



Anemia sideropenica e carenza di ferro: un problema globale per cui è necessaria una diagnosi precisa

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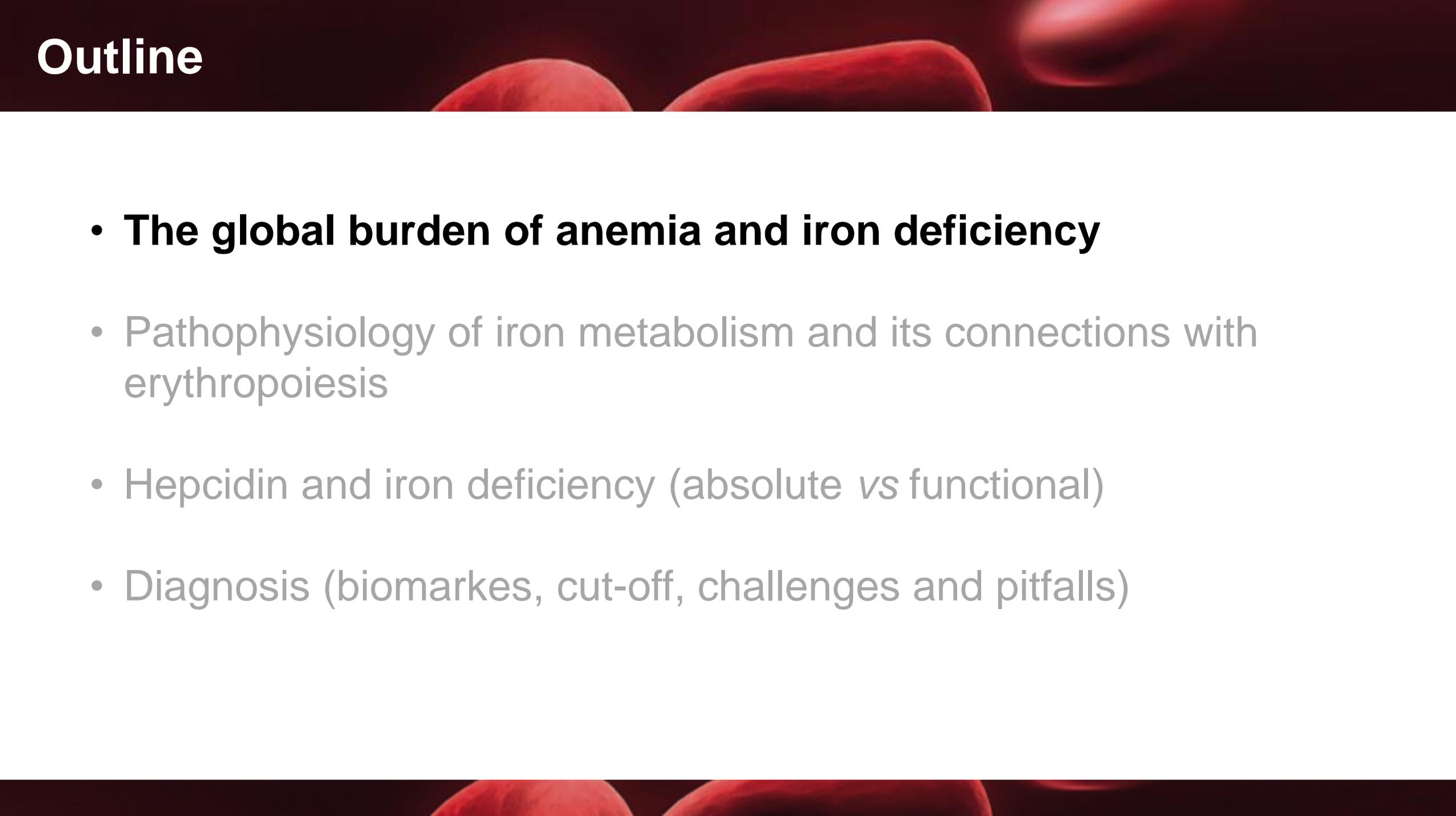
Disclosures

- Sanofi Genzyme

Outline

- The global burden of anemia and iron deficiency
- Pathophysiology of iron metabolism and its connections with erythropoiesis
- Hepcidin and iron deficiency (absolute vs functional)
- Diagnosis (biomarkers, cut-off, challenges and pitfalls)

Outline

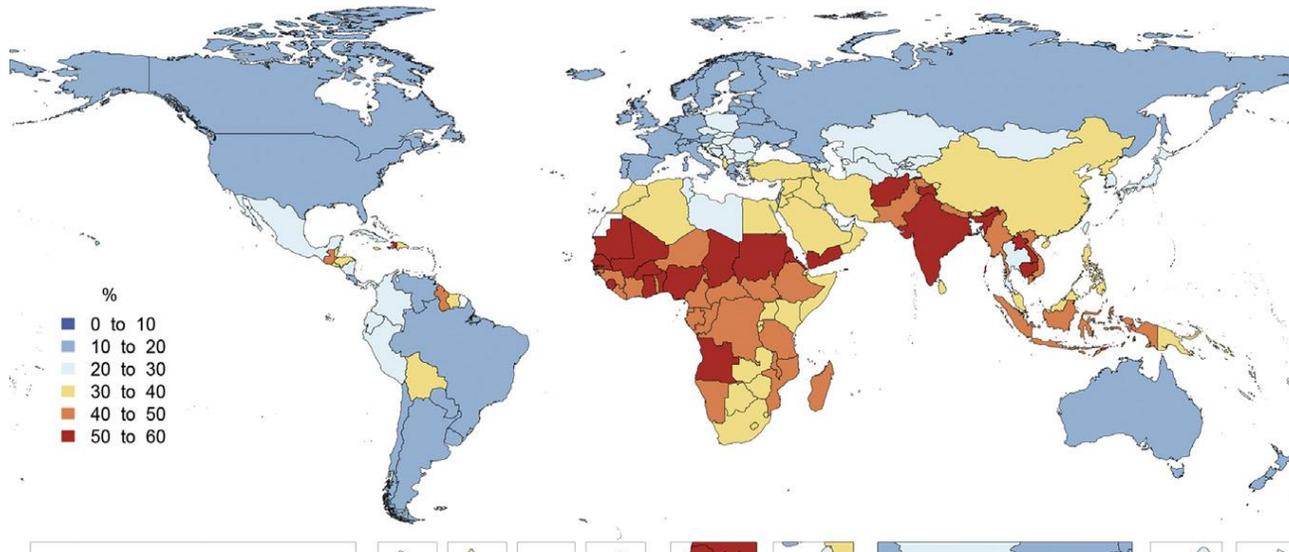
A decorative background image showing several red blood cells in a dark red, almost black, environment. The cells are biconcave and have a smooth, slightly reflective surface. They are scattered across the top and bottom of the slide, with some appearing in the foreground and others in the background, creating a sense of depth.

