Cosa c'è di nuovo per trattare l'anemia
Milano 20 Aprile 2016

Patogenesi delle Anemie Sideropeniche

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Università degli Milano

Disclosure

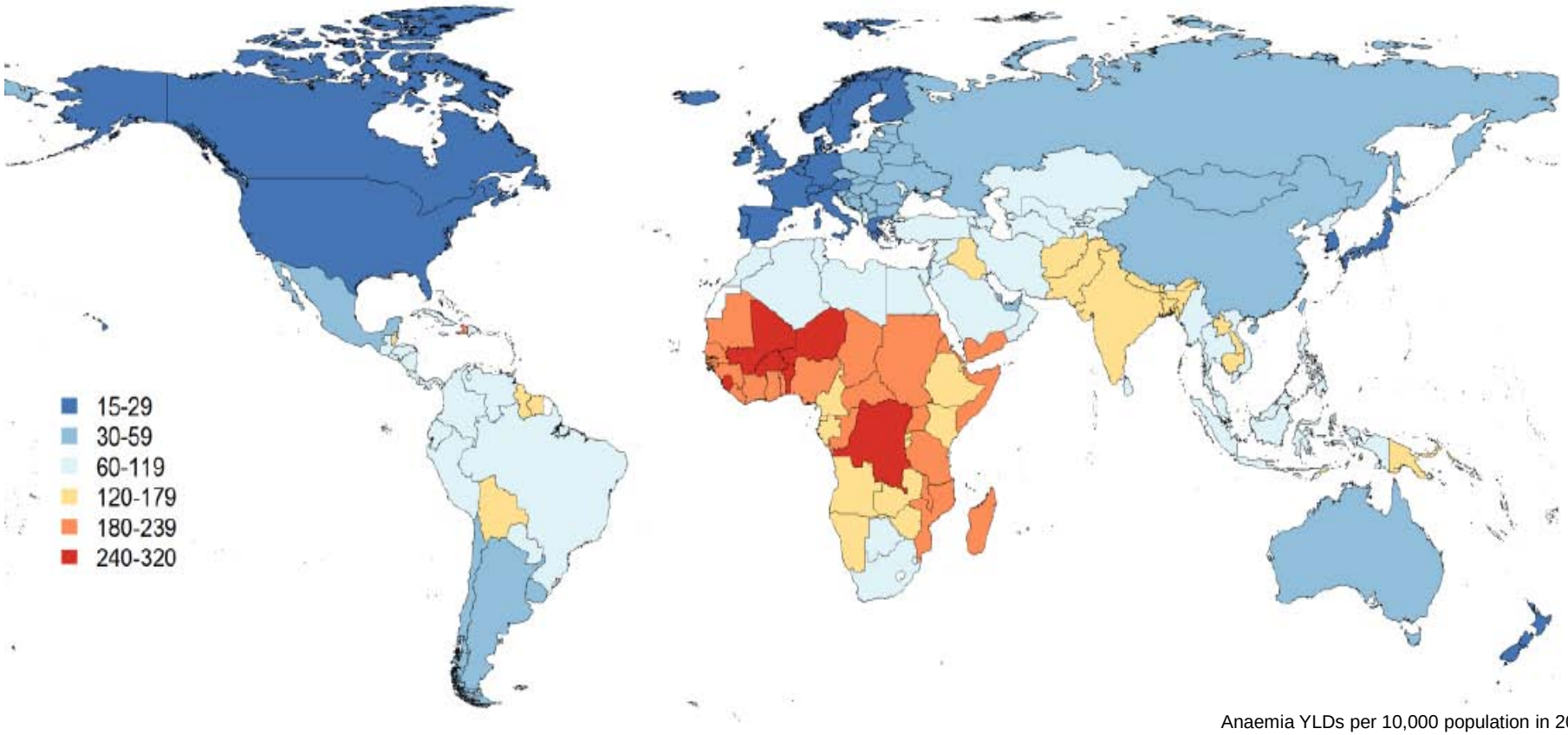
- Member of advisory board for:
  - Novartis
  - Sanofi Genzyme
  - Celgene

Agenda

- ✓ Global burden of anemia
- ✓ Definition Iron Deficiency (ID) and Iron Deficiency Anemia (IDA)
- ✓ Iron Metabolisim
- ✓ Causes of ID/IDA

The global burden of anaemia

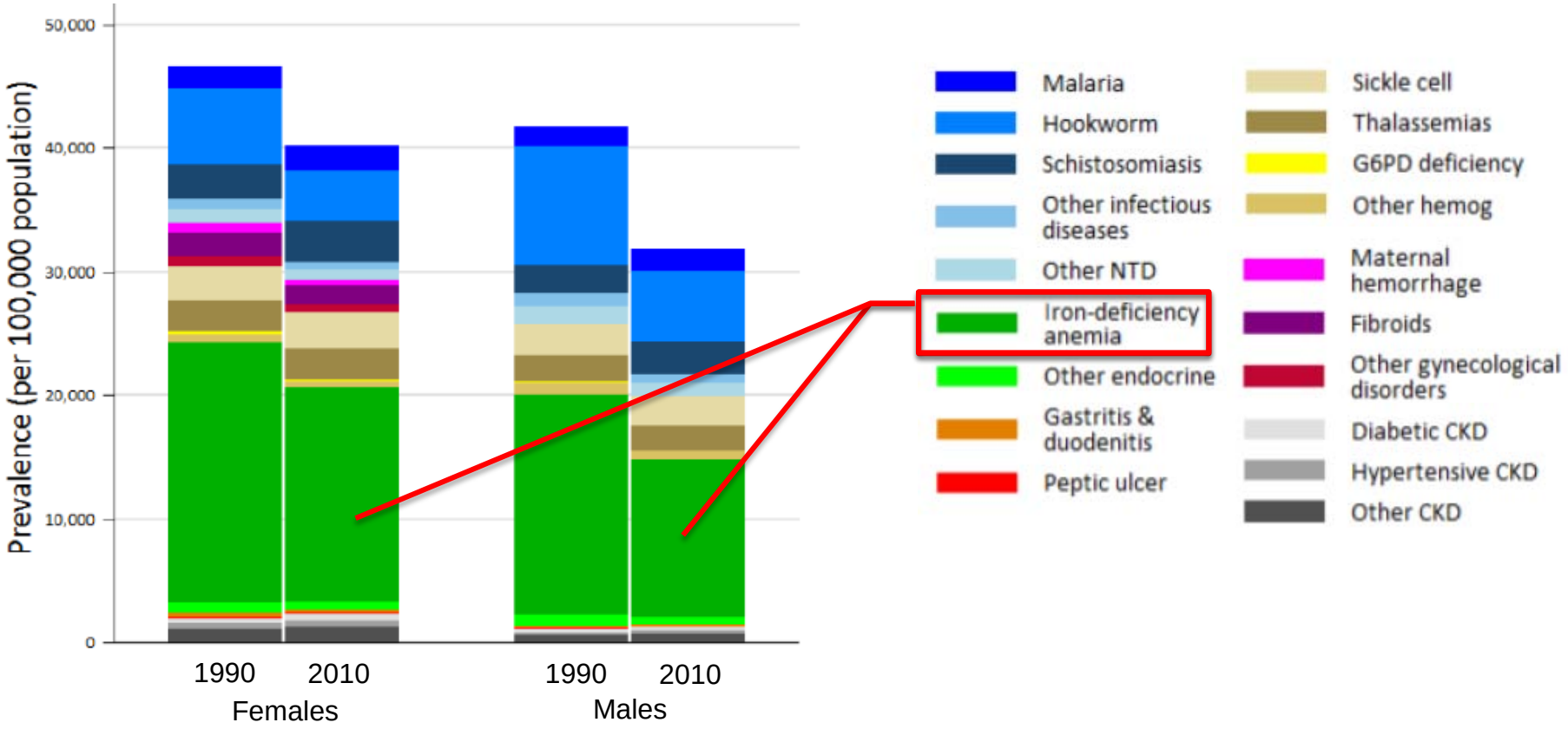
- 32.9% global anaemia prevalence
- 68.4 mio years lived with disability (YLD, anaemia)
  - i.e. 8.8% of total for all conditions



Anaemia YLDs per 10,000 population in 2010

Kassebaum NJ, et al. Blood 2014;123:615-24

Prevalence of anaemia by aetiology



Kassebaum NJ, et al. Blood 2014;123:615-24

ID and ID(A): Definition

Iron Deficiency

• Depleted iron stores

Absolute Iron Deficiency (no iron stores)

- Low Transferrin Saturation (**TSAT<20%**)
- **Serum ferritin low (<20ng/ml** – or <100ng/ml in case of inflammation)
- Elevated Serum Transferrin Receptor (sTfR)

Functional Iron Deficiency (full iron stores but ID in erythroid bone marrow)

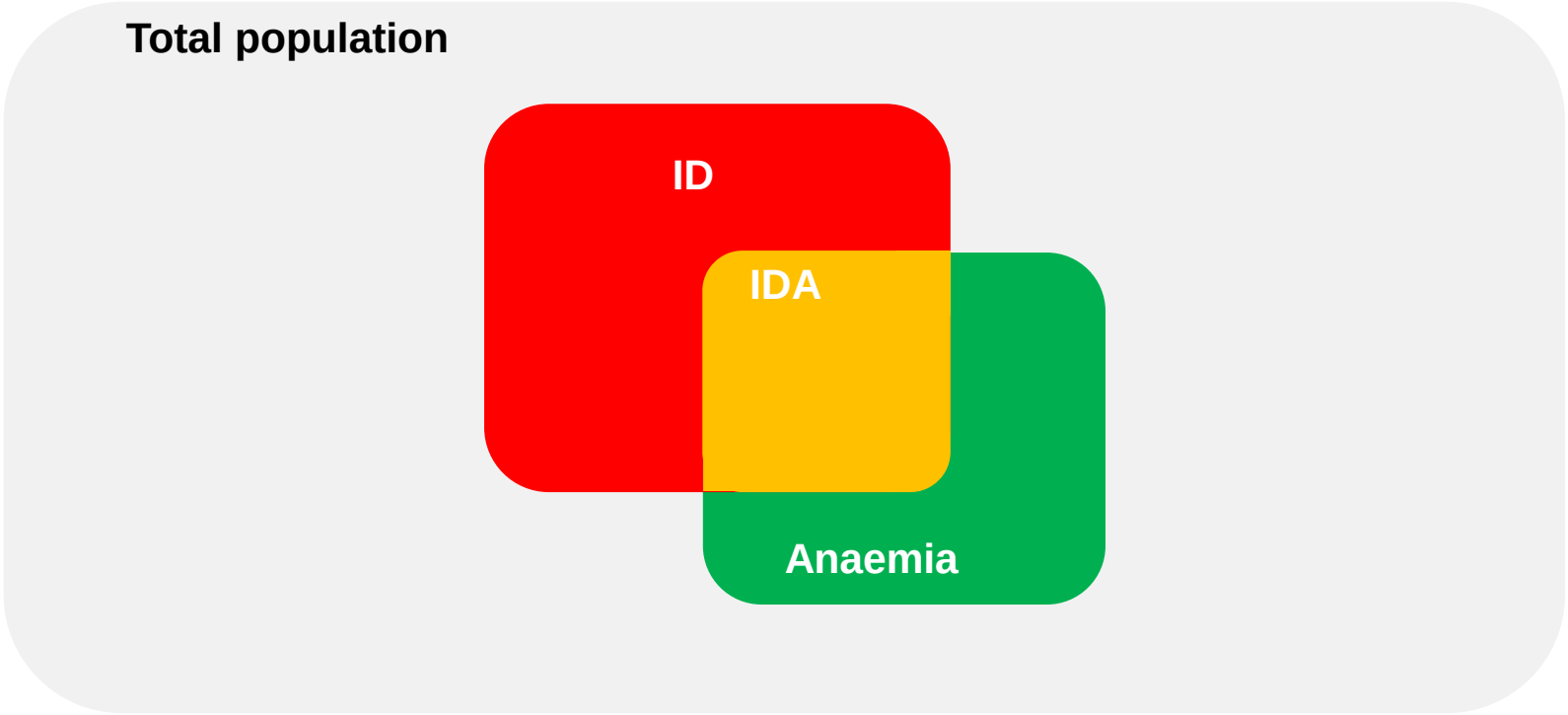
- Low TSAT (**TSAT<20%**)
- **Serum ferritin normal or elevated (>20 ng/ml** – or >100ng/ml in case of inflammation)
- Normal sTfR

