Andrea Mantegna, Polittico di San Zeno – Crocifissione (1456-1459) Tempera su tavola, cm 67 x 93, Parigi, Musée du Louvre

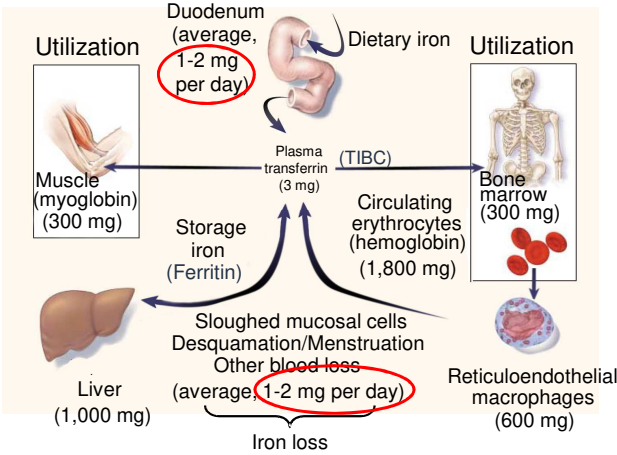
Omeostasi del ferro e patologia: carenza e sovraccarico

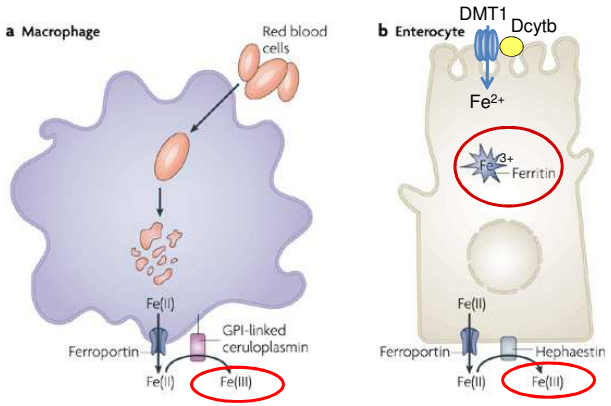
Classificazione patogenetica delle anemie

3. Ridotta sintesi di emoglobina

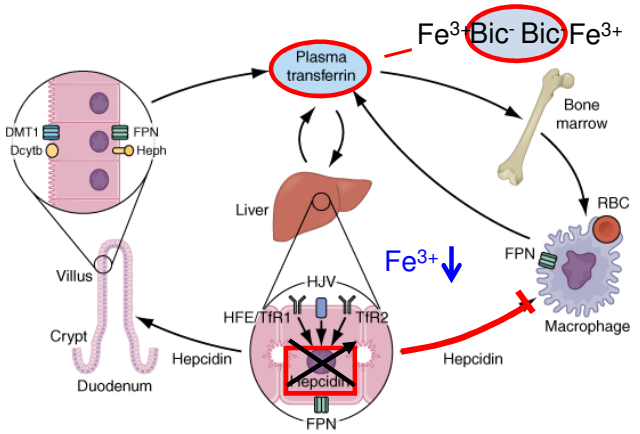
- carenza di ferro
- talassemie
- anemie sideroblastiche
- anemia da flogosi cronica

Body Iron Distribution and Storage





Nature Reviews | Molecular Cell Biology



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 2258–2262, April 1983
Cell Biology

pH and the recycling of transferrin during receptor-mediated endocytosis

(endocytic vesicle/apotransferrin/transferrin receptor)

ALICE DAUTRY-VARSAT*, AARON CIECHANOVER, AND HARVEY F. LODISH

Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Communicated by Joseph L. Goldstein, December 27, 1982

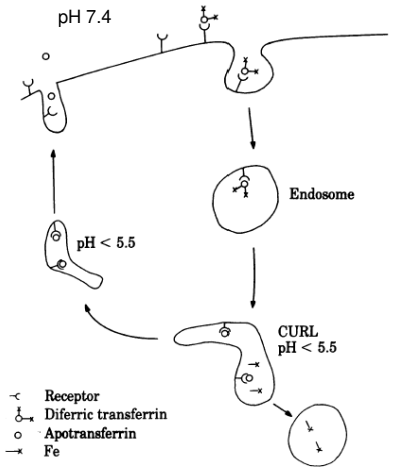
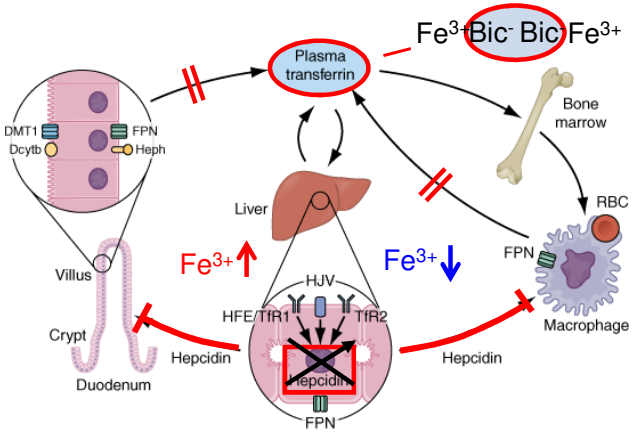


FIG. 7. The transferrin cycle. See text for details.

Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 2258–2262, April 1983
Cell Biology



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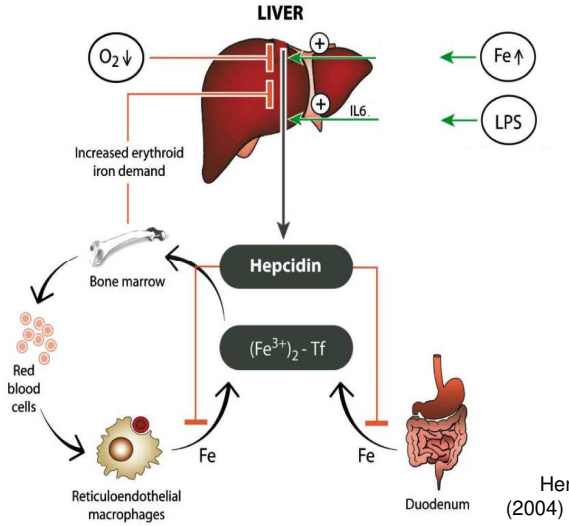
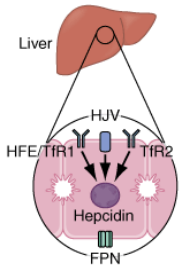


Hentze et al. (2004) Cell 117: 285



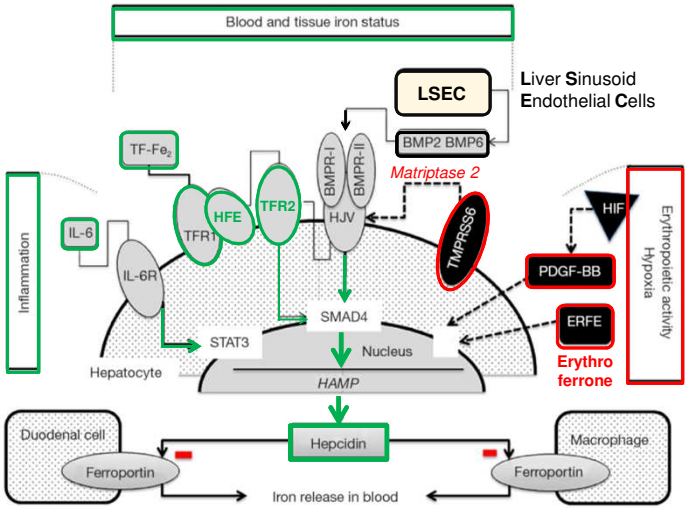
Review Article

Inherited iron overload disorders

Alberto Piperno[1,2], Sara Pelucchi[1], Raffaella Mariani[2]

Transl Gastroenterol Hepatol 2020;5:25 | http://dx.doi.org/10.21037/tgh.2019.11.15

Figure 1 Positive and negative regulators of hepcidin synthesis. Hepcidin regulators are activated by different stimuli: positive (iron status, inflammation), and negative (erythropoietic activity, and hypoxia). HFE is a component of an iron-sensing complex that involves interactions with diferric transferrin (Tf-Fe2), transferrin receptors (TFR-1 and TFR-2) at the plasma membrane of hepatocytes. High concentrations of Tf-Fe2 displace HFE from TFR1, which then forms a complex with TFR2 and HJV to promote bone morphogenetic protein (BMP)/SMAD signaling to hepcidin (28,29). HJV is a GPI-linked protein that activates hepcidin as a co-receptor for BMP cytokines. Only BMP2 and BMP6 have been so far demonstrated to activate hepcidin *in vivo* (9,21,30,31). In the liver, hepcidin is expressed only in hepatocytes while BMP2 and BMP6 are expressed almost exclusively in liver sinusoidal endothelial cells (LSECs) suggesting a paracrine function of these ligands (32). How LSECs sense changes in body iron levels and upregulate BMP2 and BMP6 is still to be defined. Two types of BMP receptors, type I (BMPRI) and type II (BMPRII) are involved in this pathway, and both types, as well as their ligands, act as dimers. The regulatory SMADs (R-SMADs), SMAD1, SMAD5, and SMAD8 are the mediators of BMP signalling, as they are phosphorylated by activated BMPRIs. The common SMAD4 translocates to the nucleus in complex with the R-SMADs to induce the expression of genes regulated by BMP-responsive elements, as hepcidin. BMP/SMAD signaling to hepcidin is suppressed by matriptase 2, a serine protease, codified by *TMPRSS6* that cleaves and generates a soluble form of HJV. Erythroferrone (ERFE), a TNFα-like protein released by mature erythroblasts in condition of enhanced erythropoiesis, is a major candidate of erythropoiesis-induced hepcidin suppression (33). Platelet-derived growth factor-BB (PDGF-BB) is the candidate of hypoxia-induced hepcidin inhibition by the hypoxia-inducible factor (HIF), likely produced by a non-erythroid Ter^{119neg} population under hypoxia stimuli (34,35). Infection and inflammation markedly increase hepcidin synthesis through the interaction of interleukin 6 (IL6) with its receptor (IL6R) and STAT3 pathway (36).



