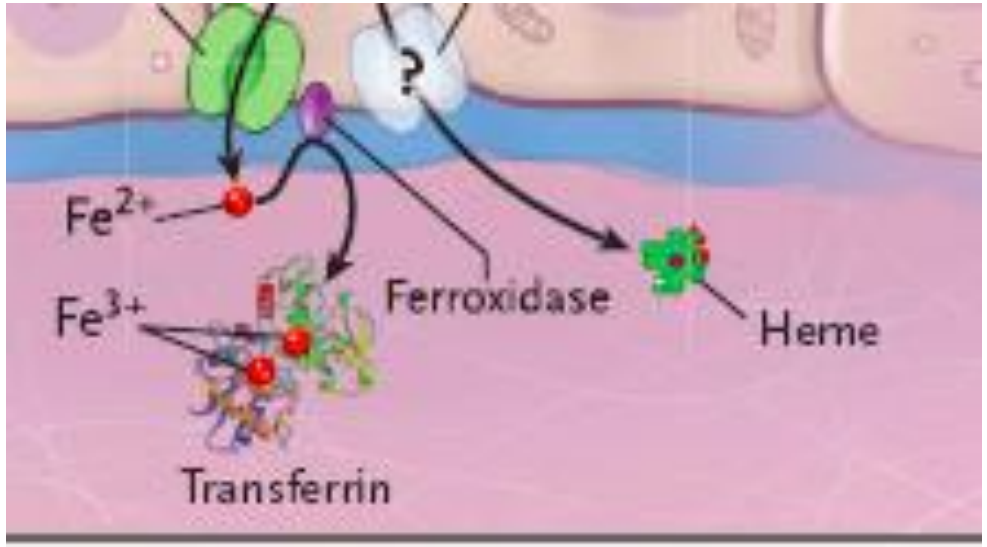
Ulcers: Bleeding ulcers result in iron loss and may affect iron absorption in the stomach or duodenum.

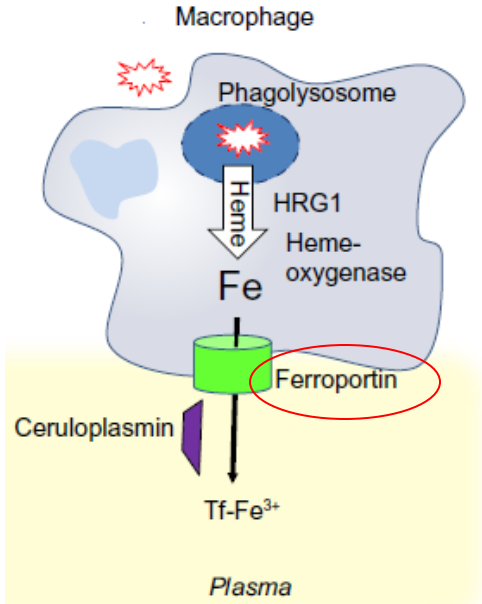
Inflammatory Bowel Disease: Chronic inflammation and ulcers from IBD hinder iron absorption and increase hepcidin, reducing iron uptake.

Hookworm Infection: Parasites feed on blood, leading to significant iron loss and anemia.

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.



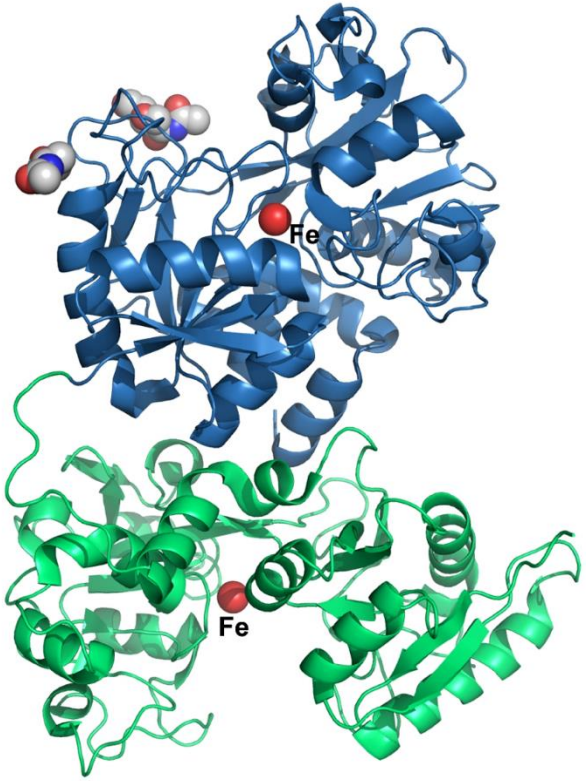


Iron transport from intestinal cells involves the following steps:

- Iron is transported **out** of the intestinal cells via a protein called **ferroportin**, which also facilitates the release of iron from macrophages. Whether iron is extracted from heme within macrophages or transported out of the cells.
- Once iron exits the cells, it needs to be converted to the ferric state (Fe^{3+}). This oxidation process is essential because iron must be in the ferric state to bind to transferrin.
- The oxidation of iron is carried out by enzymes known as **ferroxidases**, including **hephaestin**. These enzymes convert iron from Fe^{2+} (ferrous) to Fe^{3+} (ferric) to enable its binding to transferrin.
- Nonintestinal cells use the plasma protein ceruloplasmin to oxidize iron.
- Remember, for iron to be effectively transported, it must be bound to transferrin molecules after being converted to the ferric state.

Properties of transferrin

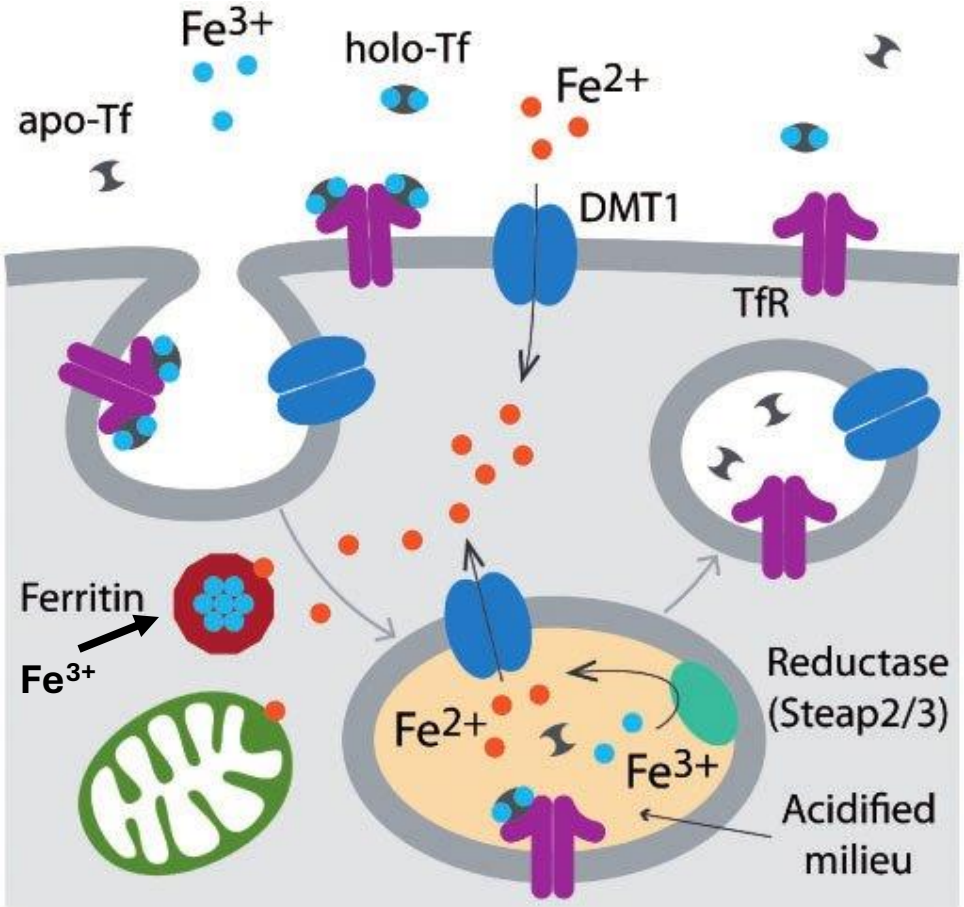
- Apotransferrin can bind several metals, but ferric, not ferrous, iron has the highest affinity forming ferrotransferrin.
- Transferrin contains two sites that bind ferric irons:
  - *iron-binding sites of transferrin are normally only about 1/3 saturated with iron.*
- When iron exceeds normal levels,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



- Transferrin is a dimer protein capable of binding up to two iron atoms. For effective binding, the iron must be in the ferric state (Fe^{3+}), as transferrin has a higher affinity for this form of iron compared to the ferrous state (Fe^{2+}).
- In the body, only about one-third of the transferrin molecules are typically saturated with iron. This leaves many available iron-binding sites on transferrin, which acts as a protective mechanism. Having a significant number of unsaturated binding sites helps prevent the presence of free iron in the bloodstream, which is essential because free iron can be toxic to tissues. It can lead to the generation of harmful free radicals, causing oxidative damage. We will address the toxicity of free iron more thoroughly later in the lec.
- If there is an excess of iron in the body that surpasses the binding capacity of transferrin, it results in what is known as non-transferrin-bound iron (NTBI), refers to iron that is bound to proteins other than transferrin or remains free. This type of iron is more likely to contribute to tissue damage because it can easily catalyze the formation of ROS and lead to oxidative stress.