Iron Deficiency Anaemia

- Depleted iron stores
- Haemoglobin (Hb) concentration falls below defined lower limit (12g/dl for women, 13 g/dl for men)

Adapted from Hush R. and Schaefer R. Pocket Atlas Special. Thiene 2006 and Prof. IY. Beguin oral communication. Parallel Symposia at EHA congress 2014, Milan, Italy

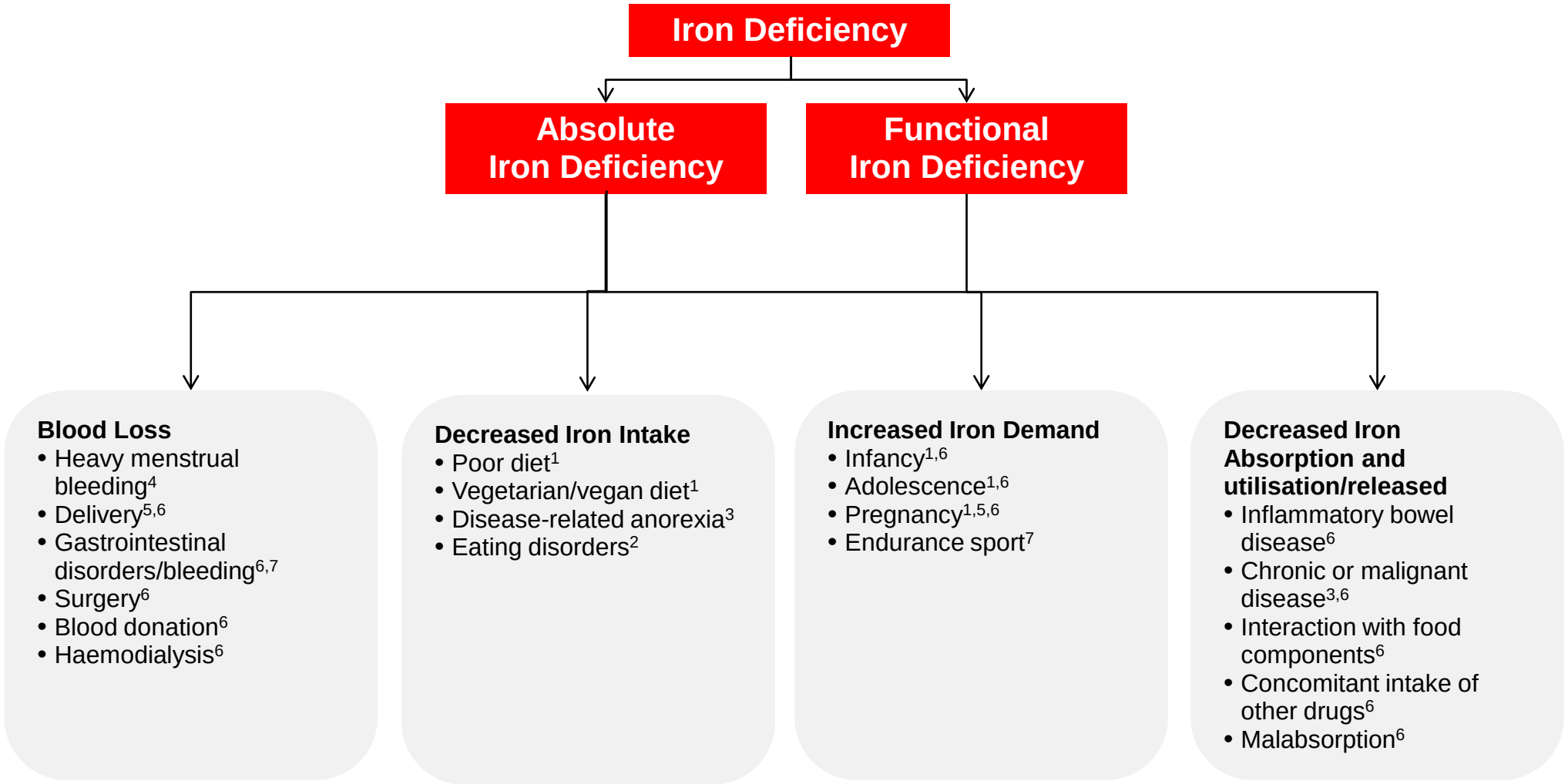
ID and ID(A): Relationship with anaemia



Schematic representation only. Areas do not reflect the real magnitude of the problem.

World Health Organization. Iron deficiency anaemia. Assessment, prevention and control: A guide for programme managers.; 2001:1-114.

ID and ID(A): Causes

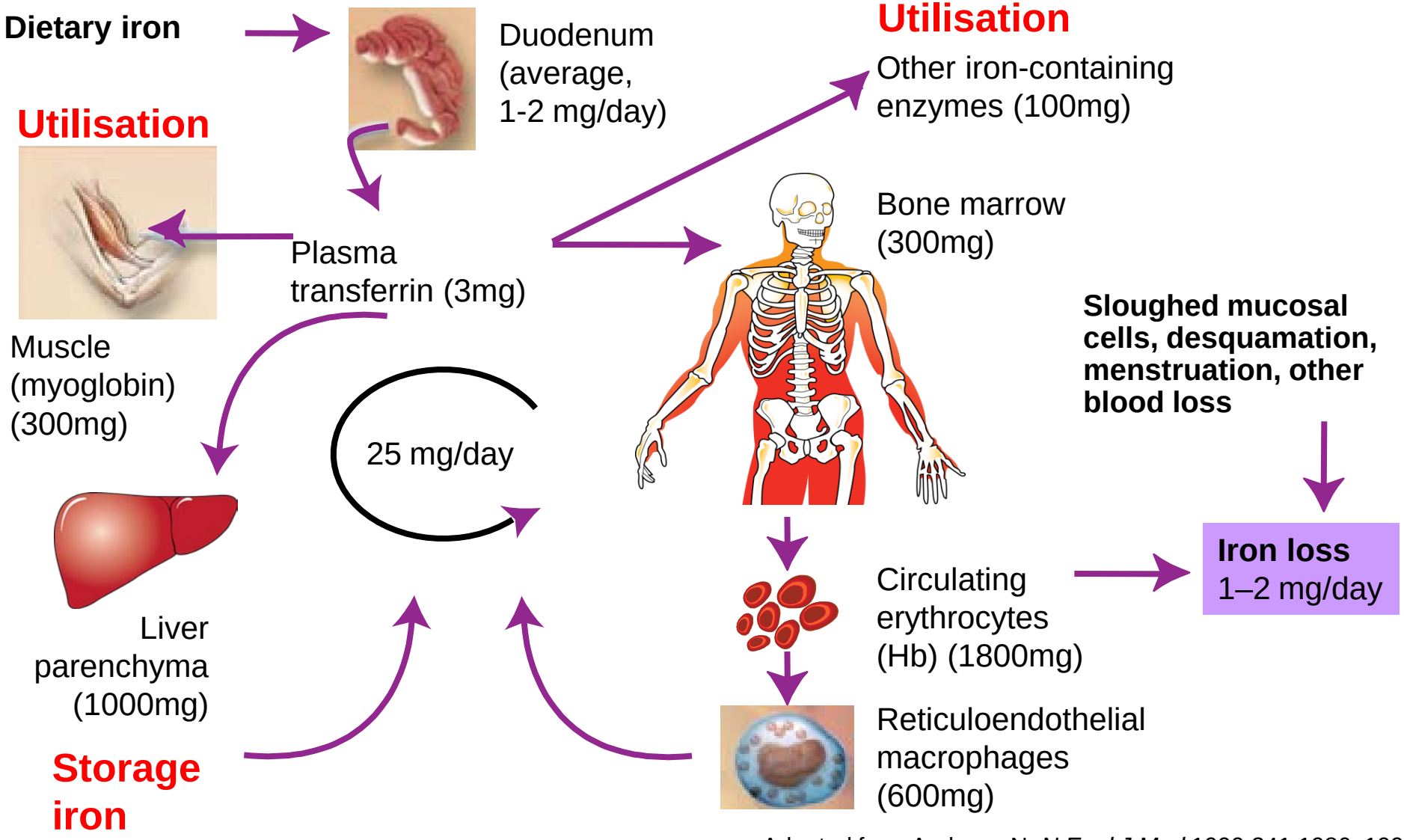


1. Zimmerman MB, et al. *Lancet* 2007;370:511-20.; 2. Roux H, et al. *Eat Weight Disord.* 2013;18(2):175-82.; 3. Aapro M, et al. *Ann Oncol* 2012;23:1954-62.; 4. Marret H, et al. *Eur J Obst Gyn Reprod Biol* 2010;152:133-7.; 5. Milman N. *Ann Hematol* 2006;85:559-65.; 6. Crichton R. UNI-MED Verlag AG, 2008.; 7. Stein J, et al. *Nat Rev Gastroenterol Hepatol* 2010;7:599-610.

Agenda

- ✓ Global burden of anemia
- ✓ Definition Iron Deficiency (ID) and Iron Deficiency Anemia (IDA)
- ✓ Iron Metabolism
- ✓ Causes of ID/IDA

Physiological iron turn-over



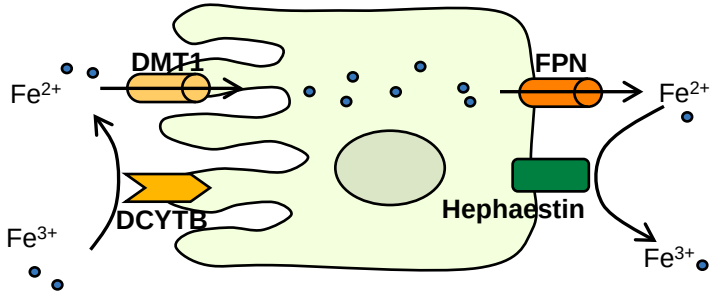
Adapted from Andrews N. *N Engl J Med* 1999;341:1986–1995

The iron cycle

Iron absorption

Enterocyte

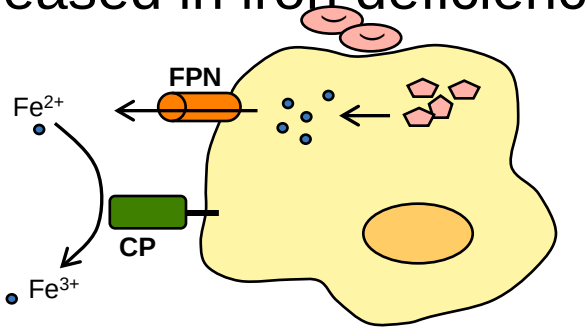
- 1–2 mg/day
- Hepcidin-regulated
- Balanced by iron losses (1–2 mg/day)
- Reduced in inflammation
- Increased in iron deficiency