Transl Gastroenterol Hepatol 2020;5:25 | http://dx.doi.org/10.21037/tgh.2019.11.15

Annual Review of Medicine

Hepcidin and Iron in Health and Disease

Elizabeta Nemeth and Tomas Ganz

Center for Iron Disorders, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, California, USA; email: enemeth@mednet.ucla.edu

Annu. Rev. Med. 2023. 74:261–77

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Keywords

hepcidin, iron, inflammation, anemia, iron overload

Abstract

Hepcidin, the iron-regulatory hormone, determines plasma iron concentrations and total body iron content. Hepcidin, secreted by hepatocytes, functions by controlling the activity of the cellular iron exporter ferroportin, which delivers iron to plasma from intestinal iron absorption and from iron stores. Hepcidin concentration in plasma is increased by iron loading and inflammation and is suppressed by erythropoietic stimulation and during pregnancy. Hepcidin deficiency causes iron overload in hemochromatosis and anemias with ineffective erythropoiesis. Hepcidin excess causes iron-restrictive anemias including anemia of inflammation. The development of hepcidin diagnostics and therapeutic agonists and antagonists should improve the treatment of iron disorders.

Article

A role of PIEZO1 in iron metabolism in mice and humans

Cell *184*, 969–982, February 18, 2021 © 2021 Elsevier Inc.

Shang Ma,[1] Adrienne E. Dubin,[1] Yunxiao Zhang,[1] Seyed Ali Reza Mousavi,[1] Yu Wang,[1] Adam M. Coombs,[1] Meaghan Loud,[1] Immacolata Andolfo,[2] and Ardem Patapoutian[1,3,*]

[1]Howard Hughes Medical Institute, Department of Neuroscience, Dorris Neuroscience Center, Scripps Research, La Jolla, CA 92037, USA

[2]Department of Molecular Medicine and Medical Biotechnologies, University of Naples Federico II, CEINGE - Biotecnologie Avanzate, Naples, Italy

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https://doi.org/10.1016/j.cell.2021.01.024

Iron overload causes progressive organ damage and is associated with arthritis, liver damage, and heart failure. Elevated iron levels are present in 1%–5% of individuals; however, iron overload is undermonitored and underdiagnosed. Genetic factors affecting iron homeostasis are emerging. Individuals with hereditary xerocytosis, a rare disorder with gain-of-function (GOF) mutations in mechanosensitive PIEZO1 ion channel, develop age-onset iron overload. We show that constitutive or macrophage expression of a GOF *Piezo1* allele in mice disrupts levels of the iron regulator hepcidin and causes iron overload. We further show that PIEZO1 is a key regulator of macrophage phagocytic activity and subsequent erythrocyte turnover. Strikingly, we find that E756del, a mild GOF *PIEZO1* allele present in one-third of individuals of African descent, is strongly associated with increased plasma iron. Our study links macrophage mechanotransduction to iron metabolism and identifies a genetic risk factor for increased iron levels in African Americans.

Article

A role of PIEZO1 in iron metabolism in mice and humans

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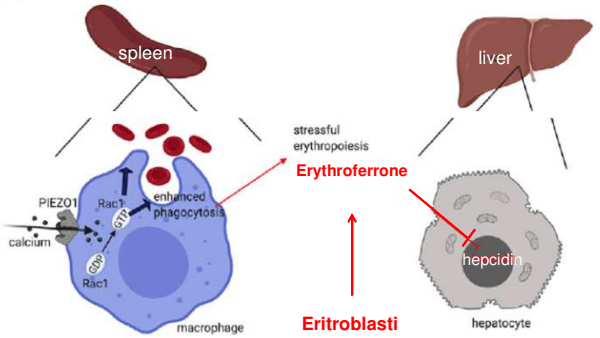
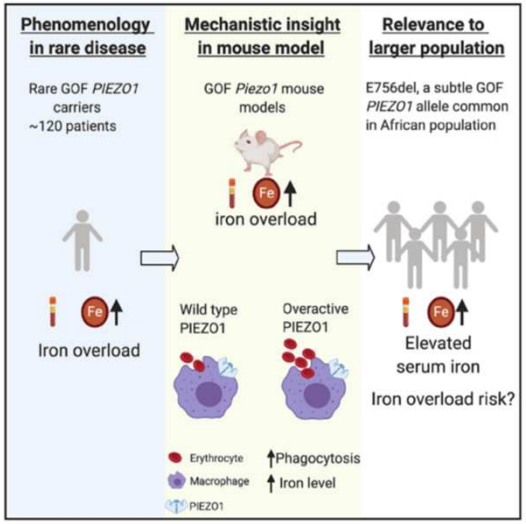
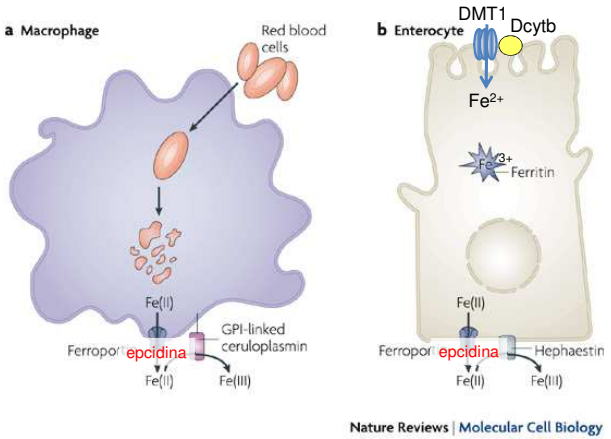
[2]Department of Molecular Medicine and Medical Biotechnologies, University of Naples Federico II, CEINGE - Biotecnologie Avanzate, Naples, Italy