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 Fe^{3+} atoms dissociate, get reduced into Fe^{2+} 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



- As we said, Transferrin is a protein that binds and transports iron throughout the body. Each transferrin molecule can carry up to two iron atoms in the ferric state (Fe^{3+}). Once iron is bound, the holo-transferrin (loaded with iron) will bind to the transferrin receptor (TfR), which is present on the surface of almost all cells because all cells require iron.
- When holo-transferrin binds to the receptor, it triggers a process called receptor-mediated endocytosis, where the transferrin-receptor complex is engulfed into the cell, forming a vesicle. These vesicles, initially called early endosomes, have a pH of about 6. As they mature into late endosomes, the pH drops to around 5, which helps facilitate the release of iron from transferrin inside the vesicle. The acidic environment in the late endosomes, along with the action of a ferrireductase enzyme called STEAP3, reduces iron from Fe^{3+} to Fe^{2+}. This reduction process is also dependent on Vitamin C .Once the iron is in the ferrous state (Fe^{2+}), it is transported out of the vesicle into the cytosol by the divalent metal transporter 1 (DMT1). This is similar to how iron is transported across the intestinal cells. Once inside the cytosol, the iron can be utilized for various functions, such as incorporation into enzymes or stored as ferritin. After the iron is released, the transferrin-receptor complex returns to the cell membrane, where the transferrin (now without iron) is released back into the bloodstream, ready to bind more iron.

- What about Affinity of Transferrin Receptor (TfR)?

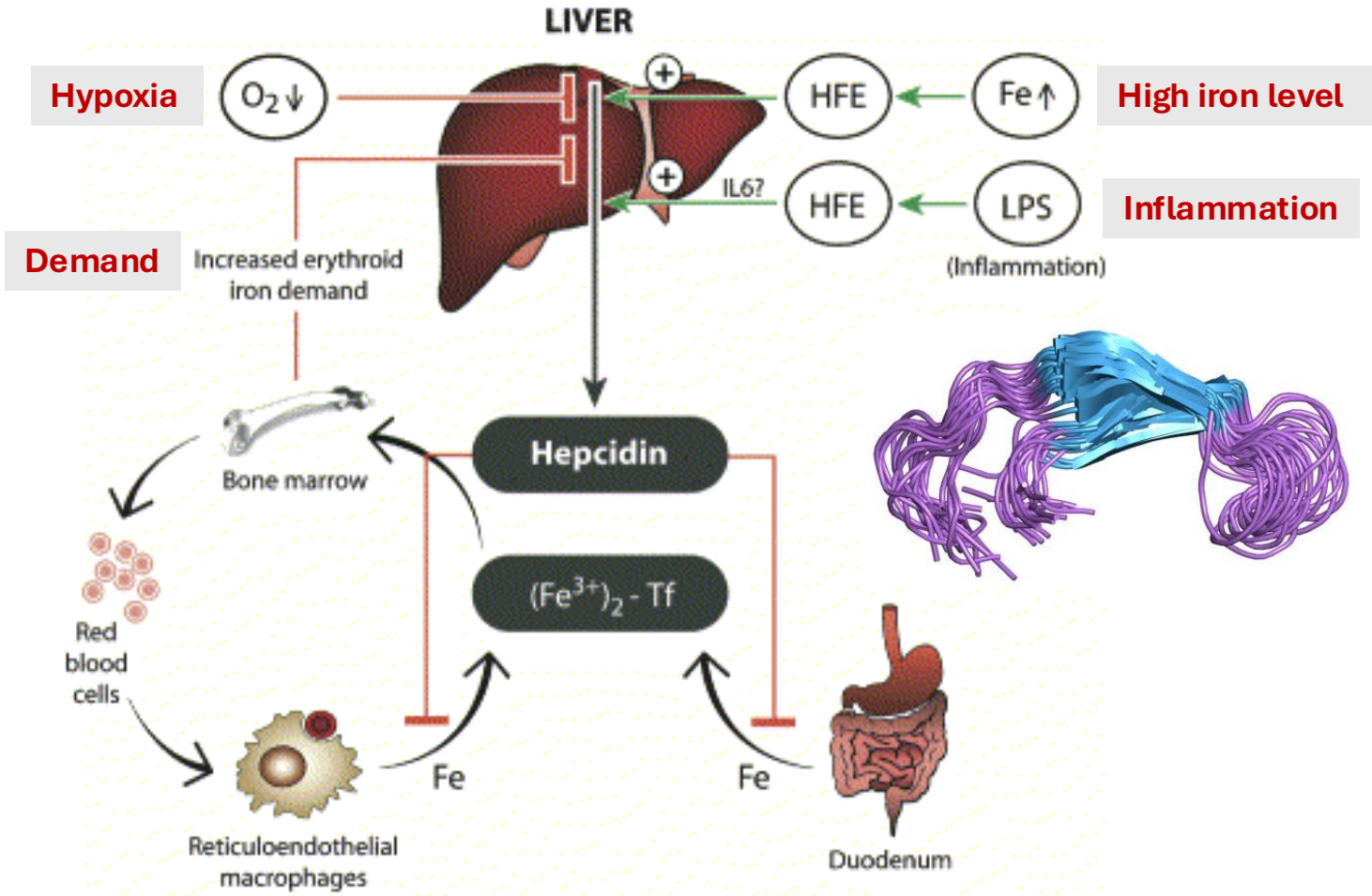
- Diferric transferrin (Fe2Tf): The form of transferrin with two iron atoms has the highest affinity for the receptor.
- Monoferric transferrin (Fe1Tf): This form, with only one iron atom, has a lower affinity than diferric transferrin.
-Apo-transferrin (apo-Tf): Transferrin without any iron has the lowest affinity for the receptor.

Regulation of protein function

Hepcidin (iron sensor)

- Hepcidin is a peptide hormone (25 amino acids) that plays a key role in regulatin iron levels in the body secreted by the liver and its main function is to **reduce** 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.



- When iron levels increase in the body, hepcidin levels also increase. This elevation in hepcidin can occur in response to: **High iron levels** or **Inflammation.**

- When hepcidin levels are high, it binds to ferroportin on the surface of intestinal cells and macrophages, leading to ferroportin's internalization and degradation. This reduces:

A. Iron absorption from the intestines
B. Iron release from macrophages and intestines
C. Transport of iron into the bloodstream

As a result, more iron is stored in cells as ferritin, increasing iron storage and reducing free iron in circulation. This helps to prevent iron overload and protect tissues from potential damage caused by excess iron.

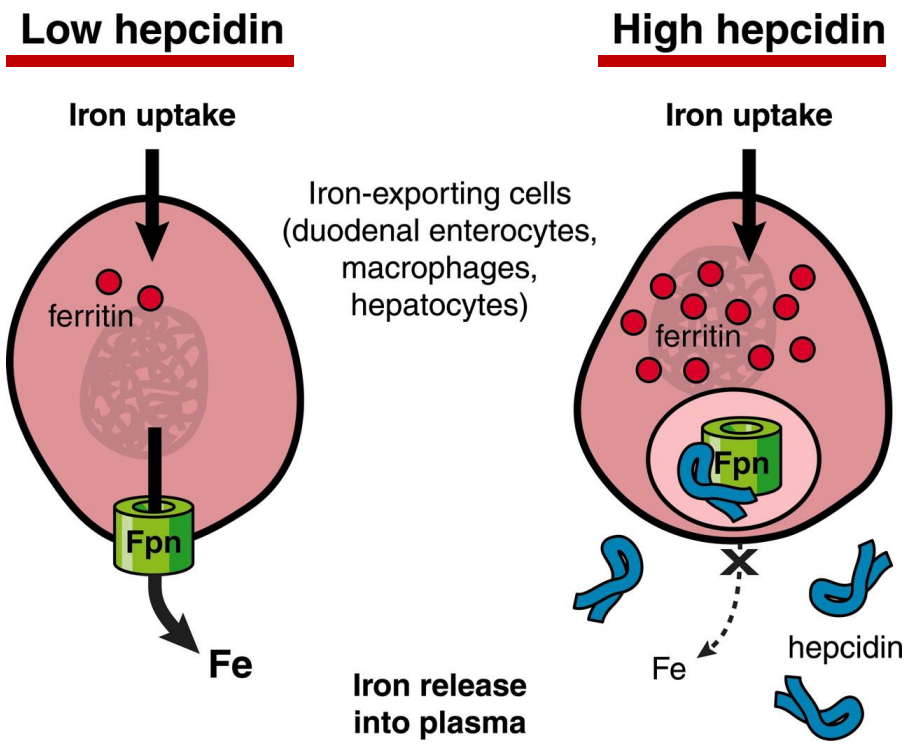
- Conversely, when iron levels are low, hepcidin production decreases, leading to:

A. Increased iron absorption from the intestines
B. Enhanced release of iron from macrophages
C. Higher levels of transferrin and transferrin receptors to facilitate iron transport
D. Reduced storage of iron in the form of ferritin

- In conditions of hypoxia (low oxygen levels), the production and release of hepcidin are also reduced, allowing the body to increase iron availability to meet its needs, such as boosting red blood cell production.

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.