Iron recycling

Macrophage

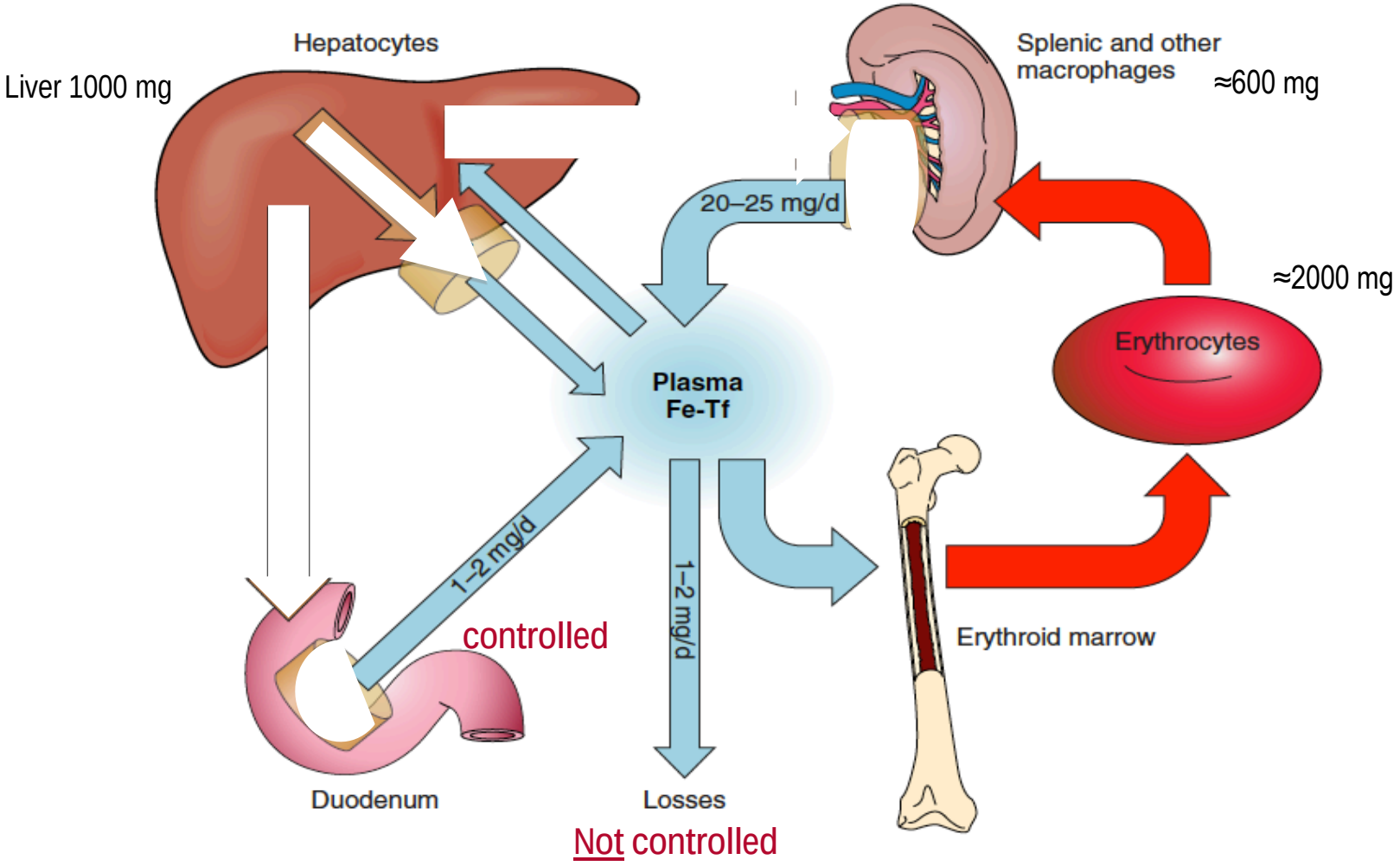
- 20–30 mg/day
- Hepcidin-regulated
- Balanced by erythroid request
- Reduced in inflammation
- Increased in iron deficiency



CP = ceruloplasmin; DCYTB = duodenal cytochrome B; DMT1 = divalent metal transporter 1; FPN = ferroportin.

Finch C. Blood. 1994;84:1697-702. Andrews NC. Blood. 2008;112:219-30.

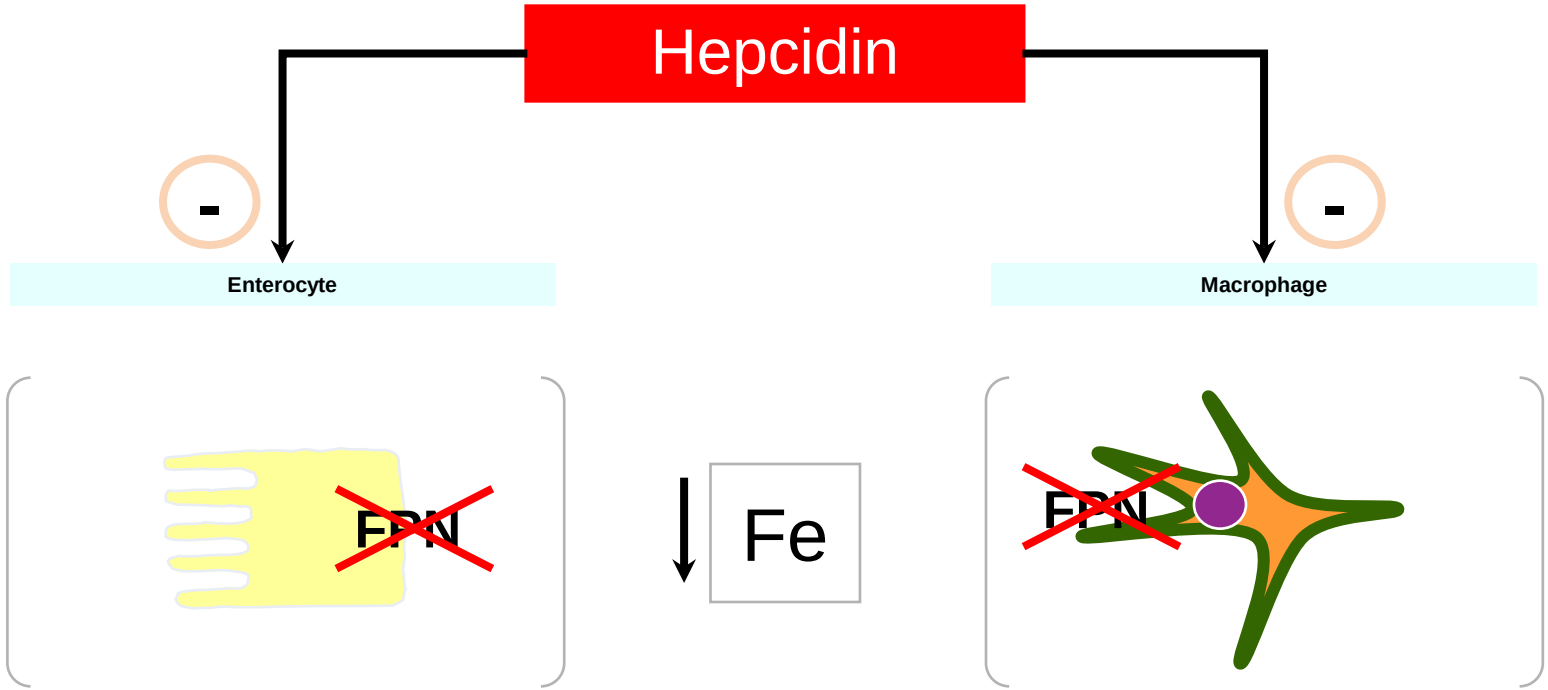
Hepcidin: The master regulator of iron homeostasis



Ganz T, Physiol Rev 2013

Hepcidin is the master regulator of systemic iron homeostasis

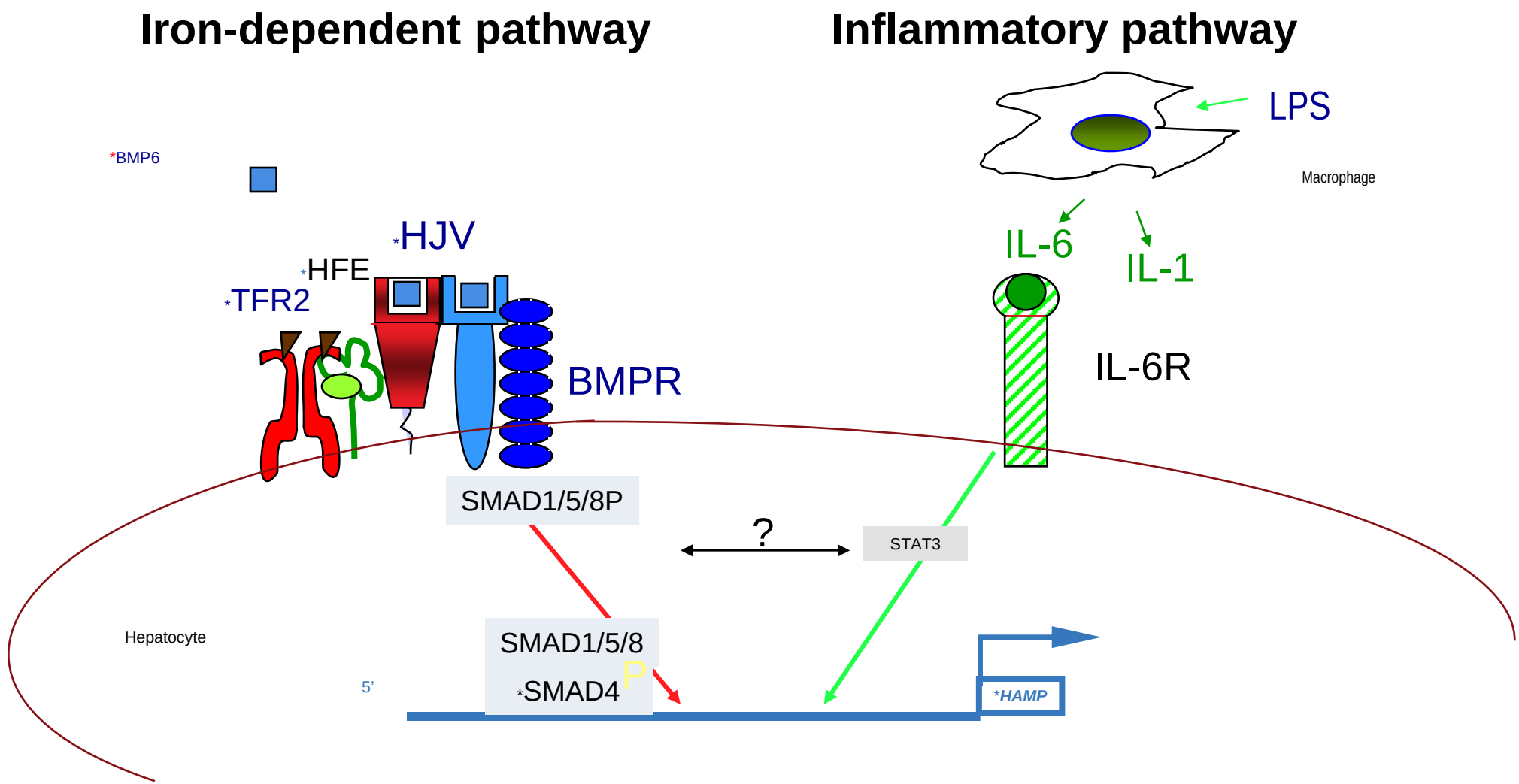
- The liver peptide hepcidin regulates intestinal iron absorption and iron release from storage cells by binding ferroportin, causing its internalization and degradation, and thus exerting a general inhibitory effect on iron release in the body



FPN = ferroportin.

Nemeth E, et al. Science. 2004;306:2090-3.