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Anemia burden is high, affecting 27% of the world's population

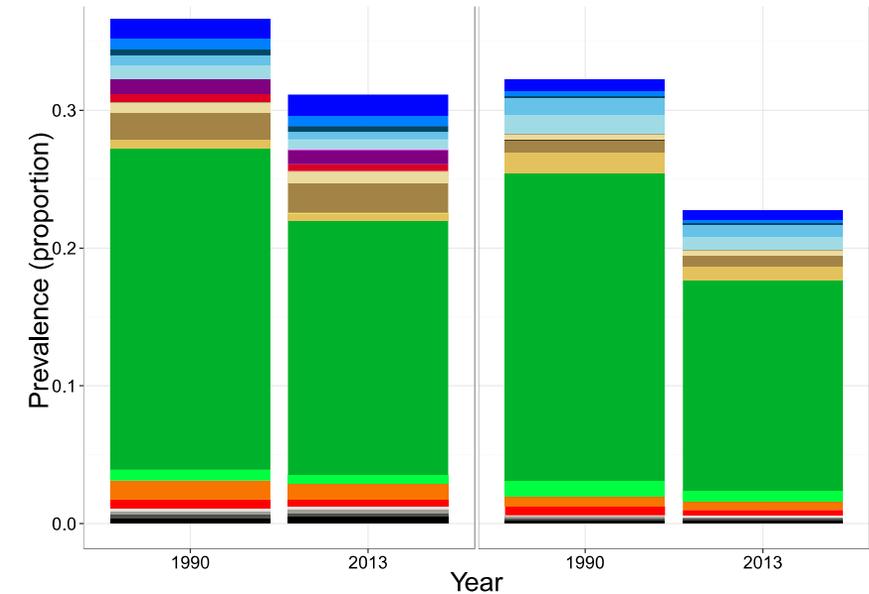
Iron-deficiency is the dominant cause ($\geq 60\%$) of anemia globally

Anemia prevalence in 2013, all ages



Females

Males



Iron deficiency anemia

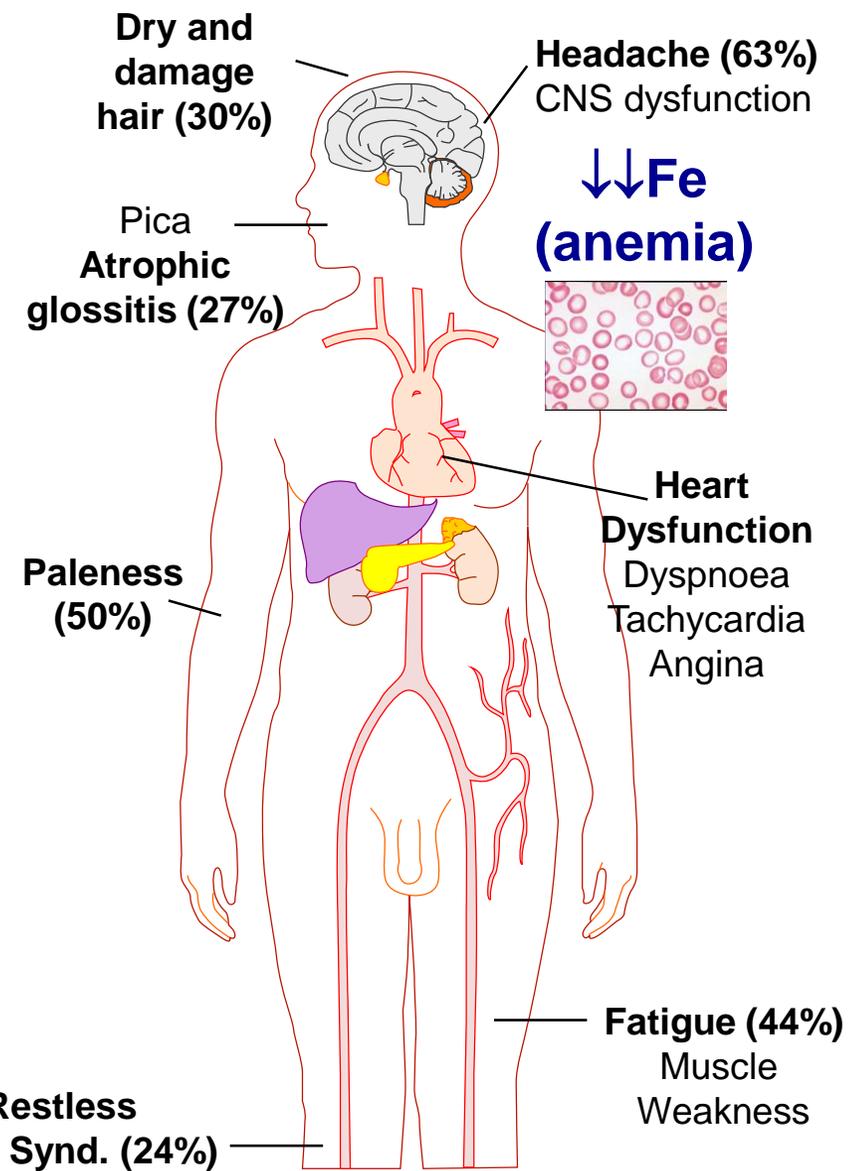
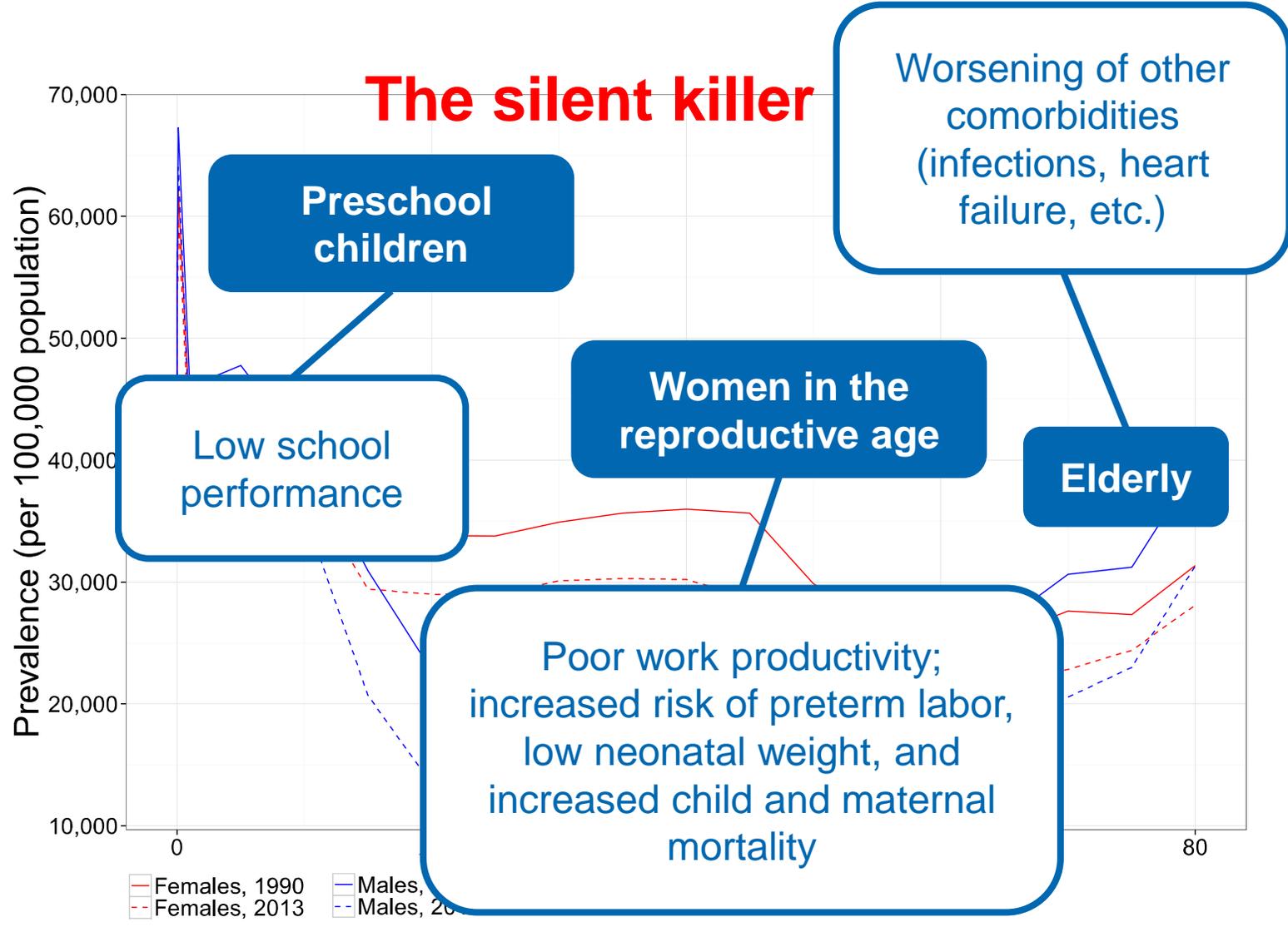
> 2 billions people globally