- **Hepcidin** primarily functions by **binding to the basolateral iron transporter**, known as **ferroportin**, which is found on the surface of **intestinal cells** and **macrophages**. When hepcidin binds to **ferroportin**, it triggers a process called **internalization**. Ferroportin is engulfed into the cells through vesicles, which then transport it to **lysosomes** where it is **degraded**. The degradation of ferroportin leads to a **reduction in the amount of iron** that can be released from the cells.
- As a result:

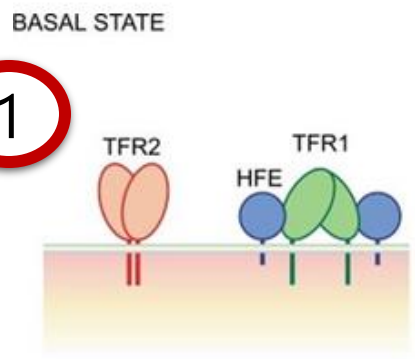
- In intestinal cells, less iron is transported out of the cells into the bloodstream, leading to **more iron being stored** within the cells. If these cells are sloughed off and shed from the intestinal lining, the stored iron is **eliminated** from the body.
- In macrophages, hepcidin prevents the release of iron that would otherwise be recycled from old red blood cells, thus limiting the amount of iron available in circulation.
- hepcidin inhibits the expression of **DMT1** on intestinal cells. By reducing their presence, hepcidin further **limits iron absorption**.

Again, the effect of hepcidin is to **reduce iron levels** in the bloodstream by:
Decreasing iron absorption from the intestines
Inhibiting iron release from macrophages
increase iron storage within cells, which can then be eliminated as the cells are shed.

Additional table to organize ideas

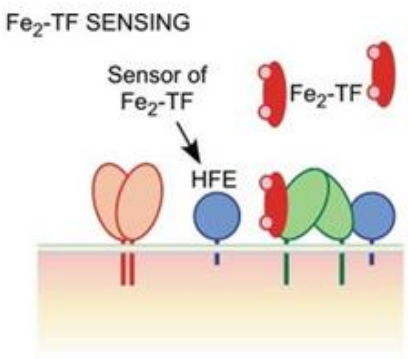
Location / Enzyme	Iron State	Helper Factors
Stomach	Fe^{2+}	
DMT1 (Intestine)	Fe^{2+}	Vitamin C (enhances absorption)
Enterocyte	Fe^{2+} (in DMT1), Fe^{3+} (stored in ferritin)	Vitamin C
Ferroreductase	$Fe^{3+} \rightarrow Fe^{2+}$	Vitamin C
Transferrin	Fe^{3+}	
Steap3 (in cells)	$Fe^{3+} \rightarrow Fe^{2+}$	
hephaestin or ferroxidase	$Fe^{2+} \rightarrow Fe^{3+}$	ceruloplasmin in non intestinal cells
Ferritin (storage)	Fe^{3+}	

Regulation of hepcidin

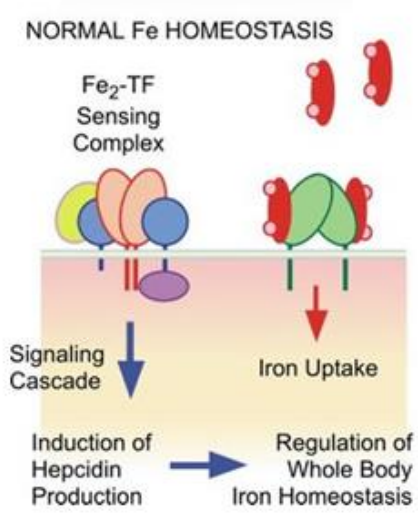


1

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



Holo-Tf (Fe_2-Tf) binds TFR1 releasing HFE.



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

2

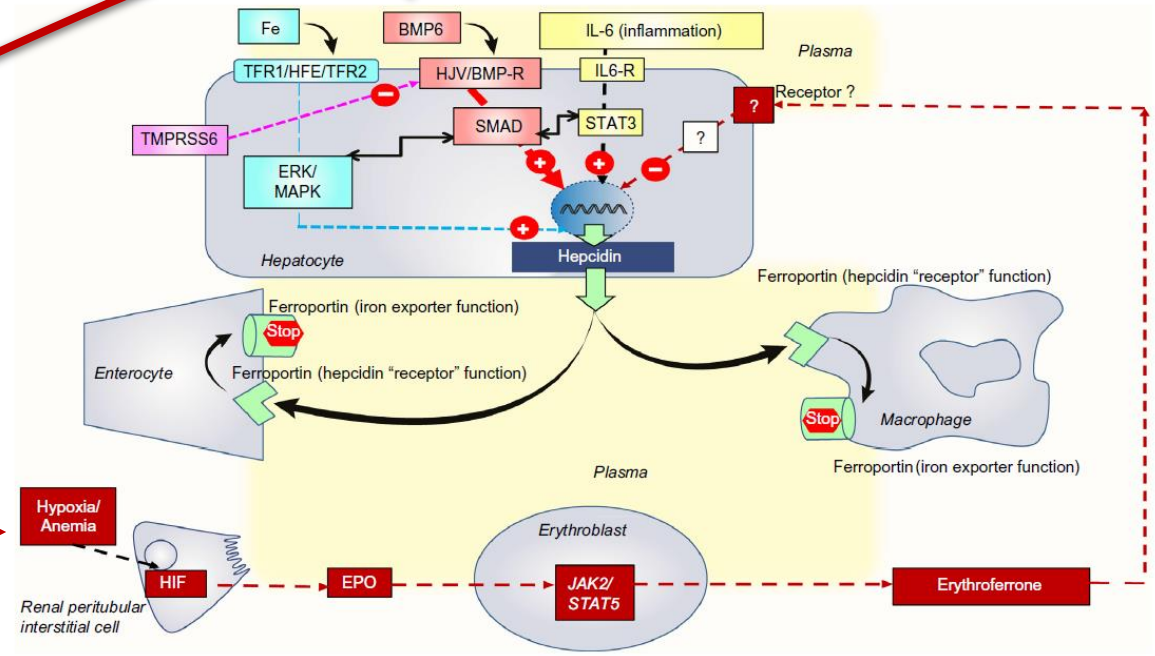
Inflammatory cytokine, IL6, induces the expression of hepcidin

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.



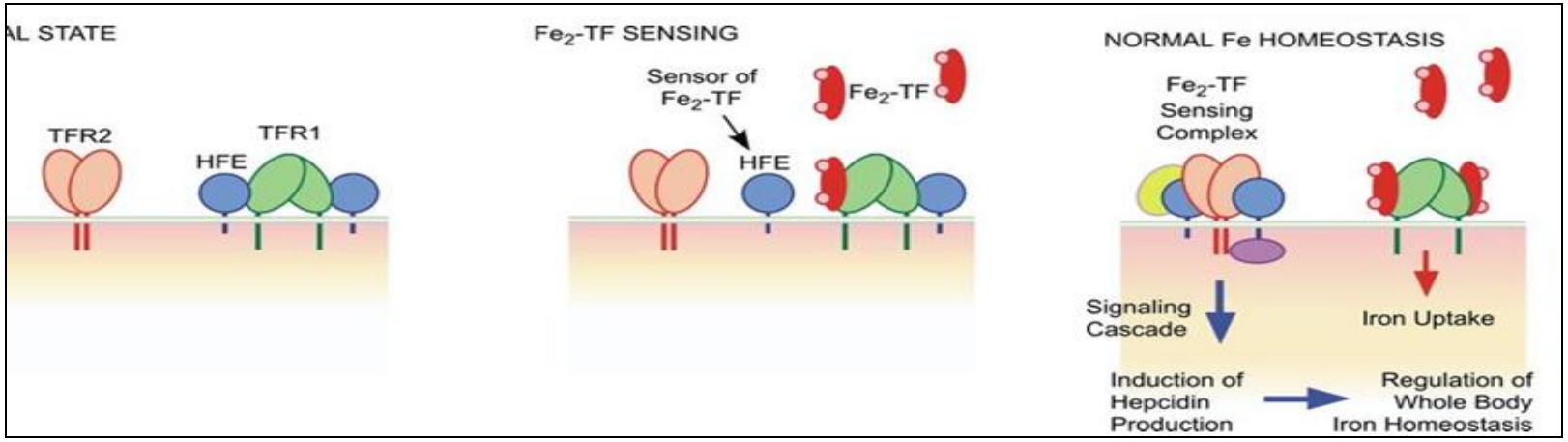
❖ **Transferrin Receptor 1 "TFR1":** is responsible for binding to transferrin and facilitating the entry of iron into the cells.

TFR1 is initially bound to a protein called HFE, but when diferric transferrin binds to TFR1(which means we start having much iron in the body and should start regulation), HFE is released and this interaction leads to a process called receptor-mediated endocytosis, allowing iron to be internalized by the cell.

❖ **Transferrin Receptor 2 (TFR2):**

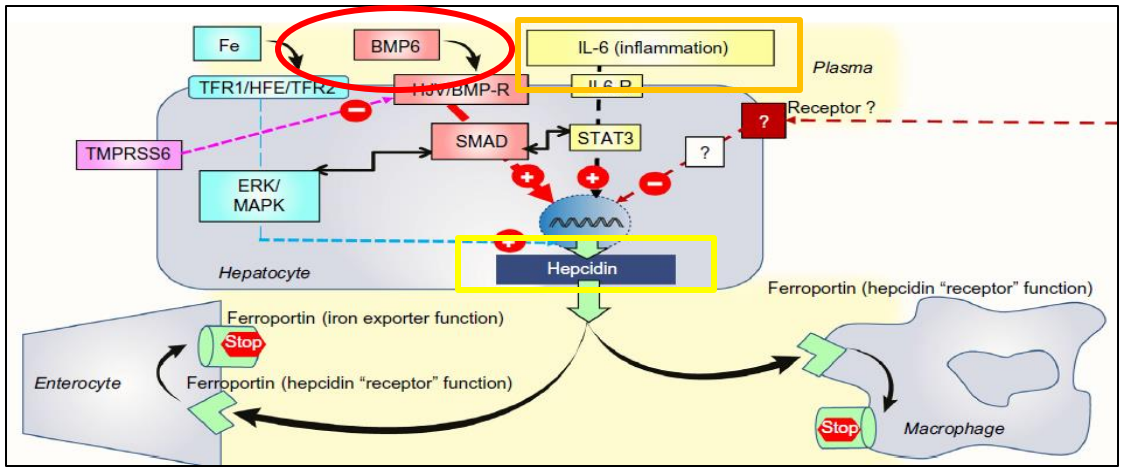
Unlike TFR1, TFR2 does not facilitate the direct entry of iron into cells. Instead, it functions as an iron **sensor**. When HFE is released from TFR1, it interacts with TFR2. This interaction signals that there is sufficient iron in the bloodstream and cells and this signal will lead to the release of hepcidin (particularly in hepatocytes) in order to balance the amount of iron in the body.