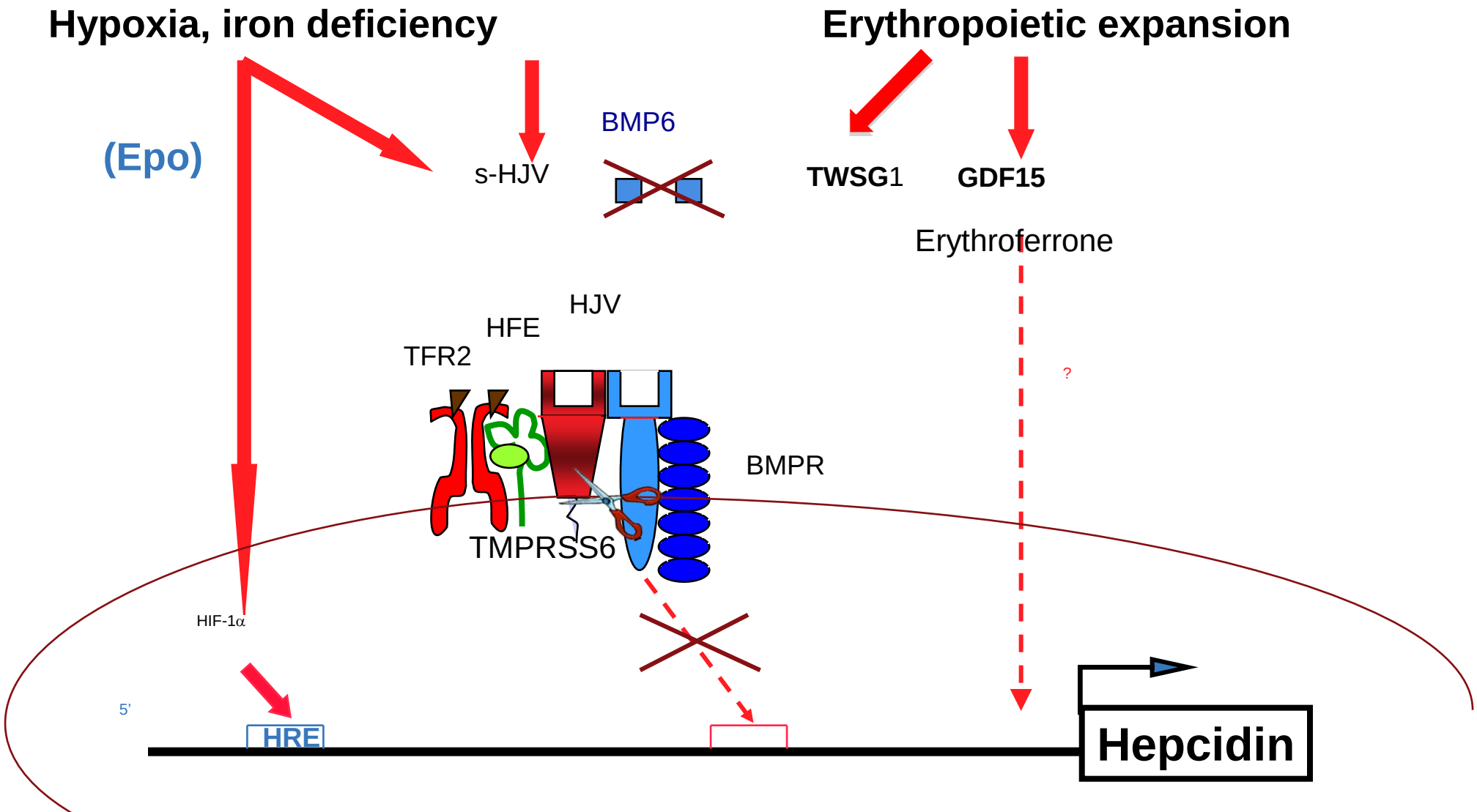
Hepcidin upregulation: two pathways



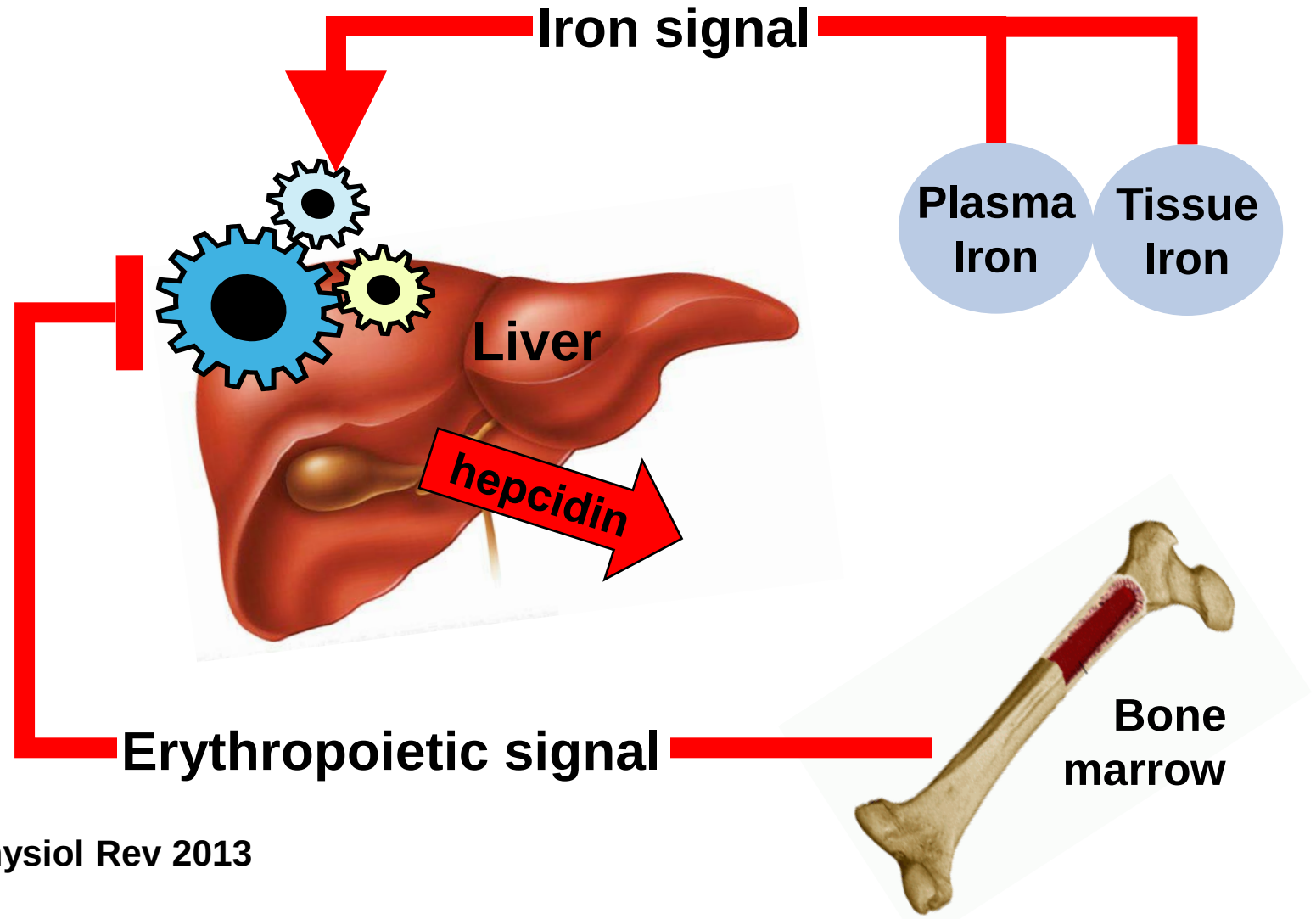
LPS = lipopolysaccharide.

* Indicates proteins whose inactivation causes iron overload.

Hepcidin downregulation: multiple pathways

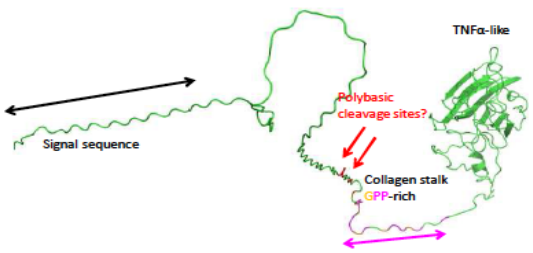


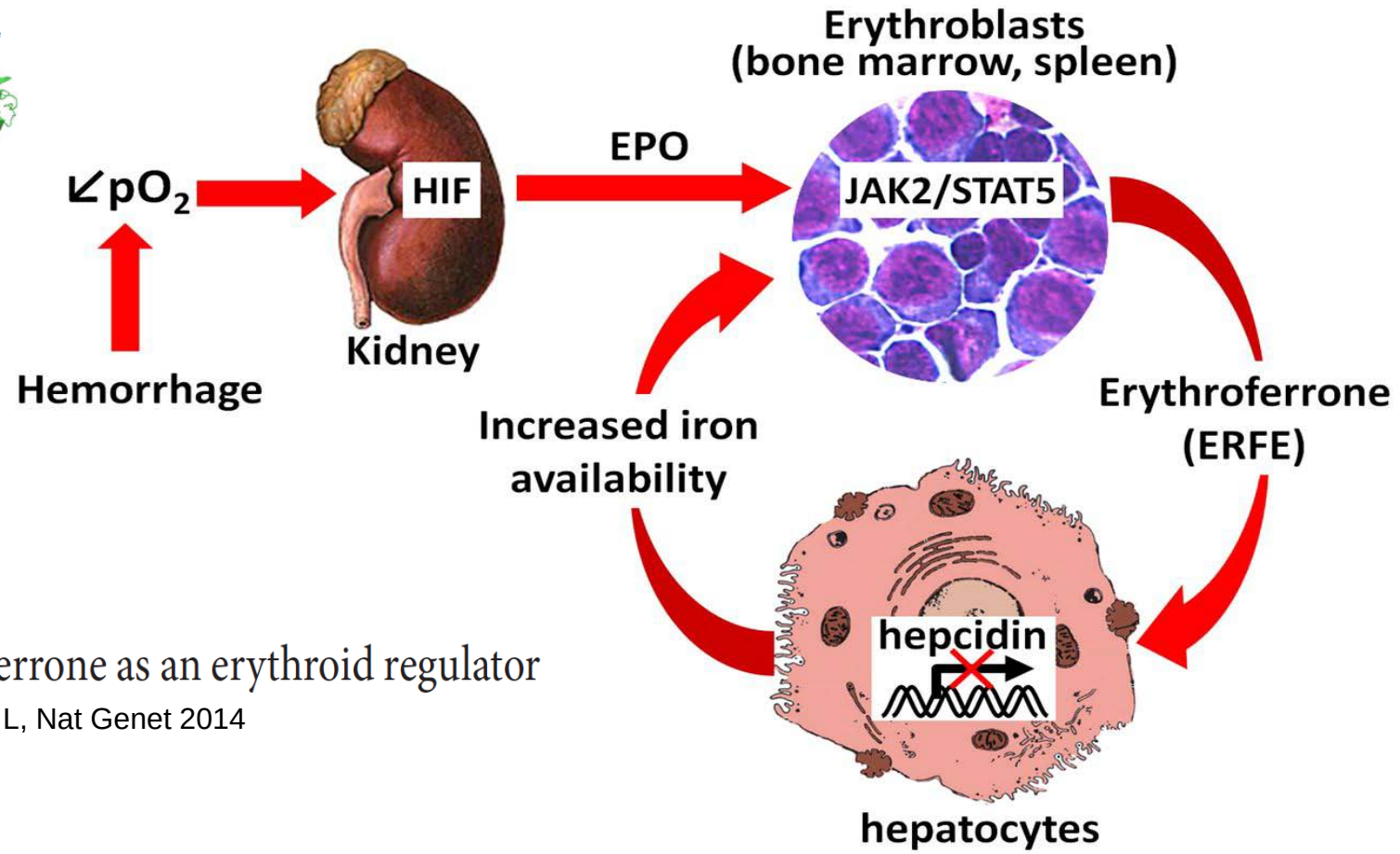
Hepcidin regulation by anaemia



Ganz T, Physiol Rev 2013

Erythroferrone (ERFE) the newly identified erythroid regulator Proposed mechanism of action