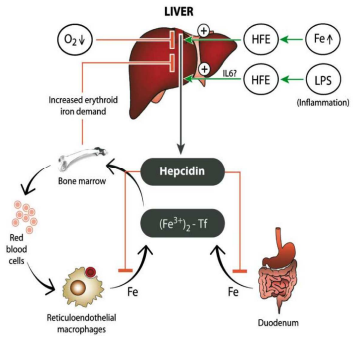


Eritroblasti
Midollo emopoietico





Iron Transfer Between Cells and Tissues: Role of Hepcidin



Hepcidin

Iron deficiency ↓

Hentze et al.
(2004) Cell 117: 285

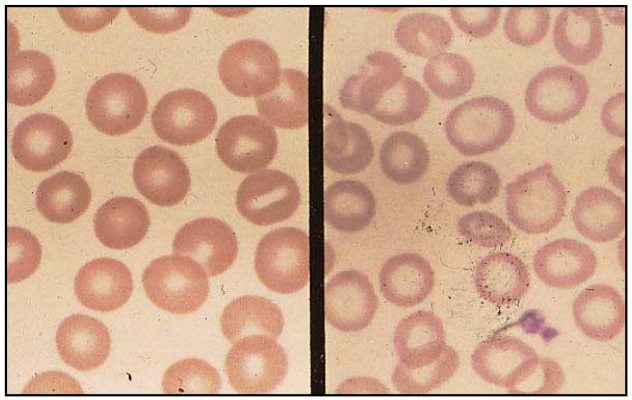
Classificazione patogenetica delle anemie

3. Ridotta sintesi di emoglobina

- **carenza di ferro**
- talassemie
- anemie sideroblastiche
- anemia da flogosi cronica

A. L'anemia da deficienza di ferro

normale Ipocromia, microcitosi

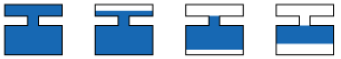


L'assorbimento del ferro

Physical State (bioavailibility)	heme > Fe^{2+} > Fe^{3+}
High Gastric pH	hemigastrectomy, vagotomy, pernicious anemia histamine H2 receptor blockers, calcium-based antacids
Disruption of Intestinal Structure	Crohn's disease, celiac disease (non-tropical sprue)
Inhibitors	phylates, tannins, soil clay, laundry starch, iron overload
Competitors	cobalt, lead, strontium
Facilitators	ascorbate, citrate, amino acids, iron deficiency

A. L'anemia da deficienza di ferro

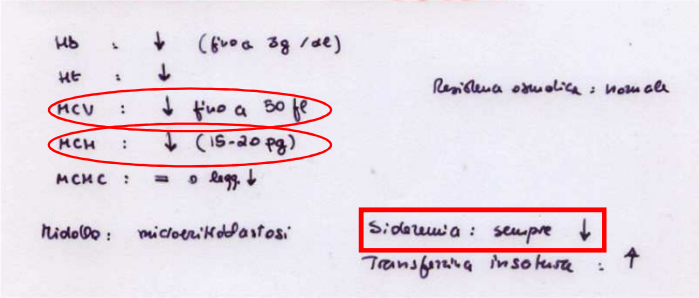
- aumentate necessità
  - · crescita post-natale
  - · pubertà
- perdita fisiologica
  - · mestruazioni
  - · gravidanza
- perdita patologica (sanguinamento)
  - · GI
  - · GU
- ridotta assunzione
  - · dieta
  - · malassorbimento

	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores / Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (μg/L)	50-200	<20	<15	<15
TIBC (μg/dL)	300-360	>360	>380	>400
SI (μg/dL)	50-150	NL	<50	<30
Saturation (%)	30-50	NL	<20	<10
Marrow sideroblasts (%)	40-60	NL	<10	<10
RBC protoporphyrin (μg/dL)	30-50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/ hypochromic