1



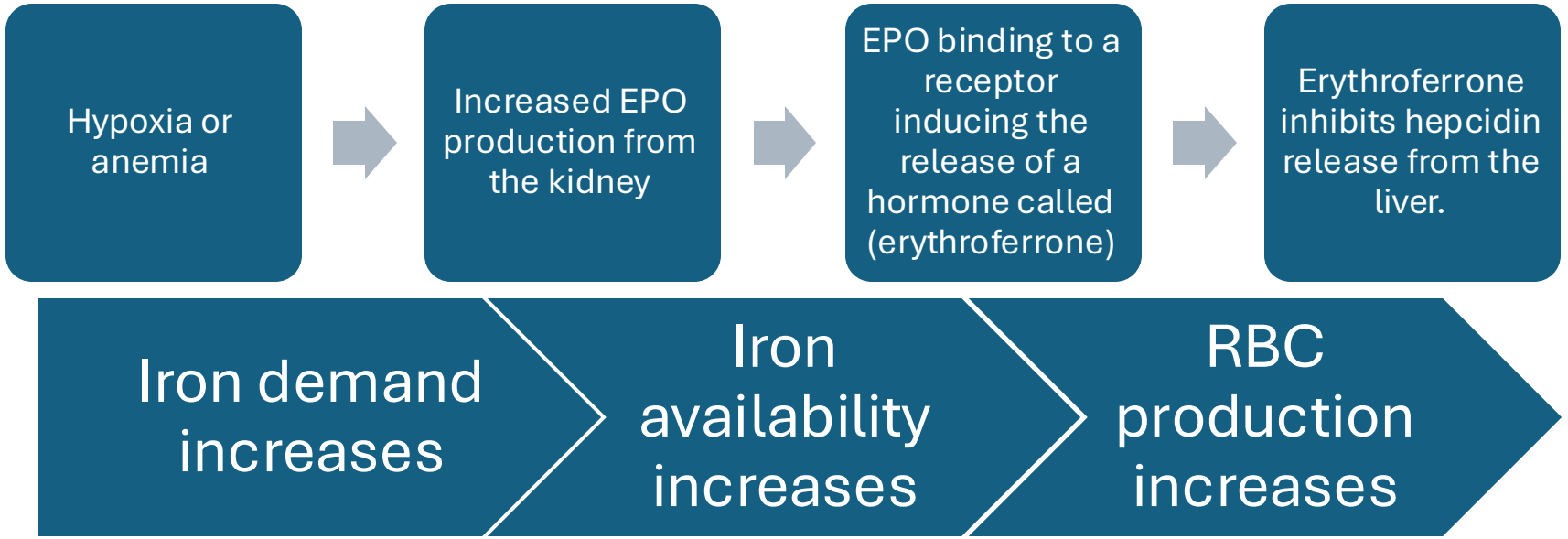
2 When the body experiences inflammation, the immune system releases a cytokine (IL-6). IL-6 binds to its specific receptors on cells, triggering a signaling cascade that leads to increased production of hepcidin, a key hormone in iron regulation. Hepcidin acts by binding to ferroportin leading to its degradation. As a result, iron is retained within cells (like macrophages and enterocytes) and less iron is released into the bloodstream. This process helps lower iron availability, which is a defensive mechanism because bacteria rely on iron for their growth and replication. By reducing serum iron levels, the body limits the nutrients available to it.

3 The BMP6 (Bone Morphogenetic Protein 6) pathway is another crucial mechanism in regulating hepcidin. When iron levels are high, BMP6 is activated and binds to its receptors on hepatocytes (BMPR). This interaction signals the cell to increase the synthesis of hepcidin. BMPR is bound to Hemojuvelin (HJV) which acts as a co-receptor in this pathway, enhancing the signal transduction. As hepcidin levels rise, ferroportin is degraded, reducing iron absorption from the intestines and release from stores



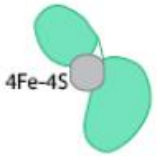
4

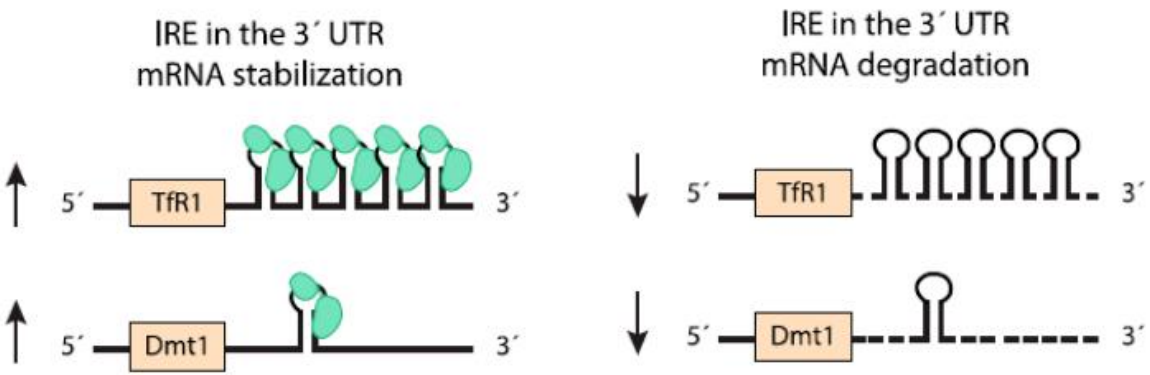
- The final mechanism is **hepcidin** being **negatively regulated** by **anemia and hypoxia**.

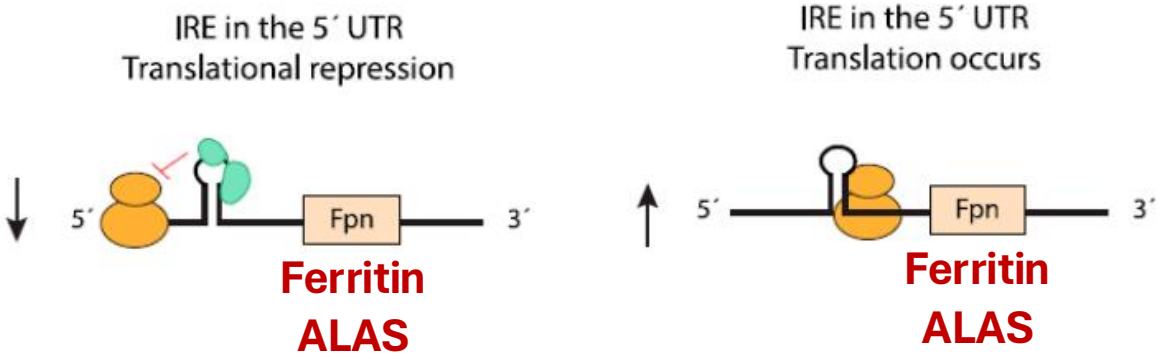


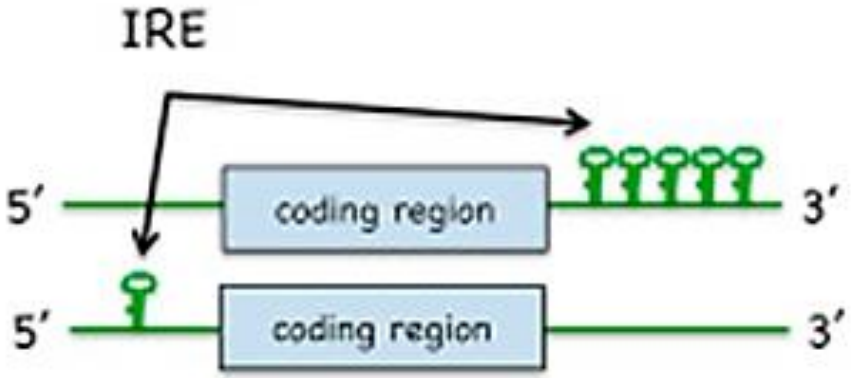
Post-transcriptionl regulation of expression