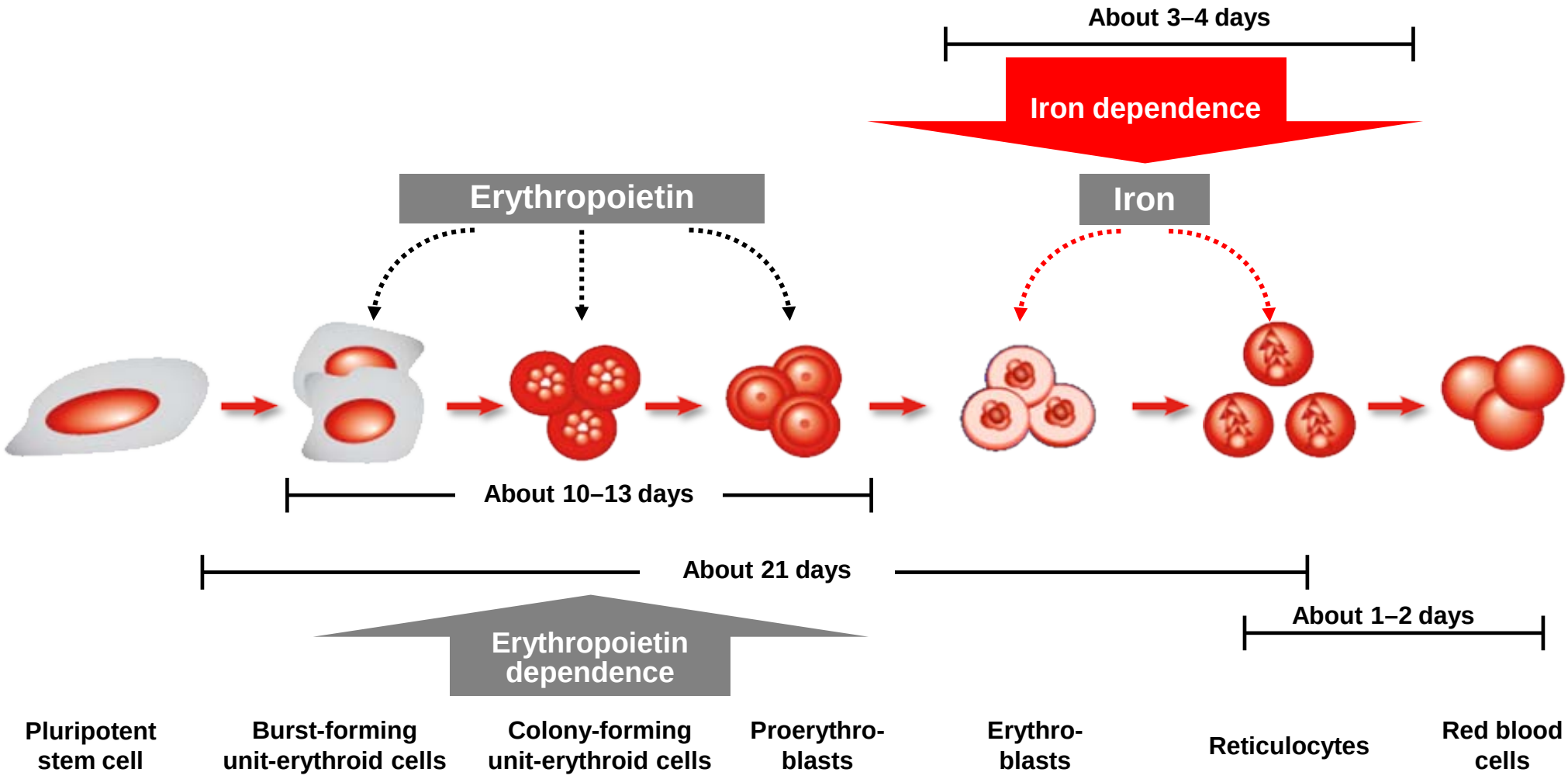


nature genetics

Identification of erythroferrone as an erythroid regulator of iron metabolism Kautz L, Nat Genet 2014

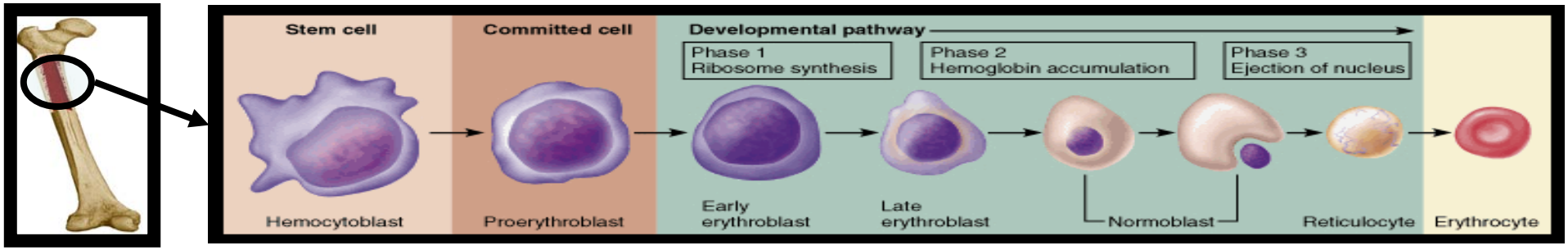
Kautz L , Nemeth, E Blood 2014 blood

‘Traditional’ view of iron –
a critical element in oxygen delivery (erythropoiesis)

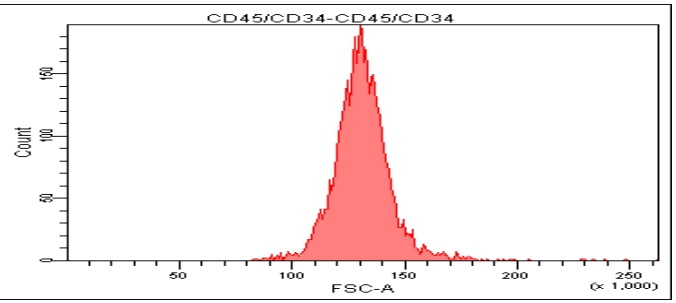


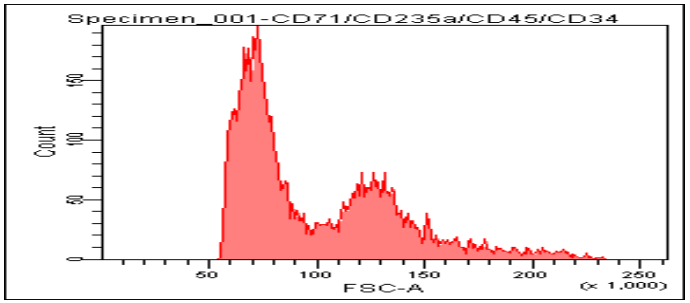
Adapted from Besarab A, et al. The Oncologist 2009;14:22–33

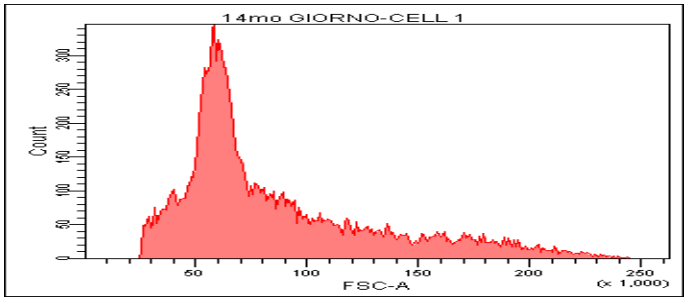
MCV During Differentiation



Globins, iron, and heme play a critical role in MCV determination

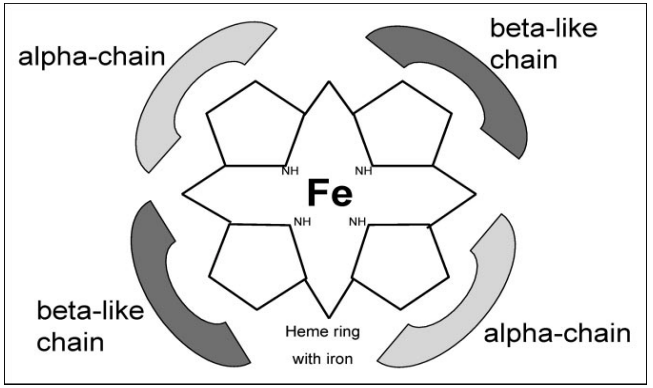






Mean MCV

0 day 131 fL
7 day 99 fL
14 day 86 fL



Data obtained from erythroid cultures (Drs. Iolascon and De Falco). Graphics courtesy of Prof. Achille Iolascon.

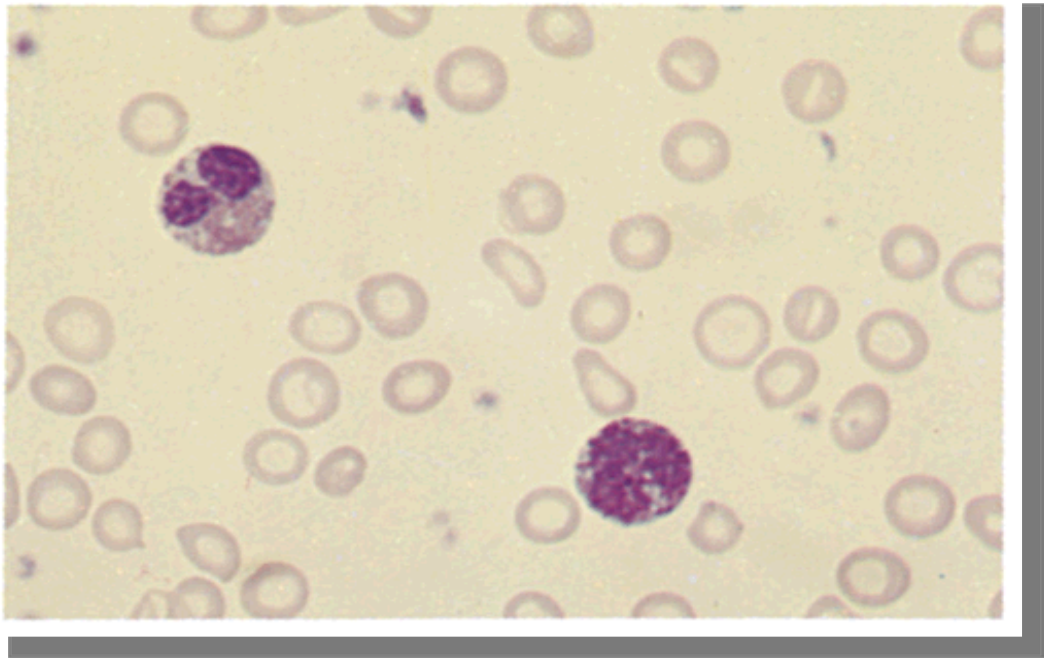
Characteristics of Microcytosis

✓**RBC:** Microcytosis hypochromia
reduced size and reduced Hb content of red blood cells,
as inferred by erythrocyte indexes

Normal values for age

Age	MCV (fl)
At born	110-128
5-24 months	80-85
2-6 years	75-90
6-12 years	78-95
>12 years	80-100

MCH: <26 pg (n.v 27-30)
MCHC: <30 g/dl (n.v.31-37)