Mainly related to socio-economics conditions

In Italy ~10% adults

65 millions (or 8%) YLDS in 2013

Children aged 0–5 years, women of childbearing age, and pregnant women are particularly at risk



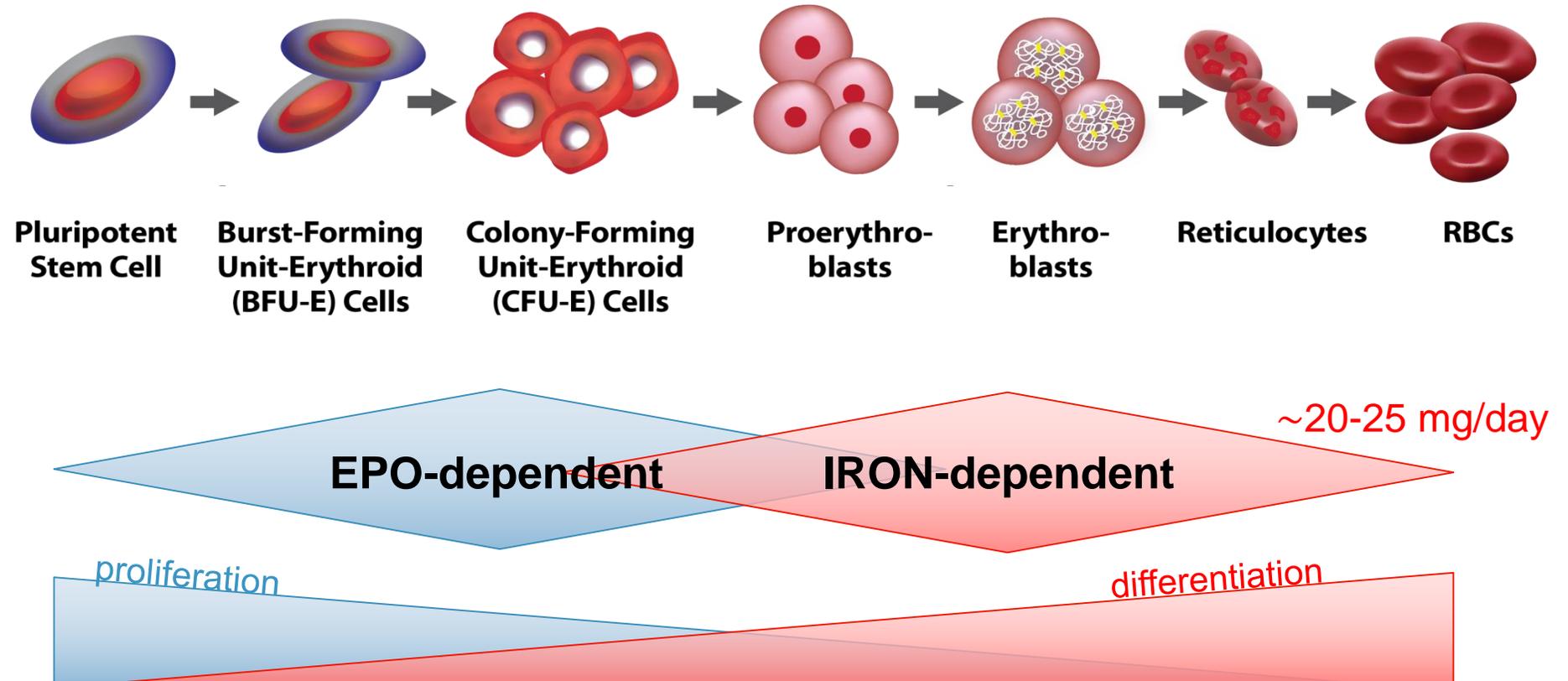
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Erythropoiesis is the greatest consumer (80%) of circulating iron