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

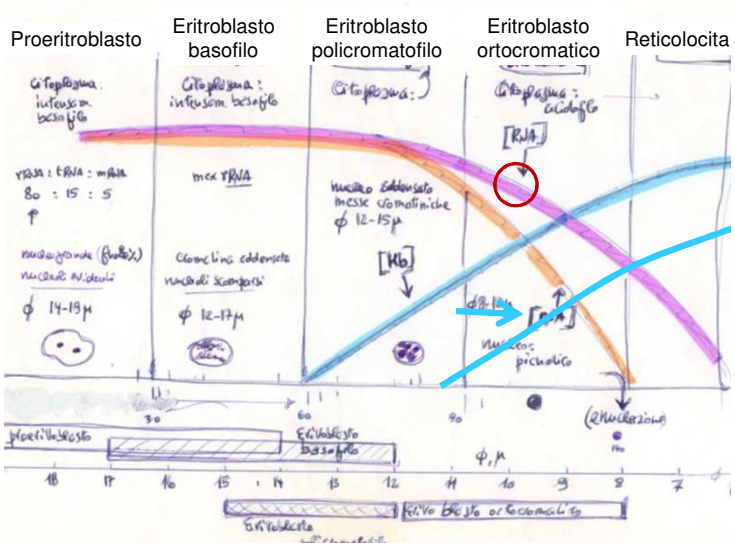
Anemia da carenza di ferro

Reperti ematologici



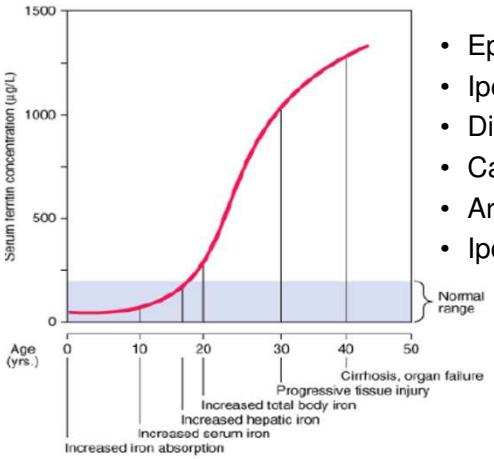
ipocromica microcitica

Claude Monet (1867) Signora in giardino a Sainte-Adresse



B. Il sovraccarico di ferro

- Emocromatosi ereditaria
  - Difetto del gene HFE (molto frequente, freq. allelica 1/10 in Nord Europa)
  - Altre mutazioni più rare (epcidina, emojuvenilina TfR)
- Sovraccarico di ferro secondario
  - Disordini dell'eritropoiesi (talassemie, anemia sideroblastica)
  - Malattie epatiche



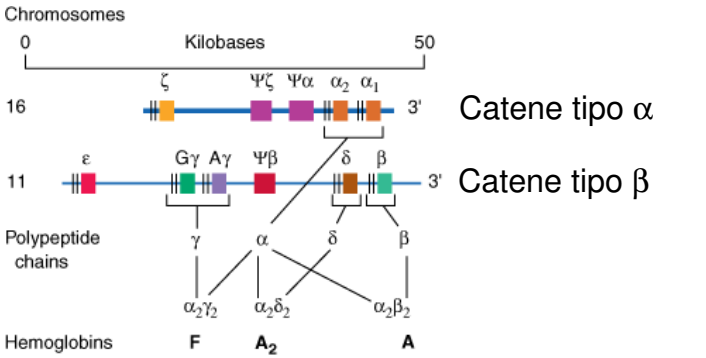
- Epatomegalia
- Iperpigmentazione
- Diabete mellito
- Cardiopatia
- Artrite
- Ipogonadismo

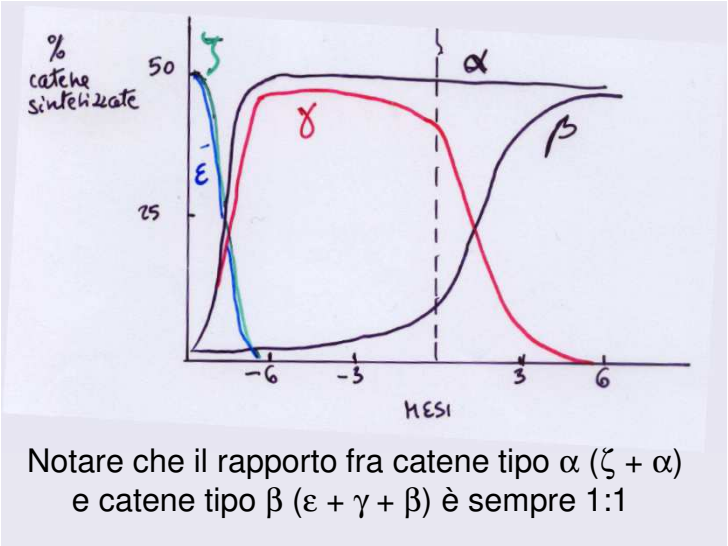
Classificazione patogenetica delle anemie

3. Ridotta sintesi di emoglobina

- carenza di ferro
- **talassemie**
- anemie sideroblastiche
- anemia da flogosi cronica

I geni delle globine





Notare che il rapporto fra catene tipo α (ζ + α) e catene tipo β (ε + γ + β) è sempre 1:1

	ε	γ	β	δ
ζ	x	x	–	–
α	x	x	x	x

$\zeta_2\varepsilon_2$ Gower I
$\zeta_2\gamma_2$ Portland
$\alpha_2\varepsilon_2$ Gower II

$\alpha_2\gamma_2$ HbF

$\alpha_2\beta_2$ HbA 1
$\alpha_2\delta_2$ HbA 2

fase mesoblastica | fase epatica | fase mieloide

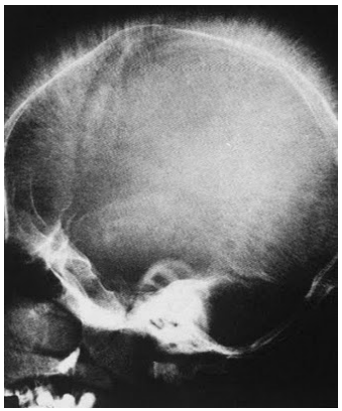
Talassemia β

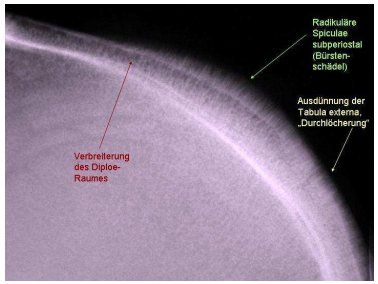
$\alpha + \beta \rightarrow \alpha\beta$ $\Big\}\rightarrow \alpha_2\beta_2$
$\alpha + \beta \rightarrow \alpha\beta$
$\alpha + \beta \rightarrow \alpha\beta$ $\Big\}\rightarrow \alpha_2\beta_2$
$\alpha + \beta \rightarrow \alpha\beta$