Peripheral blood smear

Differential diagnosis of the most common forms of microcytosis

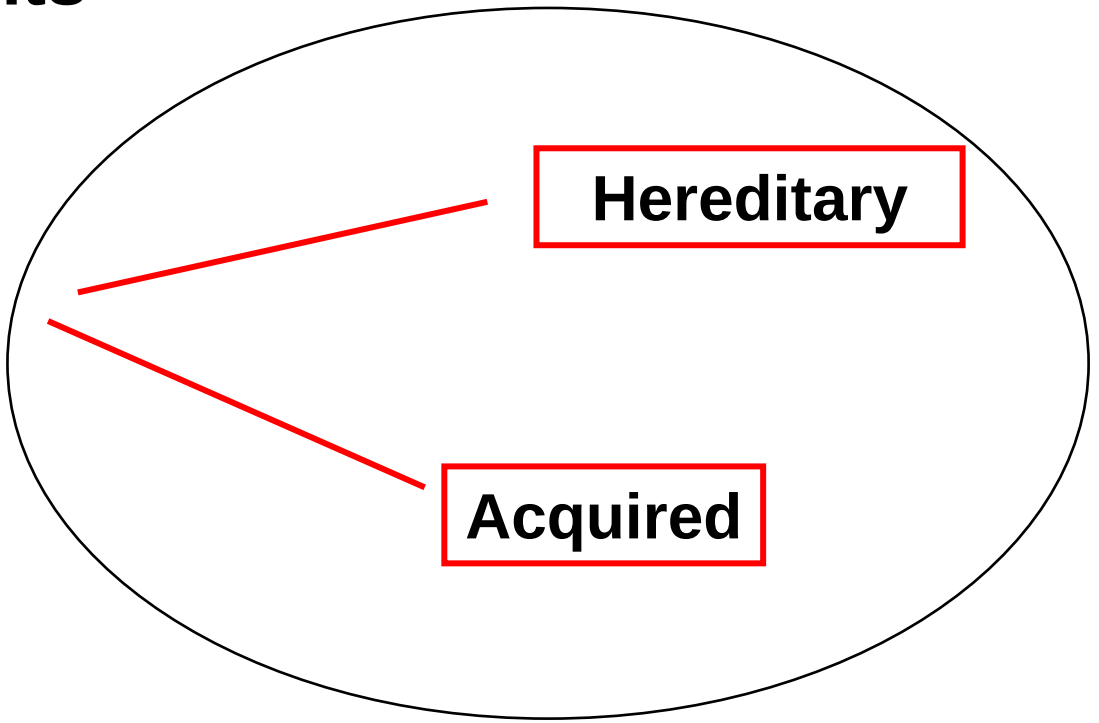
	Nutritional deficiency	Deficit of absorption	Thalassemia heterozygotes	ACD	ACD+iron deficiency
Hb	-	-	= / -	-	--
MCV	-	-	-	-	-
GR	-	-	+	-	--
RDW	=	=	= / +	= / +	+
Reticulocytes	-	-	= / +	= / +	= / + / -
IS	- / --	- / --	=	= / -	-
Ferritin	= / -	= / +	=	=	= / -
FEP	= / +	= / +	=	=	= / +
sTfR	+	+	+	=	= / +
CHr	-	-	= / -	-	--
Oral response	YES	NO	NO	Not to be expected	Partial
Iv response	YES	YES	NO	Not to be expected	Partial
Inheritance	Acquired	Acquired / multifactorial	AR	Multifactorial	Multifactorial
Suggested therapy	Oral iron	Etiological therapy / iv injection if severe anemia	Not required	Etiological therap yif possible (EPO, iv iron)	Etiological therap + oral iron

Iolascon A et al.,2013

Causes of Iron Deficiency Anaemia

- **Blood loss**
- **Limited supply (poor diet)**
- **Increased requirements**
- **Iron malabsorption**

IRIDA



Unexplained or Refractory Acquired Iron-Deficiency Anaemia (IRIDA)

- ***Helicobacter pylori***
- **Celiac disease**
- **Autoimmune atrophic gastritis**

Helicobacter pylori Infection

- In recent years, *H. pylori* has been implicated in several studies as a cause of IDA refractory to oral iron treatment[1]
  - Favorable response to *H. pylori* eradication
- Mechanisms: Occult GI bleeding? Alterations in intragastric pH and ascorbic acid concentration? Induction of IL-1β and TNF-α, (inhibitors of parietal cell function)? Induction of parietal cell apoptosis?[2]
- Diagnosis: IgG antibody screening, urease breath test[1]

1. Hershko C, et al. *Semin Hematol.* 2009;46:339-350.
2. Hershko C, et al. *Blood Cells Mol Dis.* 2007;38:45-53.

Celiac Disease

- Celiac disease is a common nonbleeding gastrointestinal condition that may result in refractory IDA[1]
  - Celiac disease accounts for 5%–6% of unexplained IDA cases
  - Approximately 50% of patients with subclinical celiac disease develop IDA
- Diagnosis: Anti-tissue transglutaminase antibodies and/or anti-endomysial antibodies

Hershko C, et al. *Semin Hematol.* 2009;46:339-350.

Autoimmune Atrophic Gastritis

- Autoimmune atrophic gastritis, or atrophic body gastritis, is associated with chronic idiopathic IDA with no evidence of gastrointestinal blood loss
- Iron deficiency may develop many years before the depletion of vitamin B_{12} stores
- Possible role of *H. pylori* in the pathogenesis of autoimmune gastritis due to antigenic mimicry of H^+K^+-ATPase
- Diagnosis: Serum gastrin, parietal cell antibodies

Hershko C, et al. *Semin Hematol.* 2009;46:339-350.

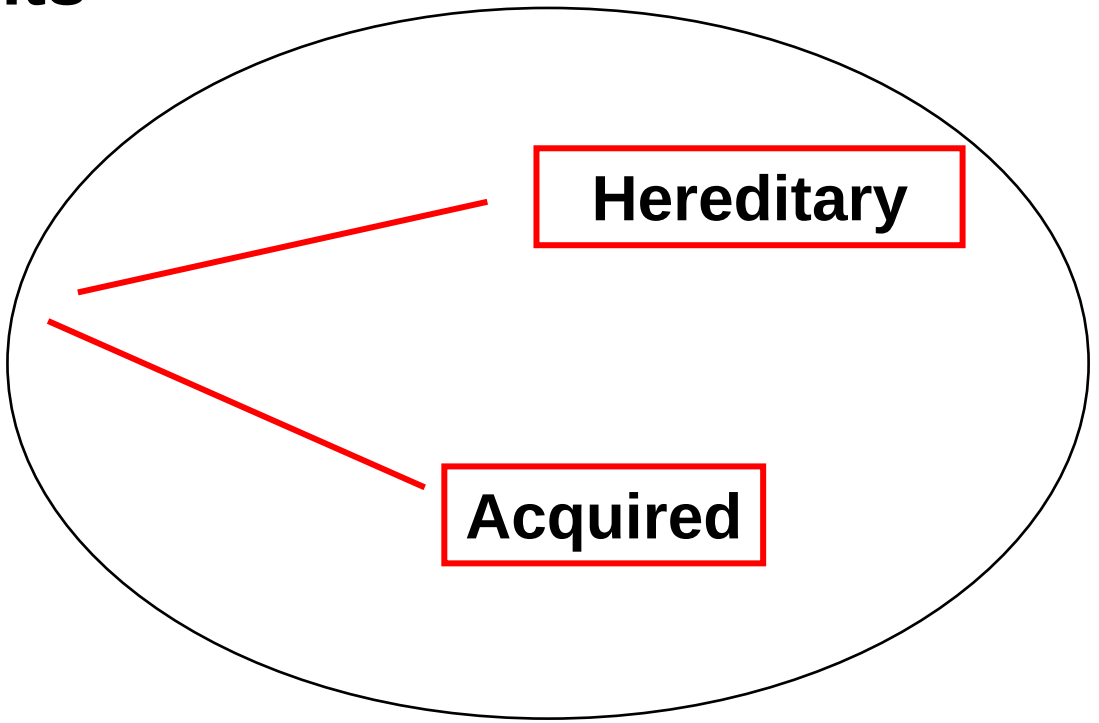
Acquired IRIDA

- Blood loss, insufficient dietary iron intake, and increased iron requirements are the main causes of iron deficiency anaemia.
- Acquired decreased iron absorption has recently been recognized in patients with unexplained or refractory IDA
- Celiac disease, autoimmune atrophic gastritis, and *H. pylori* infection are increasingly diagnosed in such patients
- In some cases, *H. pylori* may be directly implicated in the genesis of autoimmune gastritis
- We strongly recommend a diagnostic work-up for these conditions in case of acquired refractory or obscure IDA

Causes of Iron Deficiency Anaemia

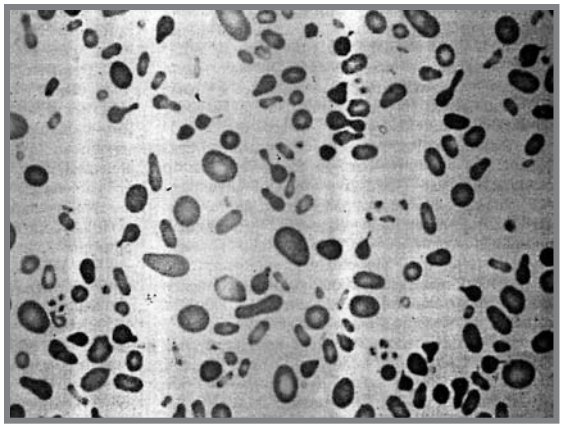
- **Blood loss**
- **Limited supply (poor diet)**
- **Increased requirements**
- **Iron malabsorption**

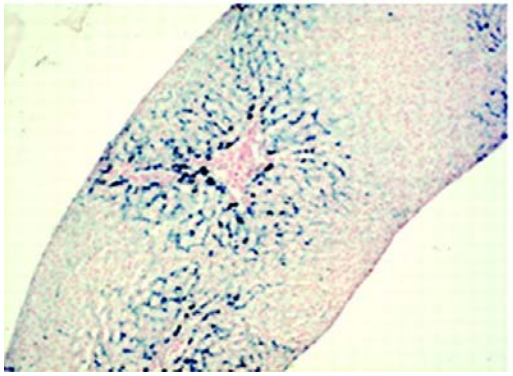
IRIDA

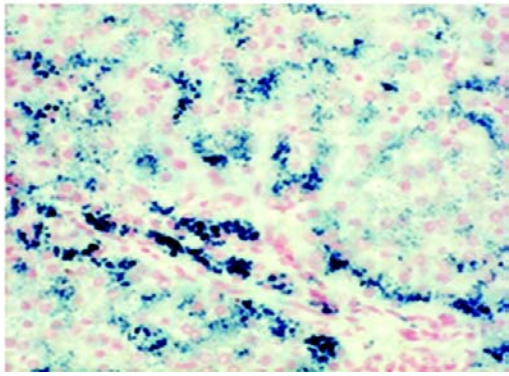


DMT1 Deficiency

delCTT intron 4 /
R416C







Severe microcytic anaemia with high transferrin saturation
Severe hypochromia with liver iron overload and normal ferritin levels

	Father, I-1	Mother, I-2	Proband, II-1							Normal values (range)
Age	35 y	32 y	Birth	2 mo	3 mo	6 mo	1 y	3 y	5 y	2-3 y
Body weight, percentile	NA	NA	< 3rd	3rd	5th	10th	15th	15th	25th	NA
Hb, g/L	149	128	40	74	76	82	98	90	85	130 (120-150)
MCV, fL	84	79.6	71	75	69	50	50	48	51	80
MCH, pg	28.8	27	14	14	15	15.3	14	13.5	15	26
Serum iron, μM	14.3	12.9	ND	29.7	28.6	30.4	26.5	34.7	36.5	14.3 (10.6-21.5)
Transferrin saturation, %	28	35	ND	85	100	80	63	80	90	7-30
Ferritin, μg/L	110	133	ND	256	864	110	70	26	34	7-140
FEP, μg/g Hb	ND	ND	ND	4.7	ND	ND	ND	ND	5.3	< 3
Treatment	None	None	18 mL PRBCs	25 mL PRBCs	30 mL PRBCs	sc rEpo	sc rEpo	sc rEpo	sc rEpo	NA

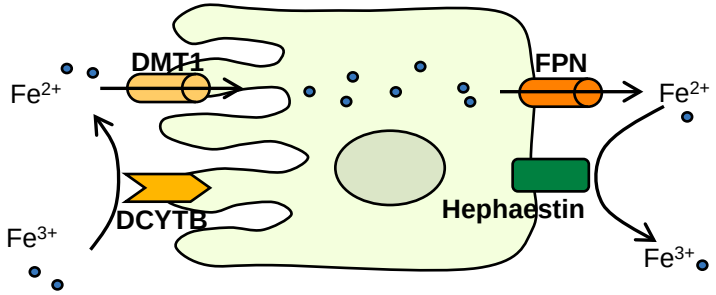
Graphics A, B, and Table with permission from Iolascon, A. et al. *Blood.* 2006;107:349-354.
Top left graphic courtesy of Dr. Achille Iolascon.