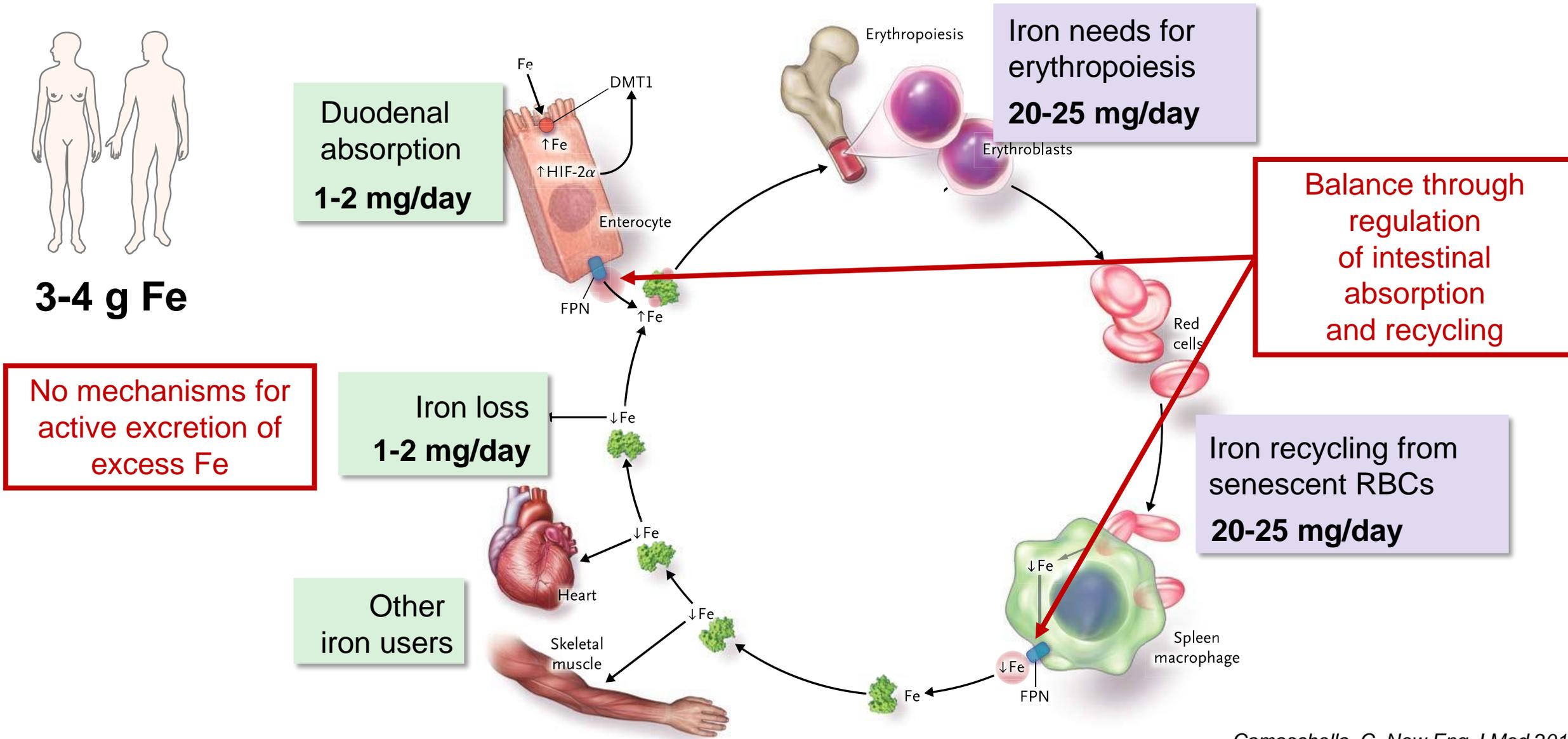
Iron is essential:

- Respiration
- Energy production
- Enzymes function
- DNA synthesis
- Cell proliferation
- **Erythropoiesis**
- ...

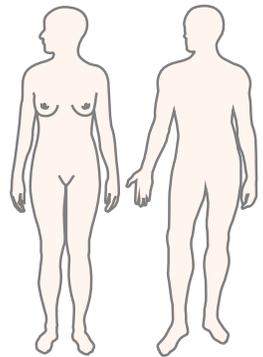


- In healthy humans, steady-state erythropoiesis involves the production of **200 billion new RBCs per day** (~2.4 million/second)