Precipitazione → Eritropoiesi inefficace
Anemia emolitica
Sovraccarico di ferro

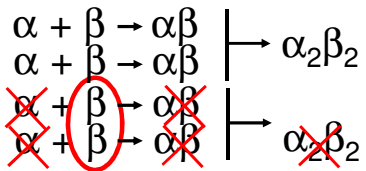
β talassemie

Sindrome	[Hb] g/dl	MCH	MCV	iperplasia midollo
1. Talassemia major (m. di Cooley)	2.5-6.5	↓↓	↓↓	++++
2. Talassemia intermedia	6-9	↓	↓	+/++
3. Talassemia minor	~ normale	↓	↓	norm.
4. Talassemia minima	normale →			norm.





Talassemia α



Elevata affinità per O_2 ← β_4 (HbH), γ_4 (HbBart) → Eritropoiesi inefficace, Anemia emolitica, Sovraccarico di ferro

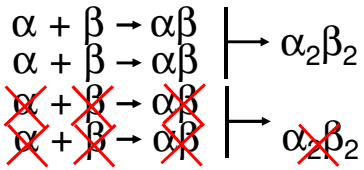
α TALASSEMIE [aplotipo: −−=α1 / −α=α2]

sindrome	genotipo	rapporto β/α	effetti
idrope fetale	−−/−−	—	morte fetale o neonatale da anemia grave
malattia da HbH	−−/−α	~3	anemia emolitica cronica moderata m. severa
α-talassemia minor (trait talassemico)	−α/−α −−/αα	1.25	anemia moderata o assente GR "talassemici"
portatore asintomatico	−α/αα	1.15	nessuno, GR normali

sindrome	[Hb] g/dl	MCH	MCV	ipoplasia midollo [fegato]
idrope fetale	4-10	↓↓	↓↓	+++
mal. da HbH	7-10	↓	↓	aa+a ++
tal. α minor	norm o ↓	↓	↓	
asintom.	normale			

anemia – ove pres. – ipocromica microcitica con cellule a bersaglio
sideremia: normale o ↑

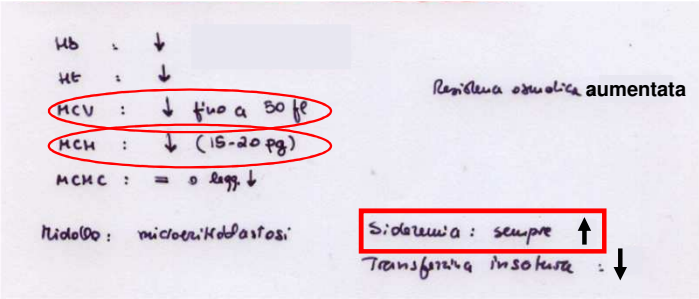
Talassemia αβ eterozigote



A parità di riduzione delle catene α o β, l'eterozigosi causa un'anemia meno grave perché la sintesi della catene globiniche è bilanciate, e non si generano i fenomeni legati all'eccesso relativo di catene α o β

Talassemia

Reperti ematologici

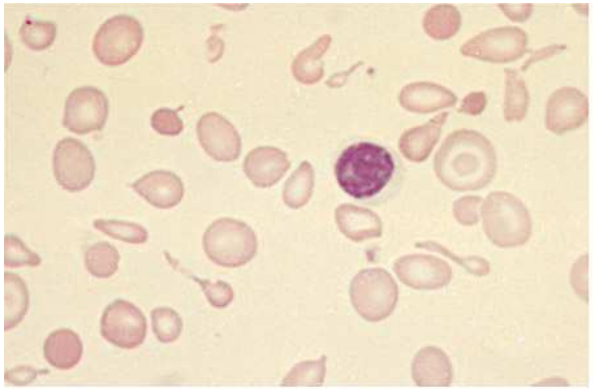


ipocromica microcitica

Attenzione

Il trait talassemico e/o le forme lievi di talassemia vengono spesso confusi con l'anemia da carenza di ferro (entrambe sono ipocromiche e microcitiche). Attenzione dunque allo stato dei depositi, al ferro circolante e alla percentuale di saturazione della transferrina!

Talassemia



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Classificazione patogenetica delle anemie

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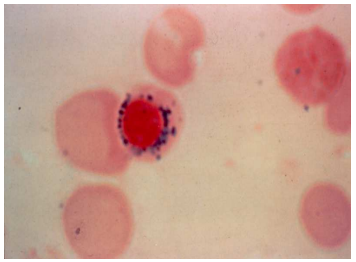
- carenza di ferro
- talassemie
- **anemie sideroblastiche**
- anemia da flogosi cronica

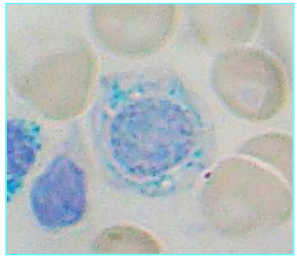
Le anemie sideroblastiche

Coesistenza di:

- Anemia ipocromica
- Iperferremia
- Depositi di ferro (mitocondri) negli eritroblasti



MCV può essere normale, diminuito o aumentato a seconda della causa



The WHO International Working Group on Morphology of MDS (IWGM-MDS) defined three types of sideroblasts:

Type 1 sideroblasts: fewer than 5 siderotic granules in the cytoplasm
Type 2 sideroblasts: 5 or more siderotic granules, but not in a perinuclear distribution
Type 3 or ring sideroblasts: 5 or more granules in a perinuclear position, surrounding the nucleus or encompassing at least one third of the nuclear circumference.