The iron cycle

Iron absorption

Enterocyte

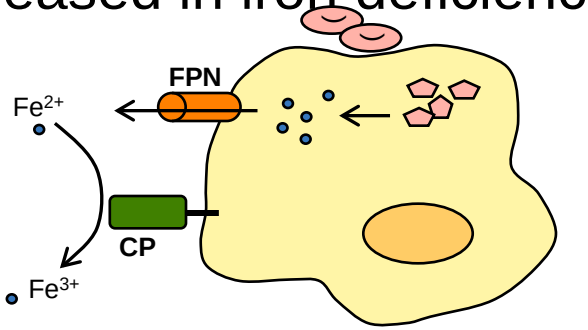
- 1–2 mg/day
- Hepcidin-regulated
- Balanced by iron losses (1–2 mg/day)
- Reduced in inflammation
- Increased in iron deficiency



Iron recycling

Macrophage

- 20–30 mg/day
- Hepcidin-regulated
- Balanced by erythroid request
- Reduced in inflammation
- Increased in iron deficiency



CP = ceruloplasmin; DCYTB = duodenal cytochrome B; DMT1 = divalent metal transporter 1; FPN = ferroportin.

Finch C. Blood. 1994;84:1697-702. Andrews NC. Blood. 2008;112:219-30.

Clinical and Laboratory Findings of DMT1 Mutations[1,2]

MCV	45–55 fL
Serum iron	++
Tf saturation	++
sTfR	++
BM sideroblasts	–
FEP	+
Liver iron	+++
Neonatal appearance	+
Effect oral/IV Fe	–/–
Serum or urinary hepcidin	–
Inheritance	AR
Therapy	Epo

- DMT1 is essential in erythropoiesis
- DMT1 is not essential for liver iron uptake
- DMT1 is not essential for duodenal iron absorption
  - Alternative pathways?
  - Heme absorption?
- Increased iron absorption occurs in the presence of iron overload because of low hepcidin levels
- Partial response of anemia to erythropoietin treatment

1. Iolascon A, et al. *Blood.* 2006;107:349-354. 2. Iolascon A, et al. *J Pediatr.* 2008;152:136-139.

Graphic courtesy of Dr. Achille Iolascon.

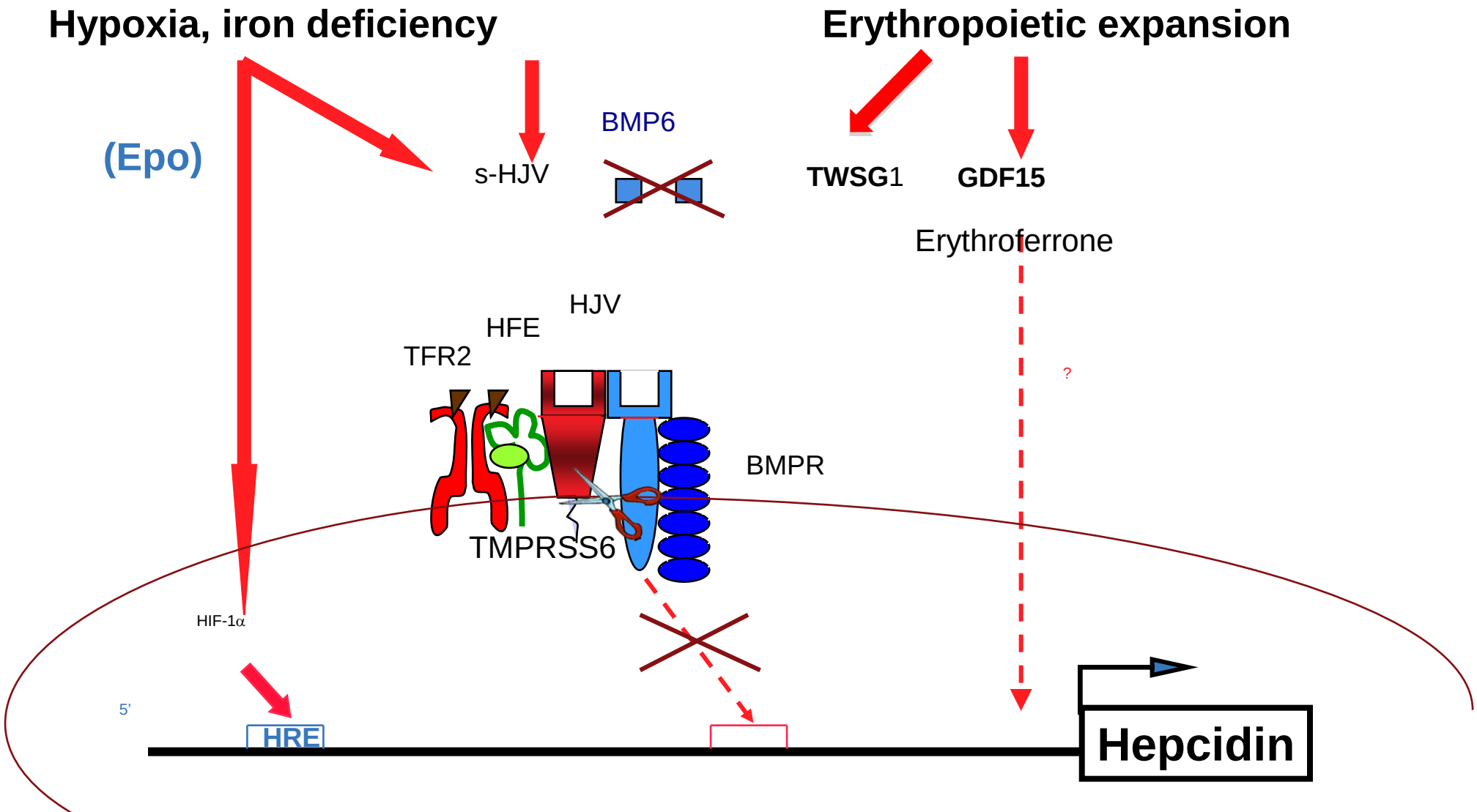
Genetic defects of iron absorption

IRIDA = iron refractory-iron deficiency anemia (OMIM #206200)

Autosomal recessive

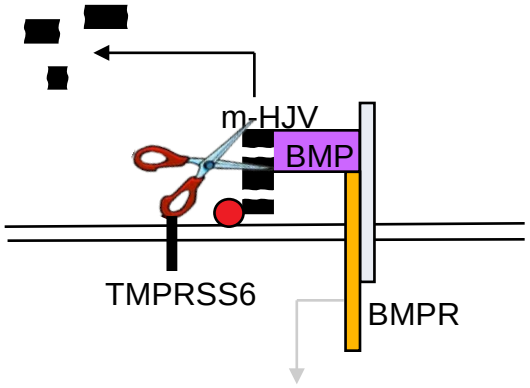
Caused by inappropriately high hepcidin production

Hepcidin downregulation: multiple pathways



Hepcidin regulation in Iron Deficiency and deregulation in IRIDA

Iron Deficiency

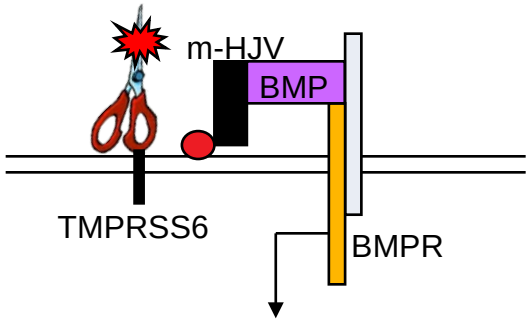


↓HAMP

↑ serum iron

Normal Erythropoiesis

IRIDA



↑HAMP

↓ serum iron

Iron Deficiency

Hematological parameters of the probands

n.	sex	age	Hb	MCV	% TF saturation	Serum Ft	Serum hepc
A	m	6	8.8	58	2	50	↑
B	f	13m	9.2	65	10	37	↑
C	m	17m	7.0	49	5	40	↑
D	f	11	8.2	56	3		↑
E	m	7	7.5	49	4	27	↑
F	f	3	9.7	61	4		-
G	m	15m	7.9	53	2	59	↑

(Finberg et al, Nature Genetics 2008;40:569-71)

Diseases/condition frequently associated with anaemia and/or ID

- Solid tumours and haematologic malignancies
  - ~40% anaemic, 32-60% iron-deficient
- Chronic kidney disease (CKD)[4,5]
  - 27-76% anaemic, 58-73% iron-deficient
- Inflammatory bowel disease (IBD)[6]
  - 6-74% anaemic, 36-90% iron-deficient
- Gastrointestinal disorders (GI)[7,8]
  - 10% (angiodysplasia) to 66% (coeliac disease) anaemic
- Chronic heart failure (CHF)[9,10]
  - 9-79% anaemic, 43% iron-deficient
- Women's Health conditions[11-13]
  - Heavy menstrual bleeding (HMB): 20% anaemic
  - Pregnancy and postpartum: global 42% anaemic, Europe 25% anaemic
  - Non-anaemic, non-pregnant, premenopausal women: 4-33% iron-deficient
- Special populations (elderly, children)[14,15]
  - Elderly: 3-61% anaemic, Children: 4-7% iron-deficient (US)

1. Ludwig. Eur J Cancer 2004;40:2293;
2. Aapro. Ann Oncol 2012;23:1954;
3. Ludwig. Eur J Cancer 2009 Jun;45(9):1603;
4. McClellan. Curr Med Res Opin 2004;20,1501;
5. Fishbane. Clin J Am Soc Nephrol 2009;4, 57;
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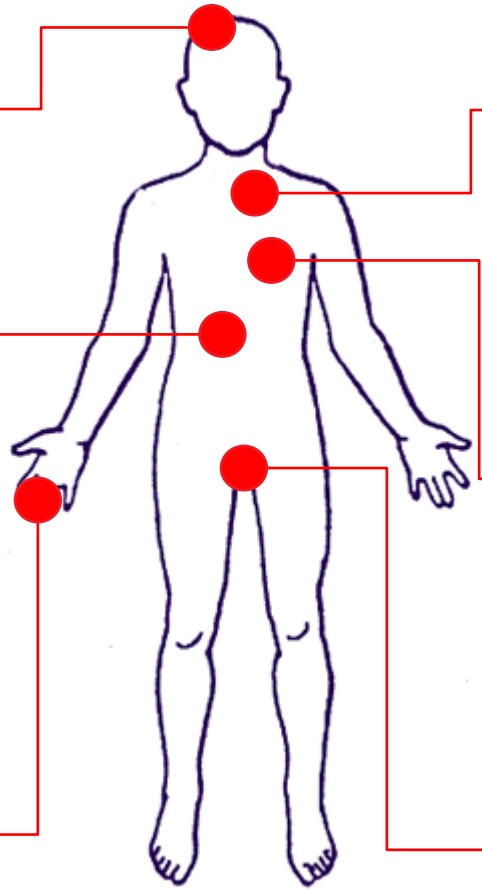
Clinical consequences of anaemia and of ID(A)

Central nervous system
- *Fatigue*
- *Dizziness*
- *Depression*
- *Impaired cognitive function*

Gastrointestinal system
- *Anorexia*
- *Nausea*

Vascular system
- *Low skin temperature*
- *Pallor of skin*



Immune system
- *Impaired T-cell and macrophage function*

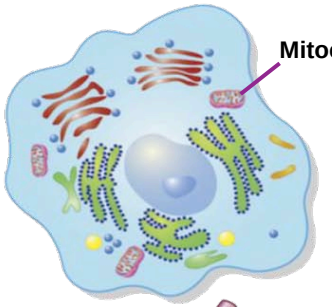
Cardio-respiratory system
- *Exertion dyspnoea*
- *Tachycardia, palpitations*
- *Hypertrophy*
- *Risk of cardiac failure*

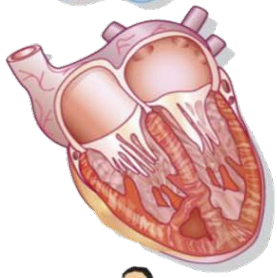
Genital tract
- *Menstruation problems*
- *Loss of libido*

Ludwig H, et al. Semin Oncol 1998;25:35-44.