Most of the iron needed daily is provided through recycling by macrophages



Body iron content is tightly regulated by the liver hormone hepcidin



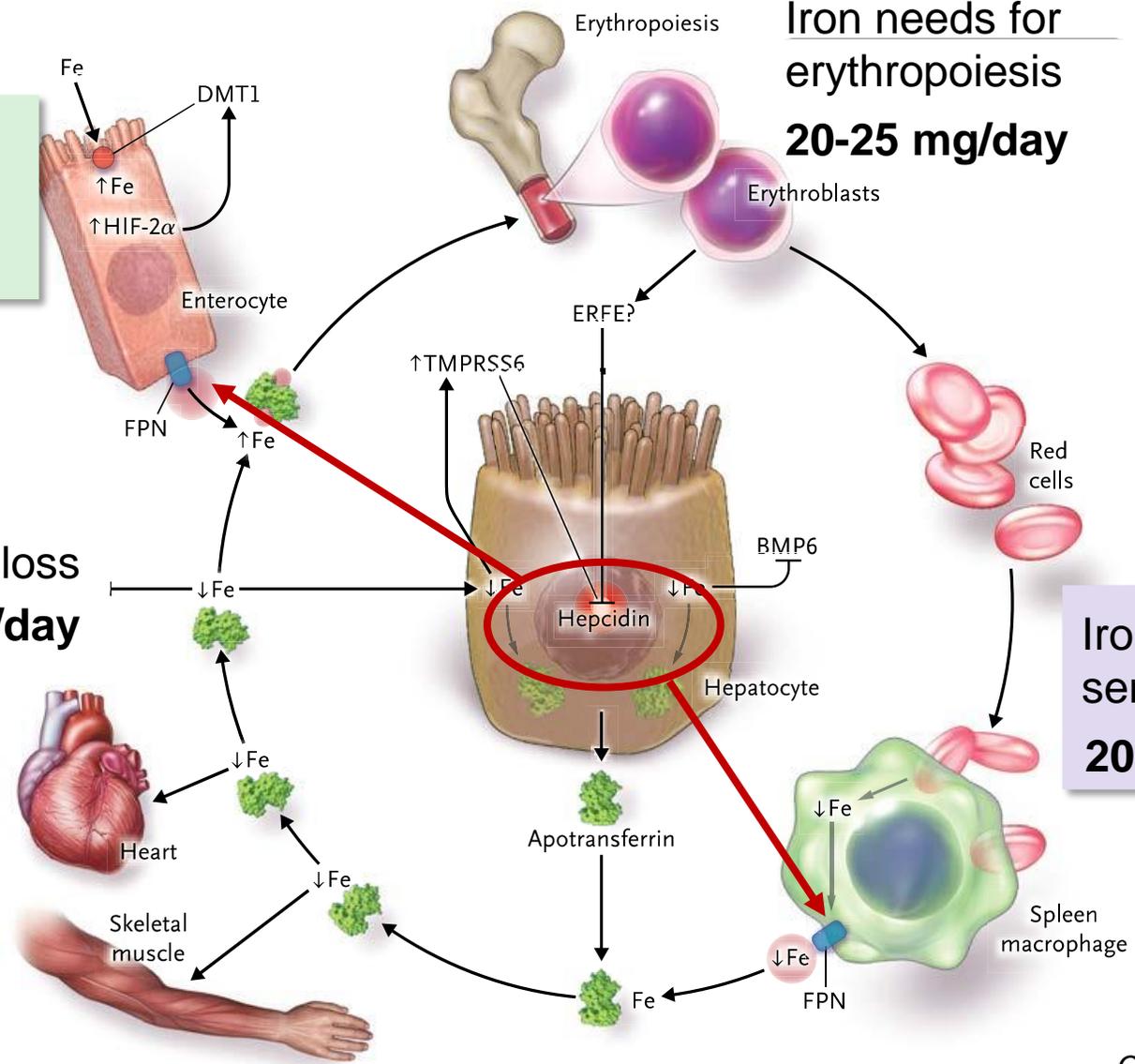
3-4 g Fe

Duodenal absorption
1-2 mg/day

No mechanisms for active excretion of excess Fe

Iron loss
1-2 mg/day

Other iron users

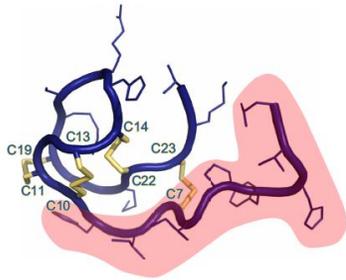


Iron needs for erythropoiesis
20-25 mg/day

Balance through regulation of intestinal absorption and recycling

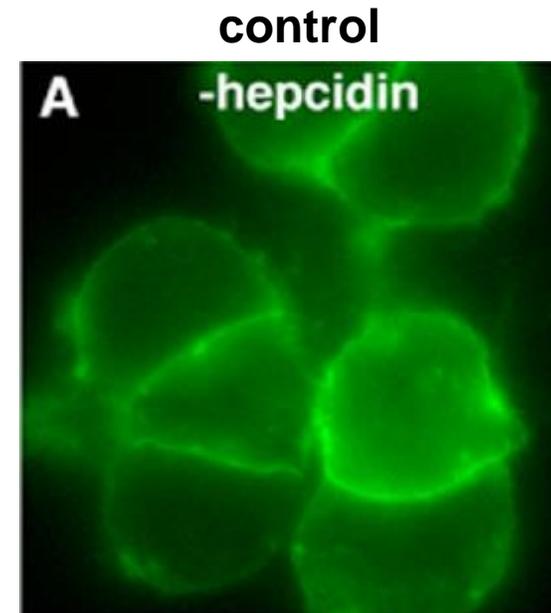
Iron recycling from senescent RBCs
20-25 mg/day

The main role of hepcidin is to control surface expression of FPN



HEP-(atic) CIDIN (antimicrobial)

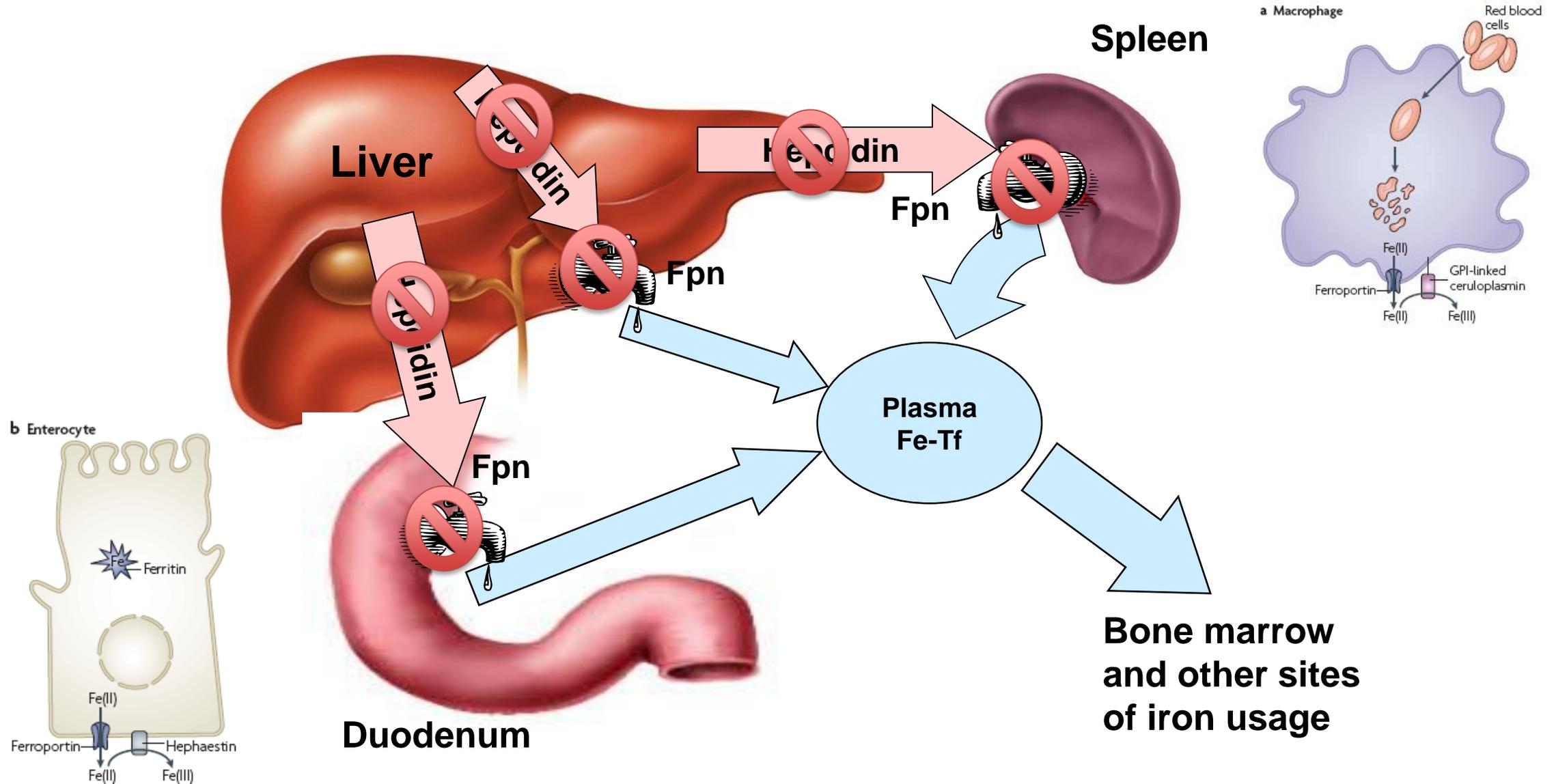
- small (25 aa) peptide mainly produced by the liver
- defensin-like (innate immunity-related peptides with natural antimicrobial activity)
- interact with its receptor (ferroportin, the only known iron exporter from the cells, ubiquitous but highly expressed in duodenal cells, macrophages, hepatocytes)