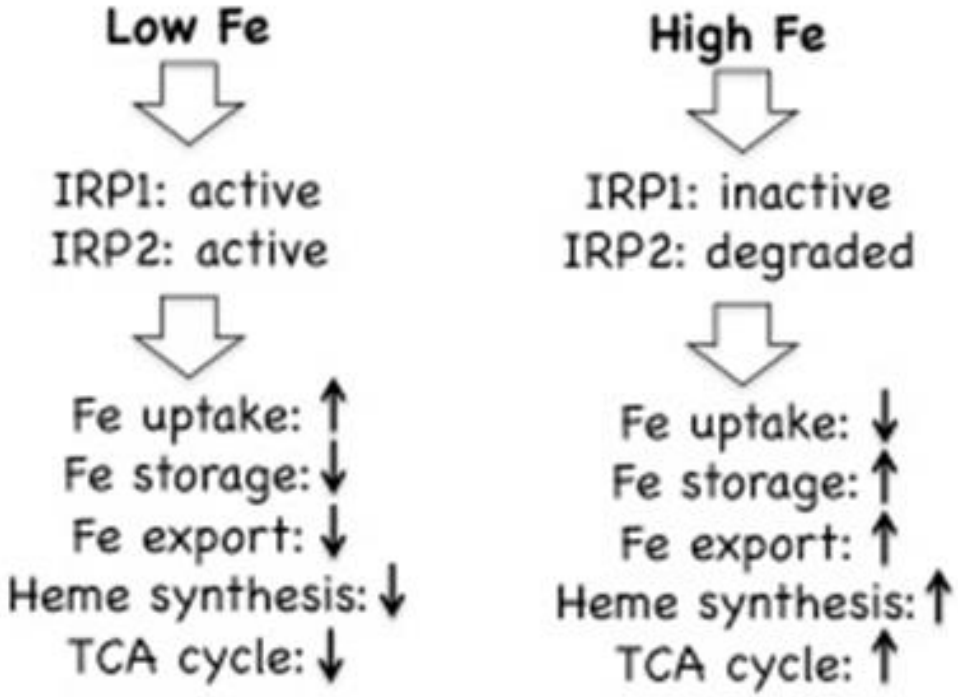
Iron-response element
Iron regulatory protein



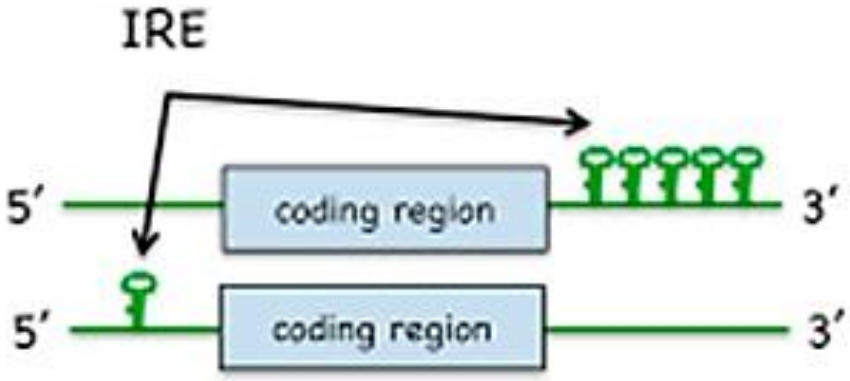








- In mRNAs or DNAs, there are untranslated areas of the gene called Untranslated regions (UTR), the could be in the 5’ region of the coding region (before it), or in the 3’ region of the coding region (after it).
- These UTRs might have what’s called elements.
- Elements are specific sequences used only for regulation and binding of transcription or translation factors.



- There are some elements called Iron response-regulatory elements (IRE), and they are the place of binding for iron regulatory proteins.
- There are also a regulatory protein called Iron Regulatory Protein (IRP).
- The genes of proteins that increase free iron entrance to the cell (like tfr,dmt) , the IREs are on the 3’ end of the mRNA (after the coding region), so when the IRP is bound to these IREs the mRNA will be more stable, therefore translated more.
- On the other hand, in the genes of proteins that store iron in cells and bind free iron in cells (like ferretin, Aminolevulinic acid synthase(ALAS)), the IREs are on the 5’ end of mRNA (before the coding region), so when the IRP is bound to these IREs, the translation is inhibited.
- This mechanism is important to prevent excess free iron in the cell because it’s toxic to the cell.

Read the 2 following slides to undersatnd it

- Our main focus is the Iron Regulatory Element (IRE), this element is found particularly at the Untranslated Region (UTR) of the mRNA either at the 5' or the 3' end.
- The translation for the specific molecules that we need for iron metabolism starts at the coding region.
- This coding region will produce either TfR 1, ferritin, DMT1 or ALAS.
- Remember that Ferritin and ALAS (enzyme used in heme synthesis) are needed when there are huge amounts of iron, and DMT 1 and TfR are needed when there are low amounts of iron and we need to get iron into the cell.

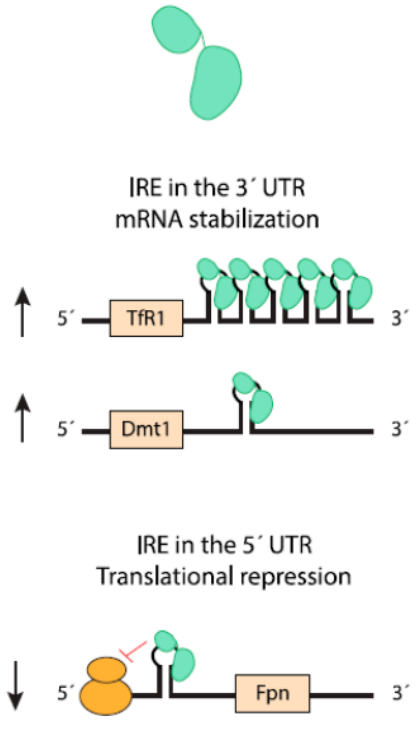
•Low amount of Iron:

1. Binding of IRP on the IRE found on the 3' UTR —> stabilizing mRNA —> increase in translation —> increase the amount of that product.

•Notice that because the amount of iron is low, the IRP was able to bound to the IRE at the 3' **stimulating the translation of TfR1** (transport of iron inside the cell) and **DMT1**(increase iron absorption), and that does make sense as we need these products to facilitate iron uptake).

2. Binding of IRP on the IRE found on the 5' UTR —> inhibit the translation of ALAS and Ferritin (to prevent unnecessary iron storage and usage).

ALAS and ferritin are used for iron metabolism and storage

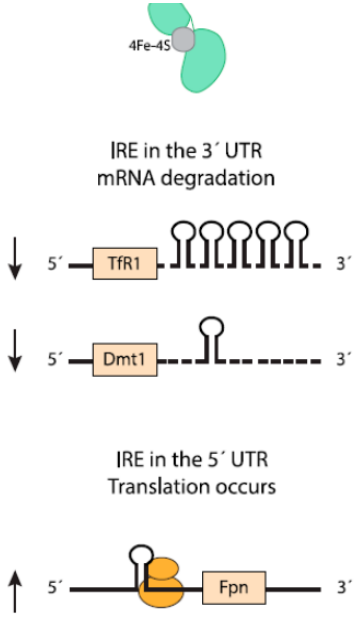


- High levels of Iron: (upregulation for storage and inhibition of absorption)

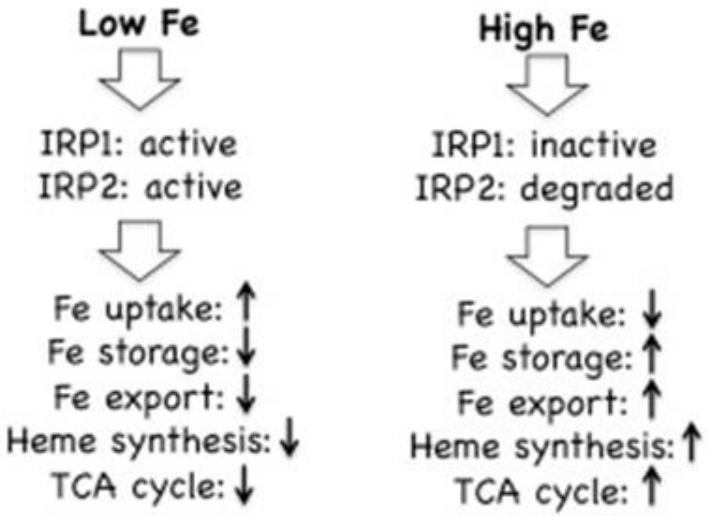
1. Iron will bind to the IRP and will remove it from the IREs

Now the IRP is removed from the 3' end —> mRNA is unstable —> degradation of mRNA —> low amounts of TfR1 and DMT1 (to limit iron absorption).

2. Iron will also remove the IRP from the 5' UTR —> the translation is resumed —> producing ferroportin, ferritin and ALAS, so that we can use the great amounts of iron in storage and metabolism.



- So that this mechanism is controlled by the iron levels in the cell, because when the iron level is high, iron binds the IRP releasing it from the IRE. And vice versa.



- Summary (from chatgpt) you can skip this slide!

The regulation of iron metabolism is controlled by the interaction between Iron Regulatory Proteins (IRPs) and Iron Regulatory Elements (IREs) located in the untranslated regions (UTRs) of mRNA.

- Low Iron Levels: IRPs bind to IREs in the UTRs of specific mRNAs to promote iron uptake and limit iron storage.

1. IRP binds to the 3' UTR of TfR1 and DMT1 mRNAs:
- Stabilizes the mRNA, preventing degradation.
- **Increases translation** of **TfR1 and DMT1** (proteins that help bring iron into the cell).

2. IRP binds to the 5' UTR of ferritin and ALAS mRNAs:
-**Blocks translation** initiation.
-Decreases production of ferritin (iron storage) and ALAS (involved in heme synthesis) preventing unnecessary iron storage and usage.

- High Iron Levels: Iron binds to IRPs, causing them to release from IREs. This promotes iron storage and inhibits further iron absorption.

1. IRP is removed from the 3' UTR of TfR1 and DMT1 mRNAs:
- The mRNA becomes unstable and degrades.
- **Reduces translation** of TfR1 and DMT1, limiting iron uptake (to prevent iron toxicity).