Importance of iron for functioning and survival across all levels of complexity of living structures

Iron is critical for optimal functioning and survival of living structures:





Iron deficiency results in:

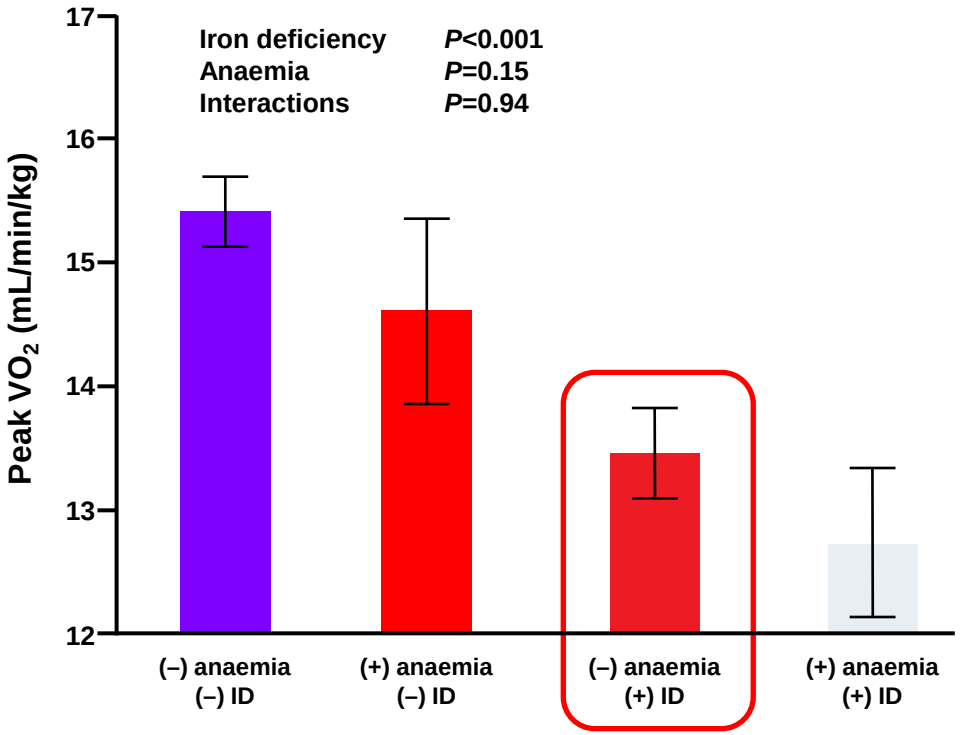
Defective energy metabolism

- **Mitochondrial dysfunction**
  - **Deranged activity of enzymes**
  - **Abnormal transport and structural proteins**
  - **Apoptosis**
- **Tissue remodelling**
  - **Impaired organ efficacy**
- **Impaired exercise capacity**
  - **Reduced work efficacy**
  - **Impaired cognitive performance and behaviour**
  - **Increased morbidity and mortality**

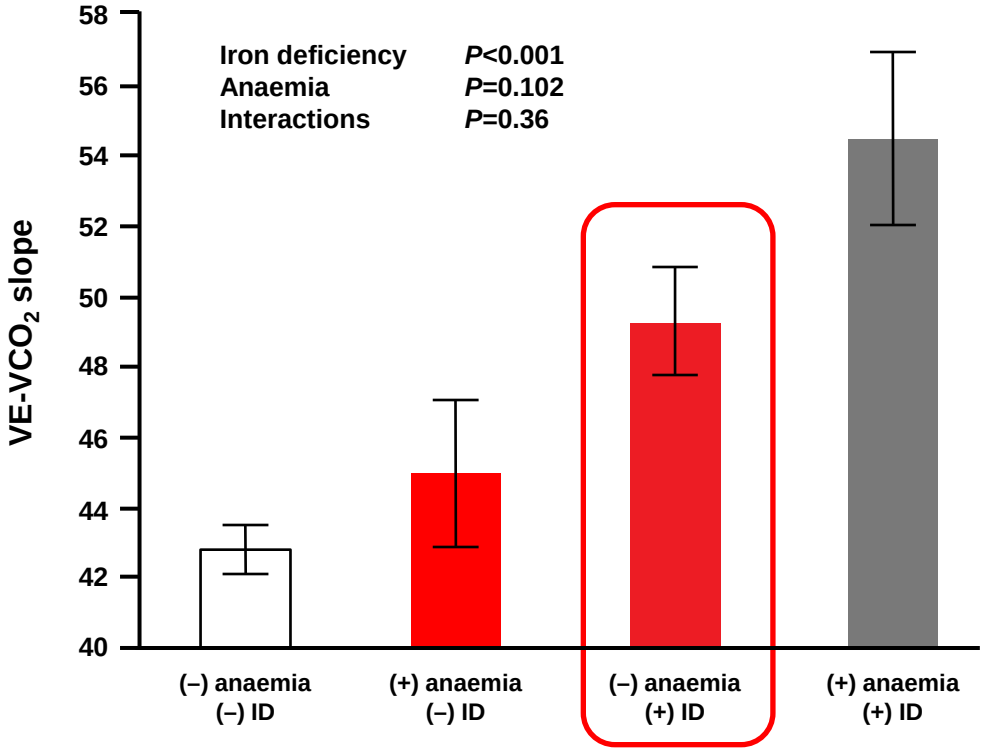
Jankowska EA, et al. Eur Heart J 2013;34:816–29.

ID is associated with reduced exercise capacity in heart failure (HF) patients

Peak oxygen consumption



Ventilatory response to exercise



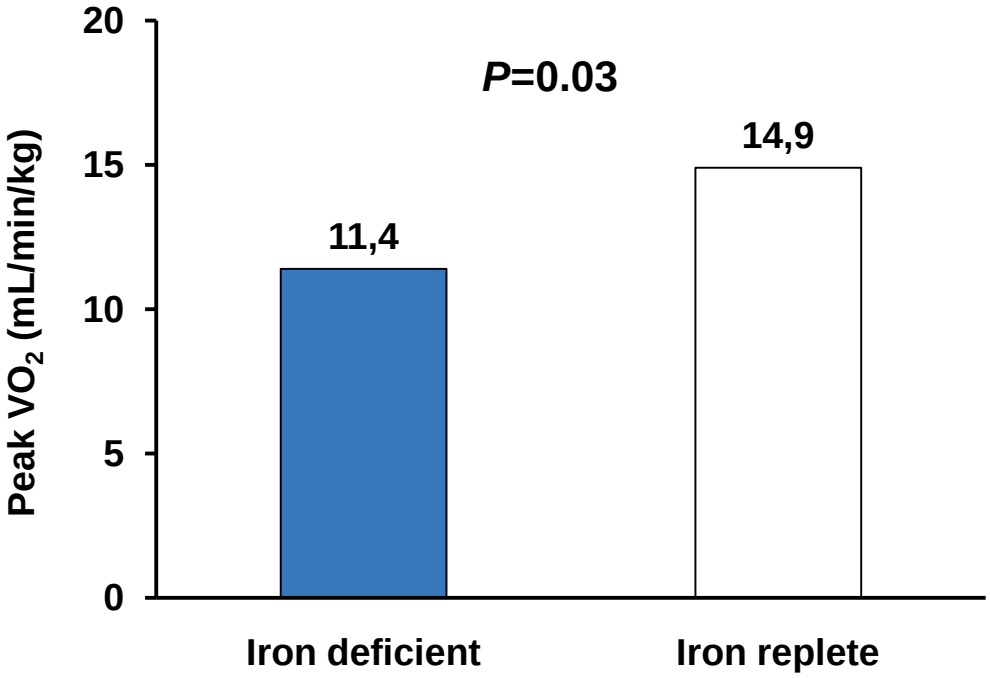
- Iron deficiency defined as serum ferritin <100 µg/L, or serum ferritin 100–300 µg/L with TSAT <20%
- Anaemia defined as haemoglobin level <12 g/dL in women and <13 g/dL in men
- Iron deficiency was present in 35% of patients

Jankowska EA, et al. J Cardiac Fail 2011;17:899–906

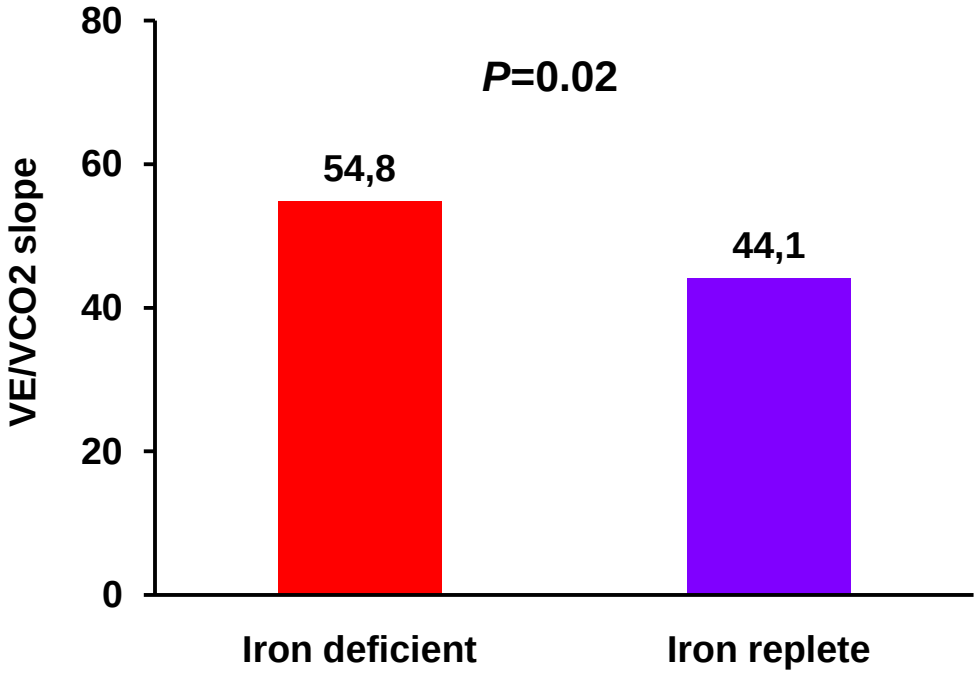
TSAT, transferrin saturation

ID is associated with reduced exercise capacity in HF patients

Peak oxygen consumption



Relationship between ventilation and VCO_2



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- Anaemia defined as haemoglobin level <12 g/dL in women and <13 g/dL in men

Okonko DO, et al. J Am Coll Cardiol 2011;58:1241–51

Summary and conclusions

- Iron is an essential nutrient
- ID deficiency is prevalent
- ID presents with a broad spectrum of clinical signs and symptoms
- ID has a considerable impact on patients' life
- Diagnosis is based on haematological parameters, which have different cut-off values depending on the disease

Anemia Work up and Differential Diagnosis