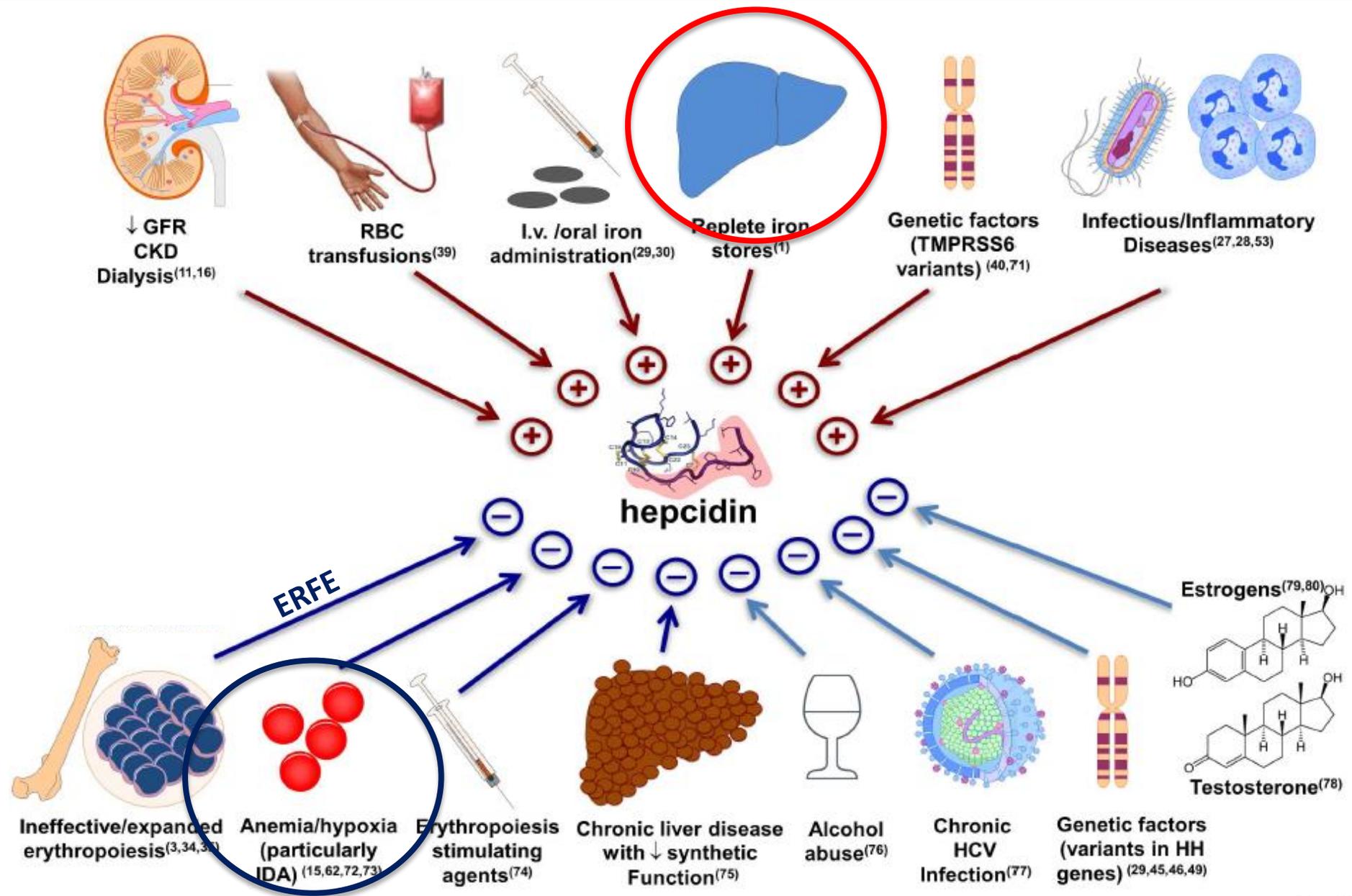
FPN localized on cell
membrane

↑ Iron export

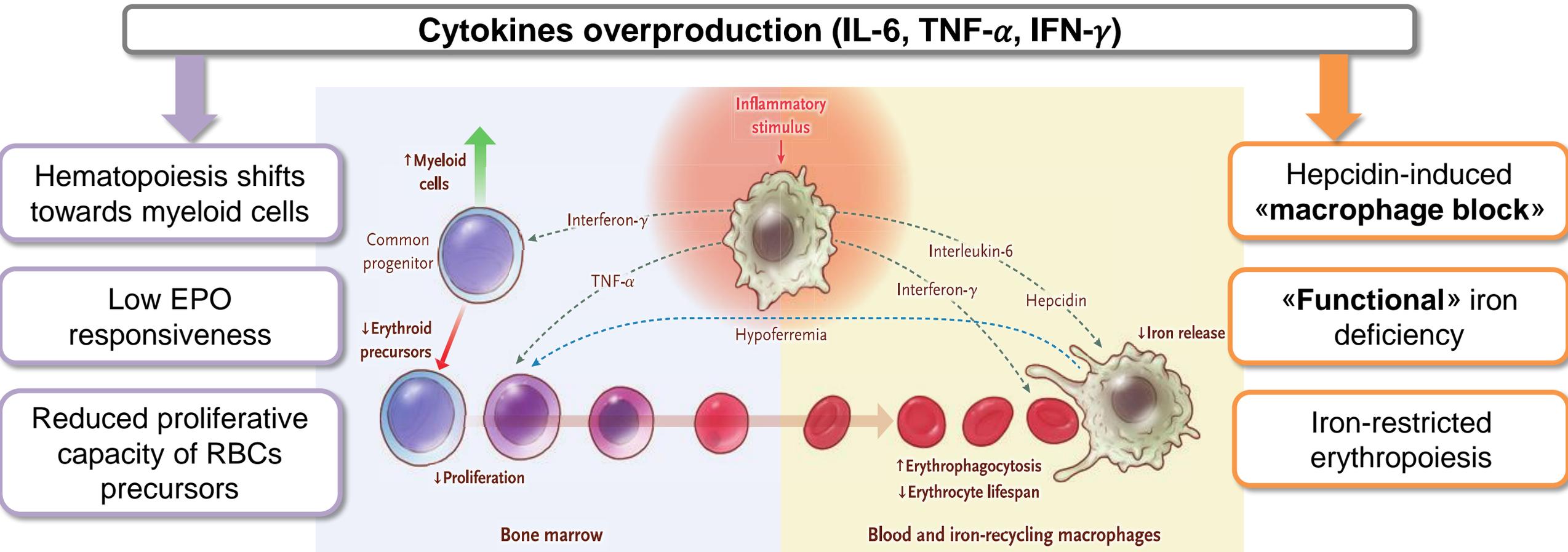
Hepcidin-ferroportin axis regulates the flow of iron into plasma, and thereby regulates the distribution of iron in the body