2. IRP is removed from the 5' UTR of ferritin, ALAS, and ferroportin mRNAs:
- **Translation resumes**.
- **Increases production** of ferritin (for iron storage), ALAS (for heme synthesis), and ferroportin.

Iron-related diseases

Iron-related diseases

- Hereditary hemochromatosis (HH) → High levels of iron
- Iron-deficiency anemia → Low levels of iron

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.

Hemosiderin : clusters of iron present in tissues caused by high iron level

Autosomal recessive : the mutation is present on both allels

Groups/classes of hereditary hemochromatosis

- Type 1 (hemochromatosis protein, HFE-dependent), HFE is the protein that interacts with TFR1
  - Most common
- Type 2A (HJV-dependent) , HJV is the protein that interacts with BMP6R
- Type 2B (hepcidin-dependent) , is related to Hepcidin production and release are mutated
- Type 3 (TfR2-dependent) ,TfR2 is the sensor of HFE
- Type 4 (ferroportin-dependent), Ferroportin is responsible for releasing iron from enterocytes and macrophages.
  - Autosomal dominant disorder (Type 4 hemochromatosis is the only one that can be autosomal dominant, the other types are always recessive).

Hemosiderin

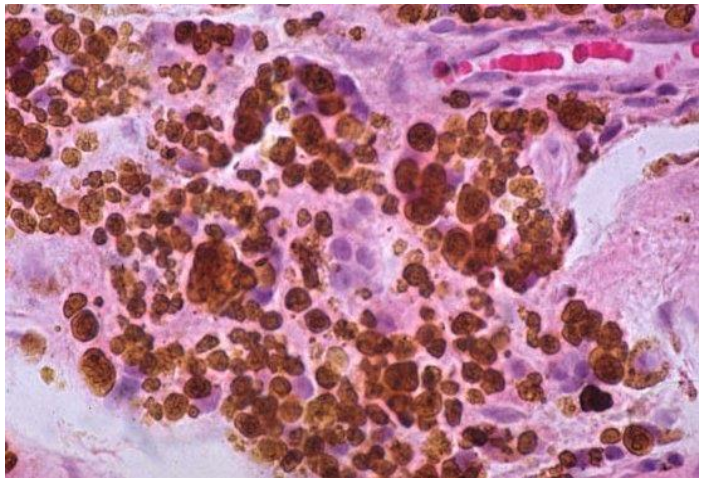
What is the risk for having high iron levels?

- The normal total body iron stores may range from 2 to 6 gm, but persons with hemochromatosis have much greater stores exceeding 50 gm.The normal level is 3 – 8 grams.
- 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.

  - The high level of iron in cells will force the hydrophobic regions of proteins to be exposed, this will lead to clustering of the proteins while bound to iron making hemosiderin.
  - Hemosiderin will cause damage to many tissues like

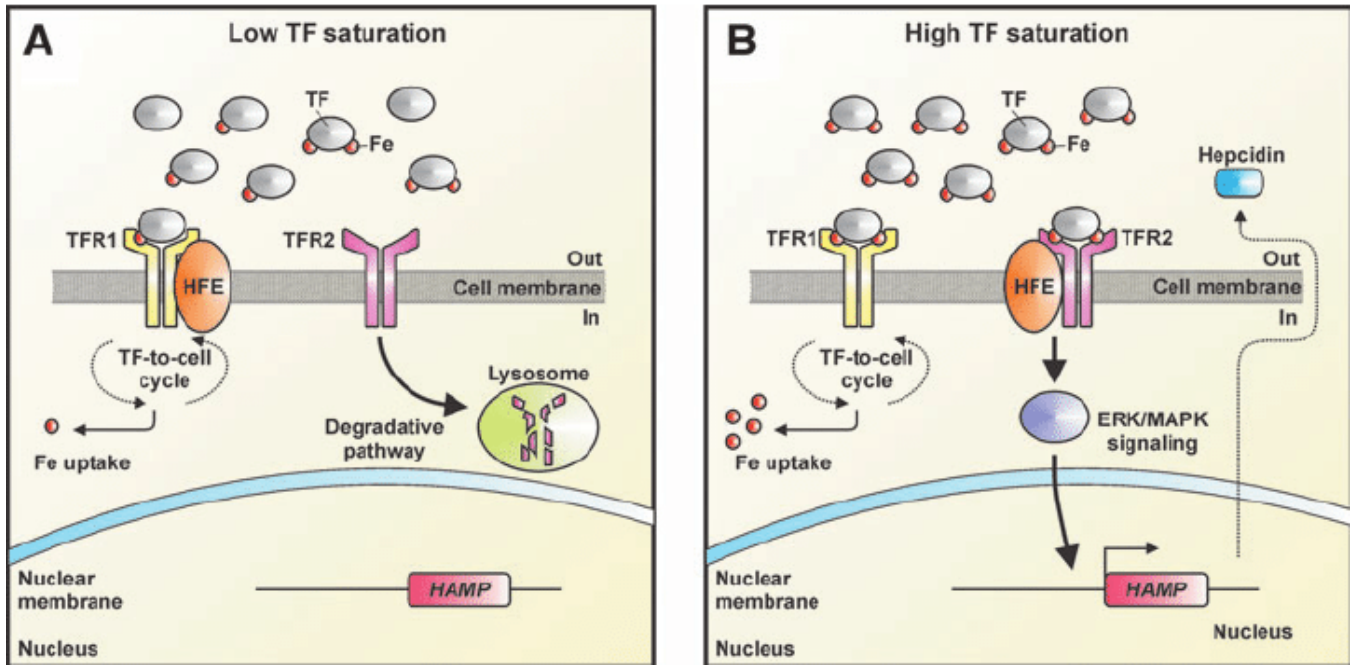
Affected organs and conditions

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



Regulation of transferrin receptor

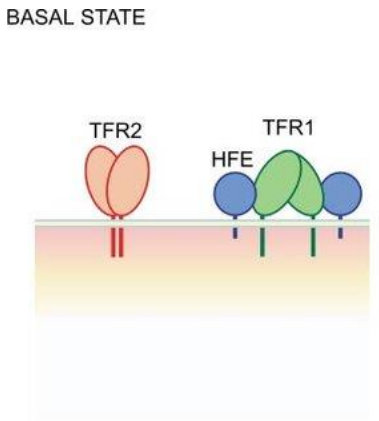
- HFE is a major histocompatibility complex (MHC) class-1 gene.
- Normal HFE complexes with TfR1 reducing iron transfer into cells.
- Mutated HFE has a reduced presence on membrane and/or lack of interaction with Tfr1, leading to the loss of inhibition of transferrin receptor, and, therefore, increased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

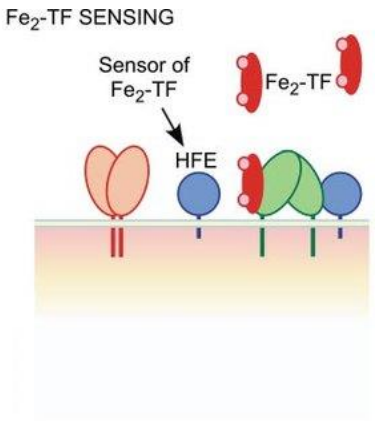


Mechanism of action

Reminding you of the mechanism

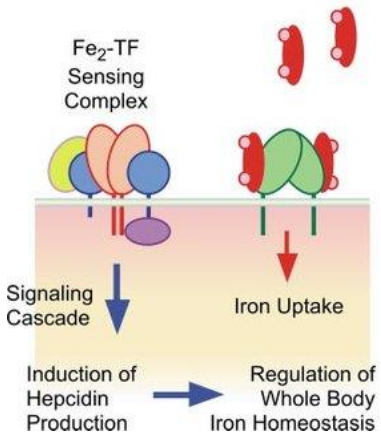
TFR1 exists as a complex with HFE at the plasma membrane during low or basal serum iron conditions.

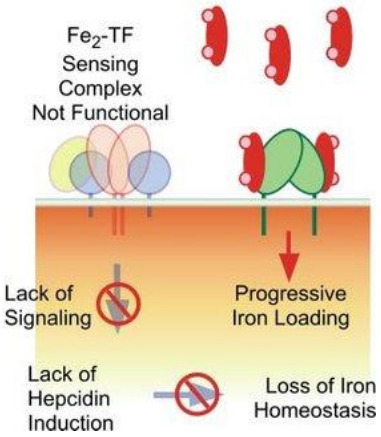




Serum Fe2 -TF competes with HFE for binding to TFR1. Increased serum transferrin saturation results in the dissociation of HFE from TFR1.