↓

Anemie sideroblastiche

Le anemie sideroblastiche

Forme congenite (difetti nella sintesi dell'eme)

- difetto di ALA sintetasi (X-linked, vit. B6-dip.)

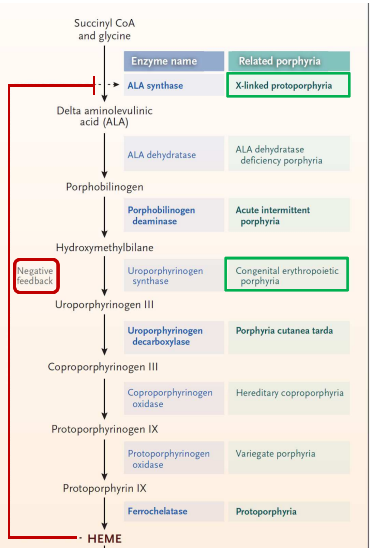
  gly + succCoA ➔ ALA

- porfirie (blocco successivo)

  Si accumulano precursori (uroprofinogeno, coproporfinogeno) che causano fotosensibilizzazione

Forme acquisite

- Avvelenamento da Pb
- mielodisplasie



Congenital sideroblastic anemia

- **X-linked sideroblastic anemia**: This is the most common congenital cause of sideroblastic anemia and involves a defect in ALAS2, which is involved in the first step of heme synthesis. Although X-linked, approximately one third of patients are women due to skewed X-inactivation (lyonizations).
- **Autosomal recessive sideroblastic anemia** involves mutations in the SLC25A38 gene. The function of this protein is not fully understood, but it is involved in mitochondrial transport of glycine. Glycine is a substrate for ALAS2 and necessary for heme synthesis. The autosomal recessive form is typically severe in presentation.
- **Genetic syndromes**: Rarely, sideroblastic anemia may be part of a congenital syndrome and present with associated findings, such as ataxia, myopathy, and pancreatic insufficiency.

Acquired clonal sideroblastic anemia: Clonal sideroblastic anemias fall under the broader category of myelodysplastic syndromes (MDS). Three forms exist and include refractory anemia with ringed sideroblasts (RARS), refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T), and refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS). These anemias are associated with increased risk for leukemic evolution.

Acquired reversible sideroblastic anemia: Causes include **excessive alcohol use** (the most common cause of sideroblastic anemia), **pyridoxine deficiency** (vitamin B6 is the cofactor in the first step of heme synthesis), **lead poisoning** and **copper deficiency**. **Excess zinc** can indirectly cause sideroblastic anemia by decreasing absorption and increasing excretion of copper. Antimicrobials that may lead to sideroblastic anemia include **isoniazid** (which interferes with pyridoxine metabolism), **chloramphenicol** (which, by inhibiting the synthesis of mitochondrial membrane protein, impairs mitochondrial respiration), **cycloserine** and **linezolid**.

Classificazione patogenetica delle anemie

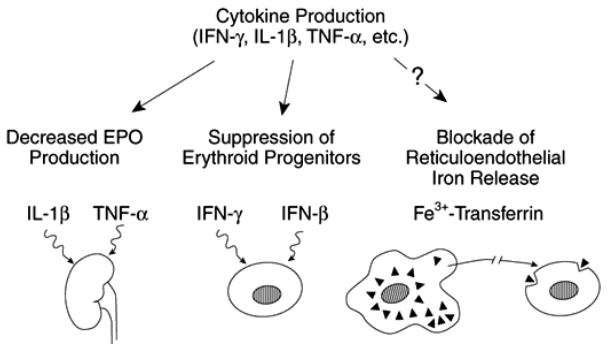
3. Ridotta sintesi di emoglobina

- carenza di ferro
- talassemie
- anemie sideroblastiche
- **anemia da flogosi cronica**

Le anemie associate a malattie croniche

- Condizione associata — Prevalenza
  - Infezione — 20-95%
    - Virus, batteri, parassiti, funghi
  - Malattie autoimmune — 8-17%
    - AR, LES, sarcoidosi, vasculiti
  - Neoplasie maligne — 30-77%
  - Rigetto di trapianto d'organo — 8-70%
- Caratteristiche
  - Anemia di gravità variabile
  - Bassi livelli di EPO
  - Bassa conta reticolociti

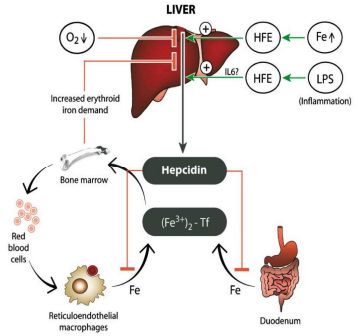
Pathogenesis of the Anemia of Chronic Disease



Ridotta eritropoiesi (normocitica)