Hepcidin is regulated by multiple (contrasting) stimuli



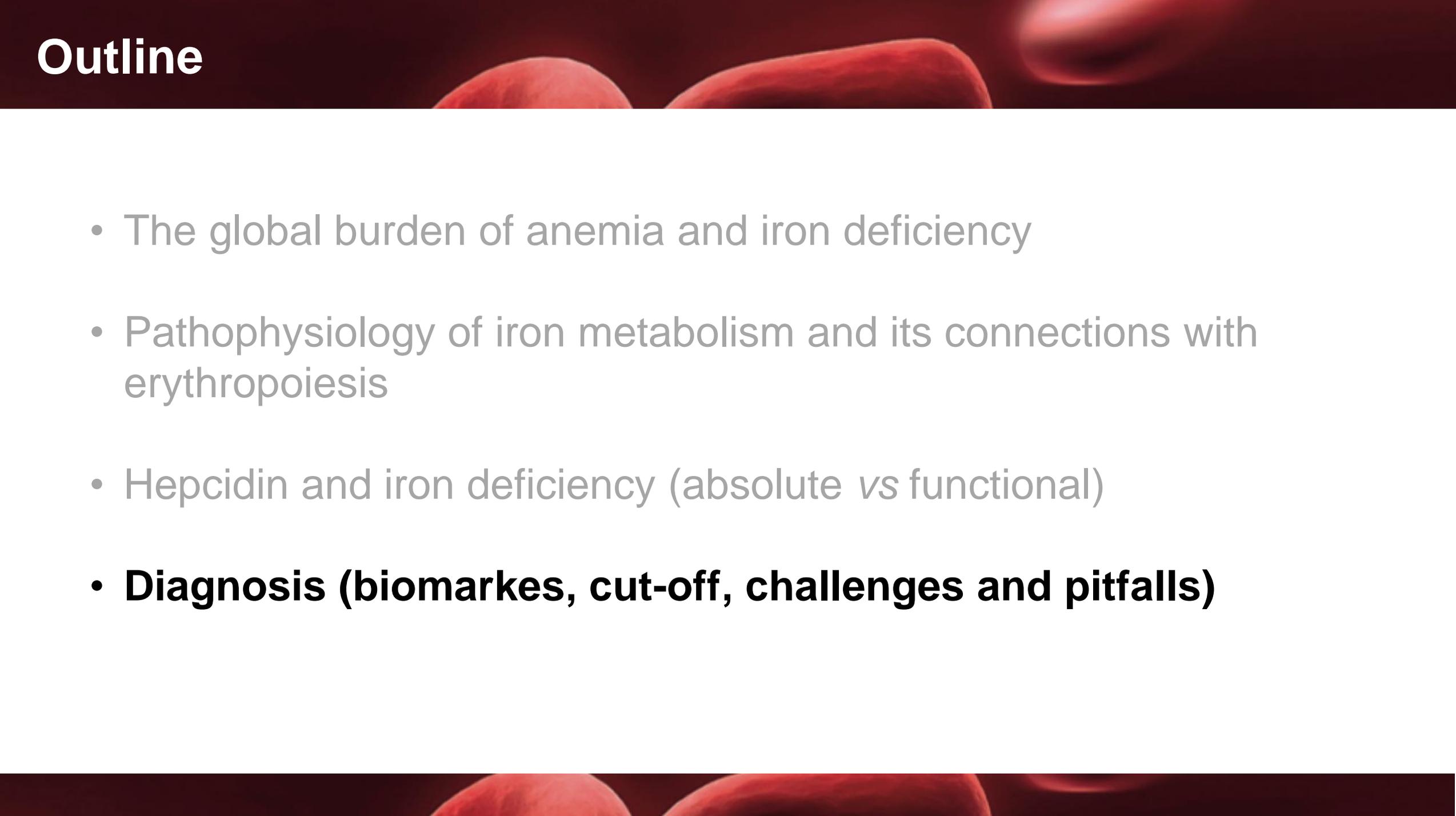
High hepcidin levels, induced by inflammation (IL-6), plays a central role in the pathogenesis of anemia of chronic disease



Anemia of inflammation (AI)

1° cause of anemia in hospitalized patients!

Outline

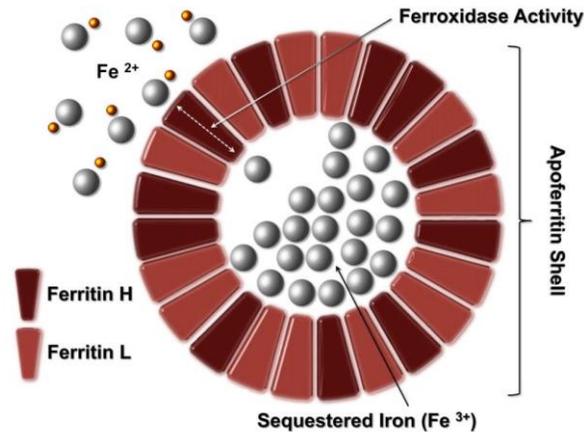
A microscopic view of several red blood cells, showing their characteristic biconcave disc shape and reddish color. The cells are arranged in a cluster, with some in the foreground and others slightly out of focus in the background.

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Classical markers of iron deficiency anemia

IDA = anemia (Hb < 12 g/dl females, < 13 males)
with ↓ MCH (< 26 pg), ↓ MCV (< 80 fl), and ↓ reticulocytes

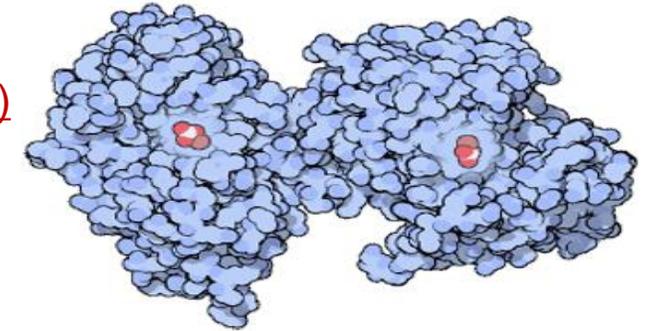
Ferritin



- Intracellular (ubiquitous)
- Function: storage
- Binds up to 4,500 Fe atoms
- trace (ng/ml) in serum
- **Ferritin < 30 ng/ml excellent marker of "pure" absolute iron deficiency**
- Acute phase reactant

TSAT

$$\text{TSAT\%} = \frac{\text{serum iron } (\mu\text{g/dl})}{\text{Tf (g/l)} \times 1,42}$$



- Extracellular
- Function: transport
- Binds 2 Fe atoms
- Abundant (g/l) in serum
- **TSAT < 20% = iron restricted erythropoiesis likely**

The diagnosis of iron deficiency anemia in the context of inflammation is challenging (but possible!)