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

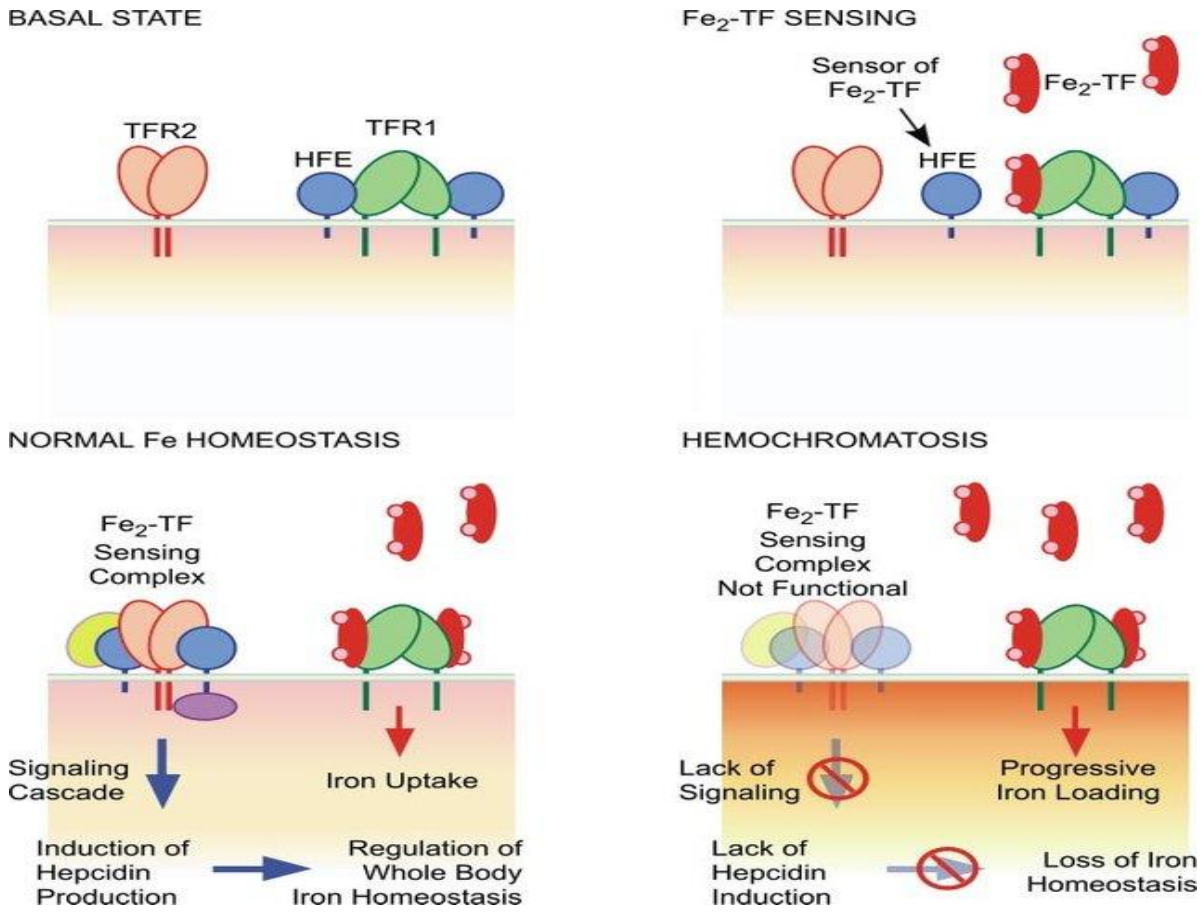




Mutation or absence of HFE or TFR2 prevents formation of a functional iron sensor and signal transduction effector complex leading to dysregulation of systemic iron homeostasis

- So in the case of absence of TfR2 or HFE, the sensing of iron is impaired therefore:

1. The cell can't control the amount of iron that is getting inside it.
2. The release of hepcidin is impaired, therefore the amount of iron absorbed from the intestines is not controlled, therefore the level of iron in the body elevates uncontrollably.

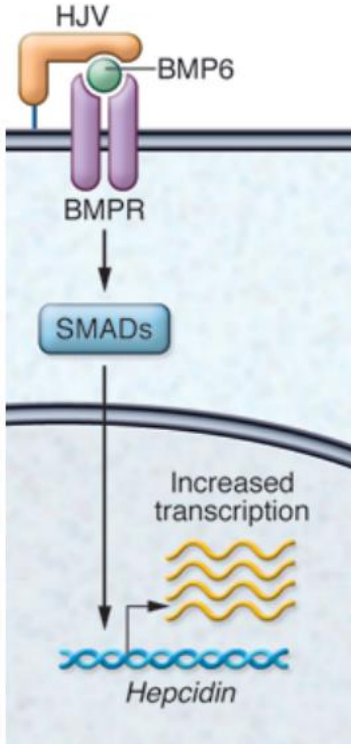


Juvenile hemochromatosis

Juvenile = children or teenagers

It has 2 subtypes, a and b

- 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.



- Notice that BMP6 (a protein that is released when there are high levels of iron) is associated with the BMPR, this receptor is dependent on the functional hemojuvelin, so when HJV is defective the receptor won't be functioning, and the signal won't enter the cell. This will result in decreased transcription of hepcidin. In type 2B, the signal is working in a good manner but the hepcidin that is produced is defective itself.

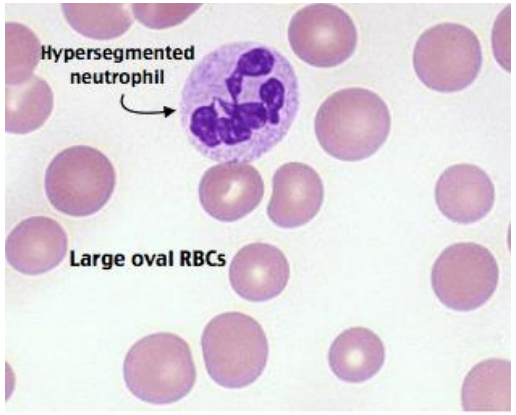
➢ **To Sumup**:

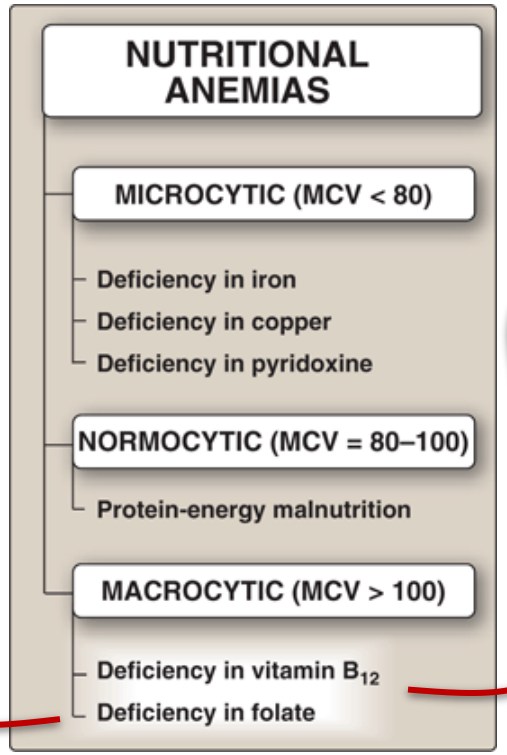
- In type 2A, HJV is impaired, therefore the signal is not initiated in the first place.
- While in type 2B, the signal in conducted normally, but the production of hepcidin is impaired.
- Remember that hepcidin is needed to control the iron levels in the body by lowering absorption and release from enterocytes and macrophages.

Iron-deficiency anemia

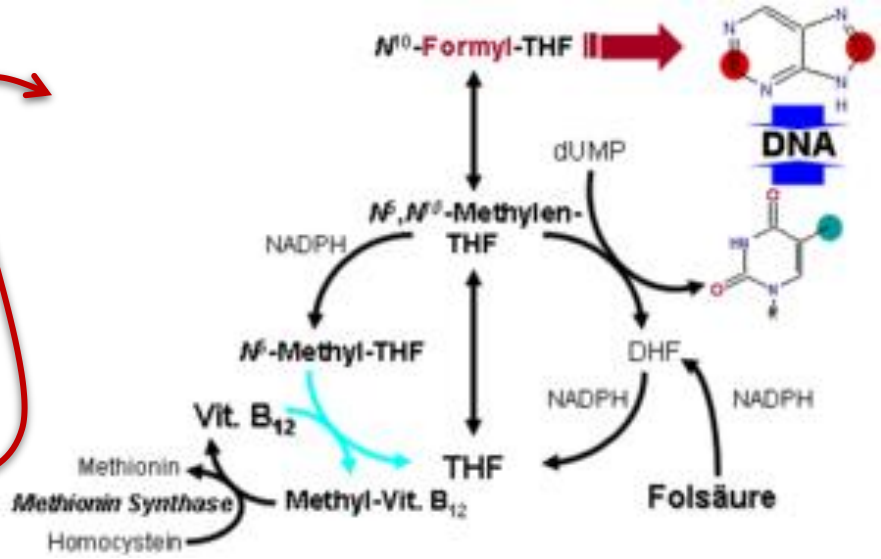
- Anemias are characterized by a deficiency in the number of mature erythrocytes in the circulation, lowering the oxygen-carrying capacity of the blood, causing tissue hypoxia, and clinical symptoms such as fatigue, weakness, increased cardiac output, as well as increased morbidity and mortality.