Ridotta sintesi emoglobina (microcitica)

Iron Transfer Between Cells and Tissues: Role of Hepcidin

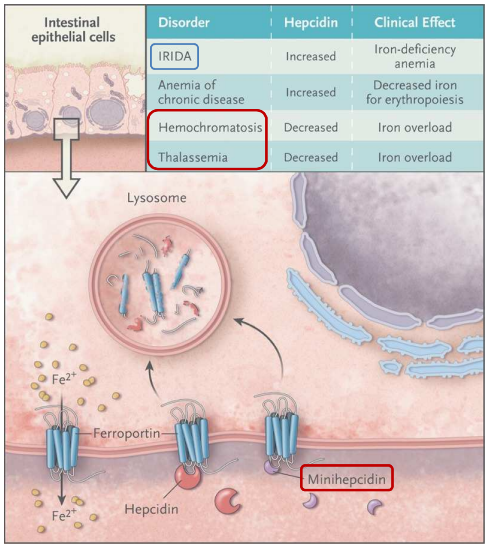


Hepcidin

Iron overload ↑

Anemia of chronic disease ↑

Hentze et al.
(2004) Cell 117: 285



Iron-Refractory Iron-Deficiency Anemia

↓

difetto del gene TMPRSS6 sul cromosoma 22, che codifica matriptasi-2, proteasi serinica transmembrana che inibisce epcidina attraverso il clivaggio di hemojuvelin

CLINICAL IMPLICATIONS OF BASIC RESEARCH

N Engl J Med 2012; 366:376-377

Closing the Iron Gate

Nancy C. Andrews, M.D., Ph.D.

Research article *J Clin Invest.* 2011;121(12):4880–4888. doi:10.1172/JCI57693.

Minihepcidins are rationally designed small peptides that mimic hepcidin activity in mice and may be useful for the treatment of iron overload

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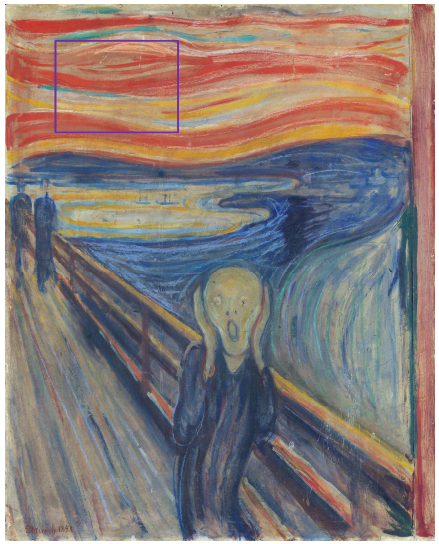
Iron overload is the hallmark of hereditary hemochromatosis and a complication of iron-loading anemias such as β-thalassemia. Treatment can be burdensome and have significant side effects, and new therapeutic options are needed. Iron overload in hereditary hemochromatosis and β-thalassemia intermedia is caused by hepcidin deficiency. Although transgenic hepcidin replacement in mouse models of these diseases prevents iron overload or decreases its potential toxicity, natural hepcidin is prohibitively expensive for human application and has unfavorable pharmacologic properties. Here, we report the rational design of hepcidin agonists based on the mutagenesis of hepcidin and the hepcidin-binding region of ferroportin and computer modeling of their docking. We identified specific hydrophobic/aromatic residues required for hepcidin-ferroportin binding and obtained evidence in vitro that a thiol-disulfide interaction between ferroportin C326 and the hepcidin disulfide cage may stabilize binding. Guided by this model, we showed that 7–9 N-terminal amino acids of hepcidin, including a single thiol cysteine, comprised the minimal structure that retained hepcidin activity, as shown by the induction of ferroportin degradation in reporter cells. Further modifications to increase resistance to proteolysis and oral bioavailability yielded minihepcidins that, after parenteral or oral administration to mice, lowered serum iron levels comparably to those after parenteral native hepcidin. Moreover, liver iron concentrations were lower in mice chronically treated with minihepcidins than those in mice treated with solvent alone. Minihepcidins may be useful for the treatment of iron overload disorders.

J Clin Invest. 2011;121(12):4880–4888. doi:10.1172/JCI57693.



Camminavo lungo la strada con due amici- il sole tramontava- il cielo si tinse improvvisamente di rosso sangue- mi fermai- mi appoggiai stanco morto al parapetto- sul fiordo nerazzurro e sulla città c'erano sangue e lingue di fuoco- i miei amici continuavano a camminare e io tremavo ancora di paura- e sentii un grande urlo infinito che attraversava la natura

Art Mystery Solved: Who Wrote on Edvard Munch's 'The Scream'?

Nina Siegal, The New York Times 22 febbraio 2021

Munch probably wrote the sentence on his painting in 1895, according to Guleng, after his exhibition of new work at the Blomqvist gallery in Oslo. During a debate about the exhibition at the University of Oslo's Students Association one night, a medical student, Johan Scharffenberg said the artwork gave him reason to question the artist's mental state, calling Munch abnormal and a "madman." Munch was deeply hurt, said Jacobsen, and wrote about it even decades later.
Guleng believes the inscription is written with irony and reflects both pain at being attacked and fear of being regarded as mentally ill. "By writing this inscription in the clouds, he took possession, in a way, or he took control of how he was to be perceived and understood," she said.