- **Higher ferritin cut-off \pm TSAT <20%**
e.g., < 100 ng/ml or <300 ng/ml if TSAT<20% in chronic heart failure
- **Proportion of hypochromic RBCs**
useful in CKD; >6% indicative of IDA
- **Reticulocyte Hb content (CHr or Ret-He)**
useful in CKD; diagnostic if <27.2 pg;
poor sensibility in thalassemia and \uparrow MCV
- **sTfR; sTfR/Log Ferritin ratio**
absence of standardized cut-off, inflammation?
useful for distinguishing IDA and AI; e.g. ratio<1 AI; ratio>2-3 IDA
- **Bone marrow aspiration**
gold standard, but invasive and expensive

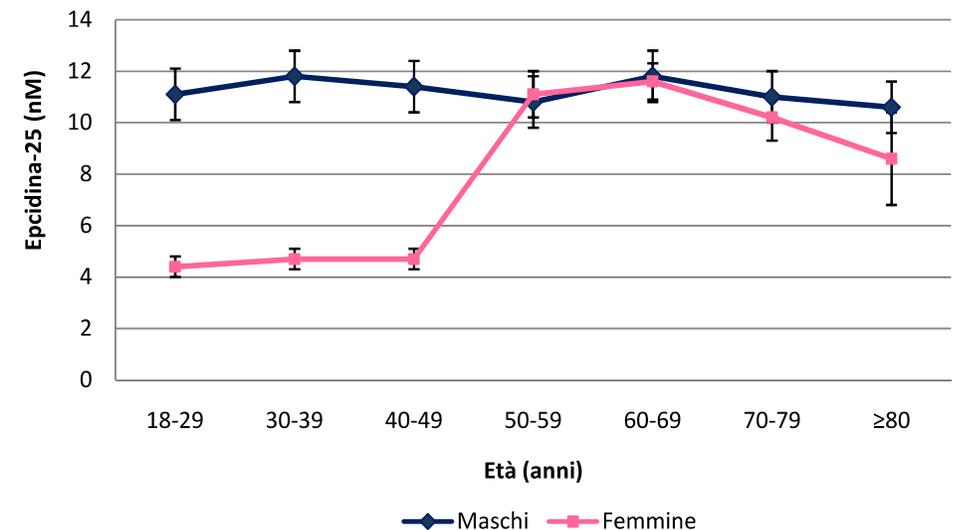
Parameter	Value	Reference Range	Alert
TSAT	18%	20-50%	
Ferritin	120 ng/ml	30-400 ng/ml	
CHr	28.5 pg	27.2-38.1 pg	
Ret-He	27.2 pg	27.2-38.1 pg	
sTfR	1.2	0.5-1.5	
sTfR/Log Ferritin ratio	1.2	0.5-1.5	

Hepcidin measurement in clinical practice

Most promising applications

6. Evaluation of suspected IRIDA	Virtually diagnostic in an appropriate clinical context
7. Evaluation of IO disorders	For example, ferroportin disease due to hepcidin resistant mutations (see text)
8. Diagnosis of concomitant ID in patients with ACD	Promising reports in rheumatoid arthritis and inflammatory bowel disease patients, and in African children
9. Guide for iron therapy	For example, selection of patients for direct IV supplementation; oral administration in children from developing countries with high prevalence of infectious diseases (see text)
10. Monitoring of treatments targeting the hepcidin/ferroportin axis	To be confirmed by further studies

- Refer to **age- and sex-specific** ranges
- Interpret the value into a **minimum laboratory context** (full blood count, ferritin, transferrin saturation, C reactive protein, serum creatinine, liver function test)
- Be aware of **many potential confounders/comorbidities** in the individual patient



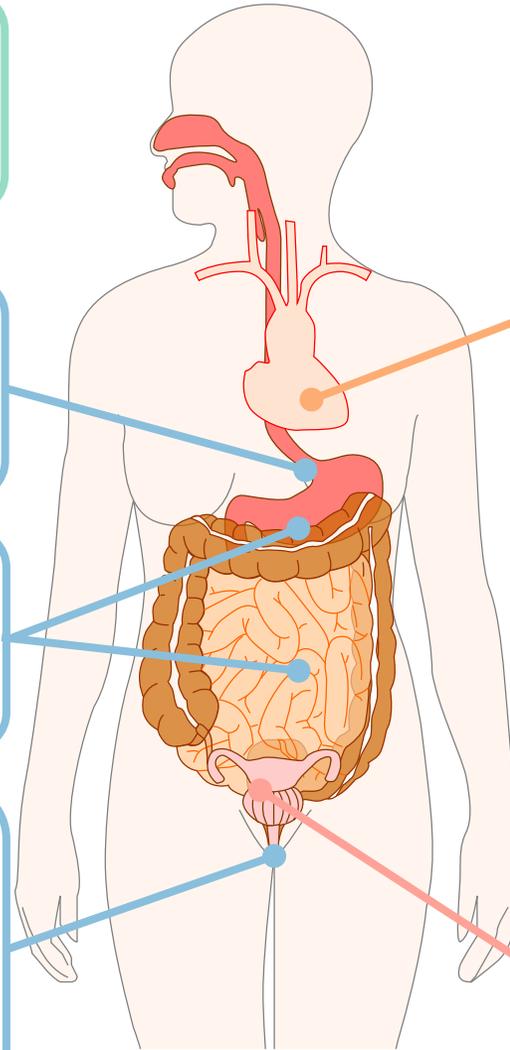
Management of ID/IDA requires a systematic search for the causes (physiologic and pathologic)

Increased demand: infancy, rapid growth (adolescence), menstrual blood loss, pregnancy, blood donation, elite athletes

Upper GI blood losses: esophagitis, gastritis, ulcers, cancer* or pre-malignant lesions, (antithrombotic drugs, NSAIDs)

Malabsorption: HP infection, atrophic gastritis, celiac disease, inflammatory bowel disease*, hookworm infest., drugs (e.g. PPI)

Lower GI blood losses: colon-rectal cancer or pre-malignant polyps, IBD*, ano-rectal lesions (e.g. hemorrhoids), angiodysplasia, hookworm infestation, (antithrombotic drugs)



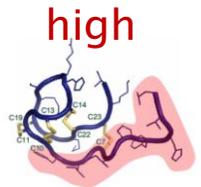
Insufficient intake: poverty, malnutrition, diet (e.g. vegeratian, vegan, iron-poor)

Chronic hemolysis: e.g. damage heart valves, paroxysmal nocturnal hemoglobinuria, mycroangiopathic hemolysis

Genetic: IRIDA (TMPRSS6 mutations)

Iron-restricted erythropoiesis:** inflammation, ESAs, CKD

Genitourinary blood losses: heavy menses, menorrhagia, march hemoglobinuria



*also anemia of inflammation; ** functional and absolute ID may coexist

Concluding remarks

- ID/IDA are global health problems and common medical conditions in everyday clinical practice
- Associated with multiple adverse outcomes in all age groups
- Diagnosis is based on ferritin <30 ng/ml \pm TSAT $<20\%$ (but determination of iron status may be more challenging if inflammation coexists \rightarrow it is necessary to consider more indicators)
- Detection of causes is mandatory in order to:
 - recognize evolutionary and potentially fatal diseases (e.g. GI cancer)
 - improve symptoms and patient's quality of life
 - avoid relapse after the treatment
 - ensure optimal treatment's efficacy