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



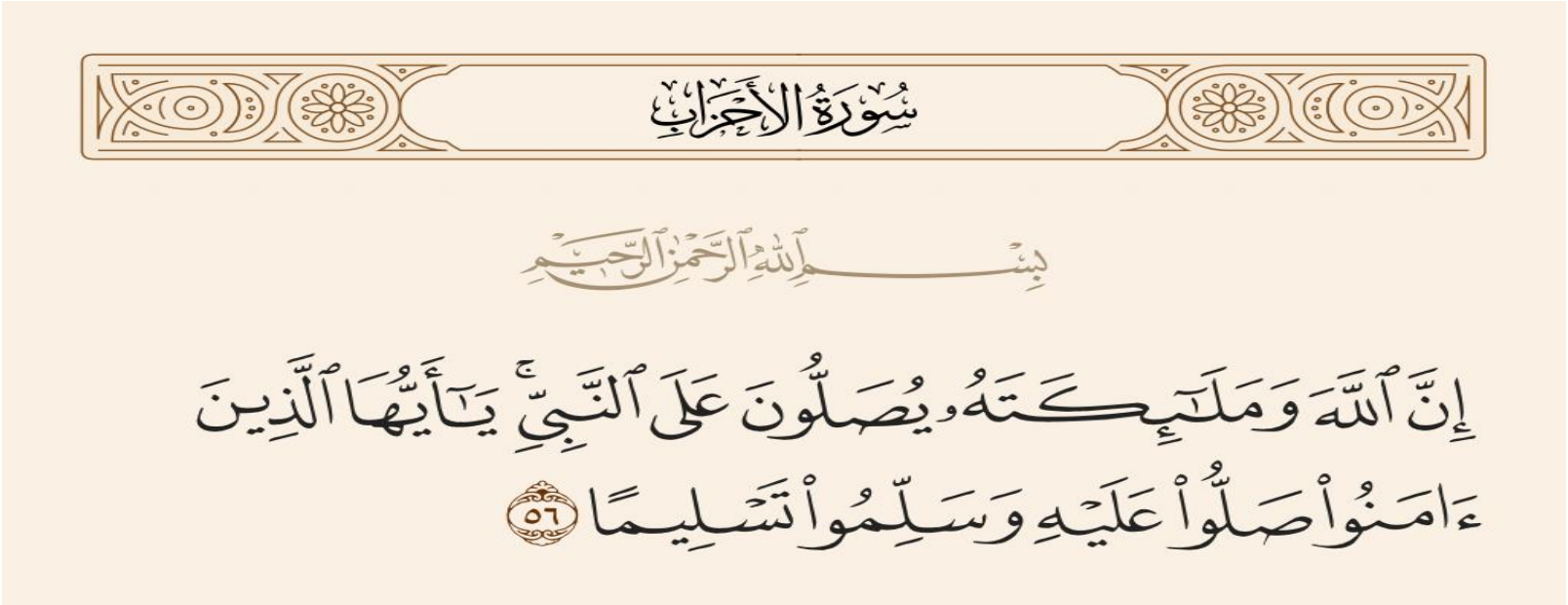


Folate is not regenerated



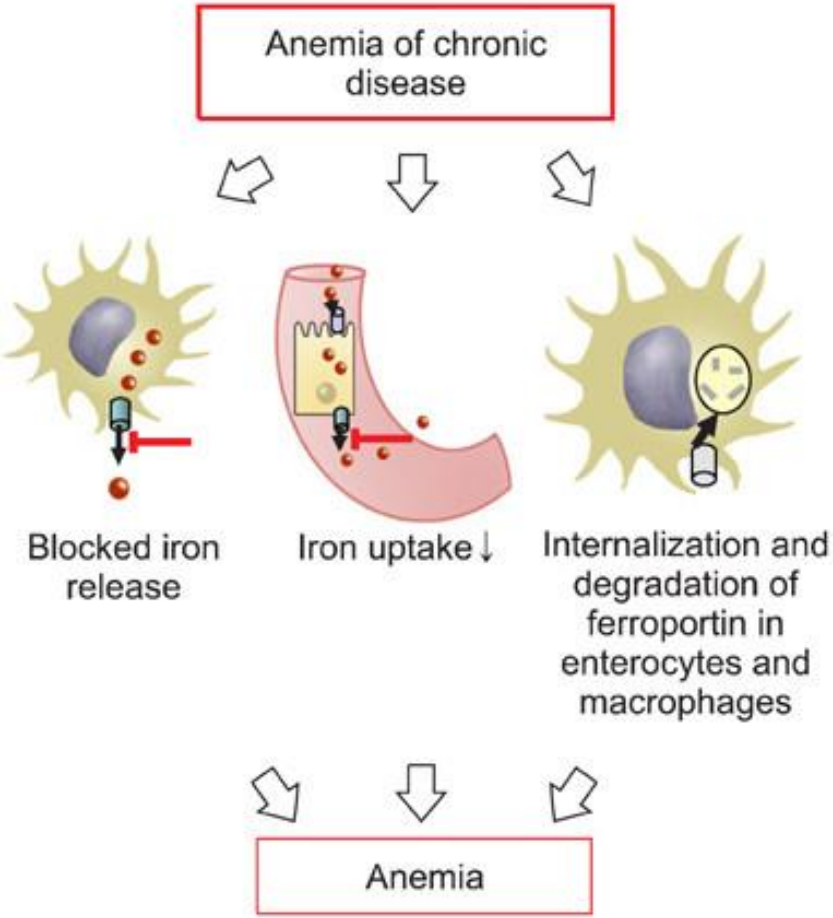
•Deficiency in vitamin B12 or folate are common causes for anemia (IDA), in this case we will have macrocytic cells, megaloblasts, as they will not be able to divide.

•Vitamin B12 and Folate are important for the production of nucleotides which is dependent on the presence of THF(tetrahydrofolate) and the renewal of THF depends on vitamin B12. So, the deficiency in these vitamins will result in defective DNA synthesis.



Anemia of chronic disease

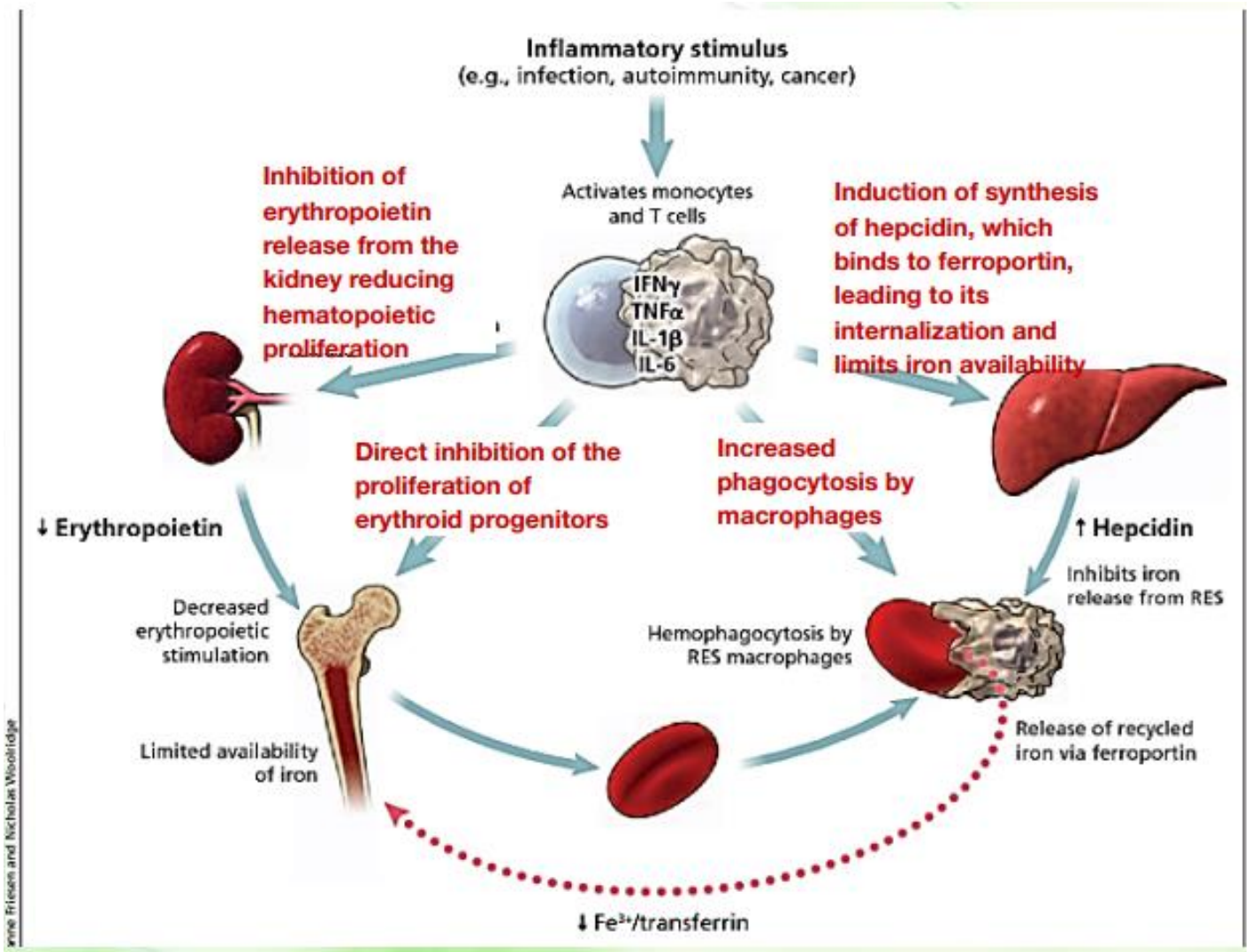
- Causes: chronic kidney disease, chronic infections and chronic inflammatory diseases
- Inflammatory cytokines → increased hepcidin production by hepatocytes → downregulation of ferroportin expression in major iron-exporting cells such as macrophages, duodenal enterocytes, and hepatocytes → decreased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



Chronic disease could cause anemia

- For example, in case of chronic inflammation, there is a chronic elevation in inflammatory cytokines (IL-6) which will lead to a constant high level of hepcidin, which as we mentioned before, will eventually lead to low level of iron in the body, especially the bone marrow, which will lower the production of RBCs.
- This is common in developed countries who has a relatively weaker immunity because they are less frequently exposed to antigens that develops their immunity, which makes them prone to chronic inflammatory diseases in contrast to developing countries.

Additional molecular consequences of chronic inflammation



اللهم انصر إخواننا المجاهدين في غزة وفلسطين، اللهم كن لهم ولا تكن
اللهم انتقم من أعدائهم واقذف الرعب في قلوبهم عليهم ،

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!