

Iron deprivation anemia

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Disclosures

- Employment: St Mary's, McGill,
- Consultancy: Novartis, Health Life Sciences
- Research: Oncology clinical trials
- Honoraria: Celgene, Roche, GSK, Pfizer, Novartis, HLS

IRON DEPRIVATION ANEMIA

- The most common type of anemia
- Anemia is microcytic (to normocytic) $< 87 \text{ fl}$
normal MCV is 87 (80 – 99)
- It is caused by decreased content within each red blood cell
(% of which is **hemoglobin**)
- Hemoglobin is composed of 4 globin chains, each chain is composed of:
 - 1 **heme** (protoporphyrin + **iron**) molecule
 - 1 **globin** molecule
- Decreased synthesis of either heme or globin leads to **microcytic anemia**

MICROCYTIC ANEMIA

1. Decreased production of **heme**
 - **IRON DEPRIVATION ANEMIA**
 - SIDEROBLASTIC ANEMIA
2. Decreased production of **globin** chains:
either alpha, beta, gamma, delta
 - THALASSEMIA

IRON DEPRIVATION ANEMIA

*There has to be a steady supply of **iron** to make heme (hemoglobin)*

- 1. Iron is not available to the erythron because of lack of iron within the organism

IRON DEFICIENCY ANEMIA

- 2. Iron is not available to the erythron while there is plenty of iron within the organism

ANEMIA OF INFLAMMATION

Iron

- **Indispensable for life**

 - O₂ transport (Hb)**

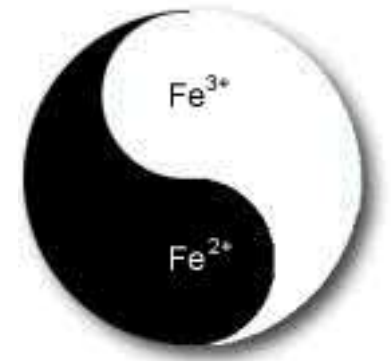
 - Electron transfer (Cytochromes)**

 - DNA synthesis (Ribonucleotide Reductase)**

 - Neurotransmitter production (Tyrosine Hydroxylase)**

- **Insoluble (10⁻¹⁷M)**

- **Toxic (Fenton chemistry):**



courtesy P Ponka

Fe “CONCENTRATION” [M]

- **Water** (pH 7.0)

Max [Fe ³⁺]	0.000 000 000 000 000 000 01
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- **Plasma**

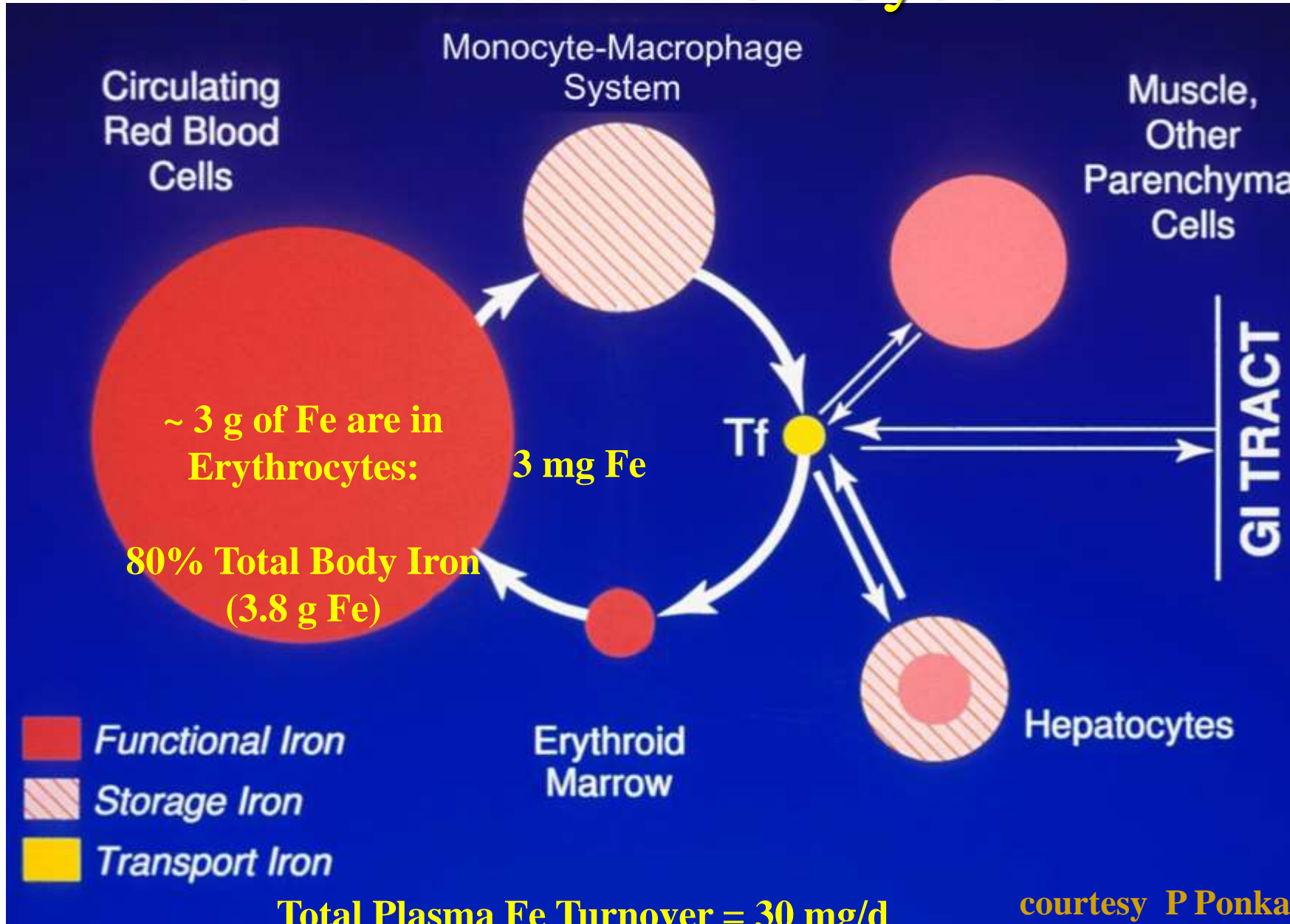
Fe ₂ -Tf	0.000 002
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- **Erythrocyte**

Heme	0.020
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Non-heme	0.000 001
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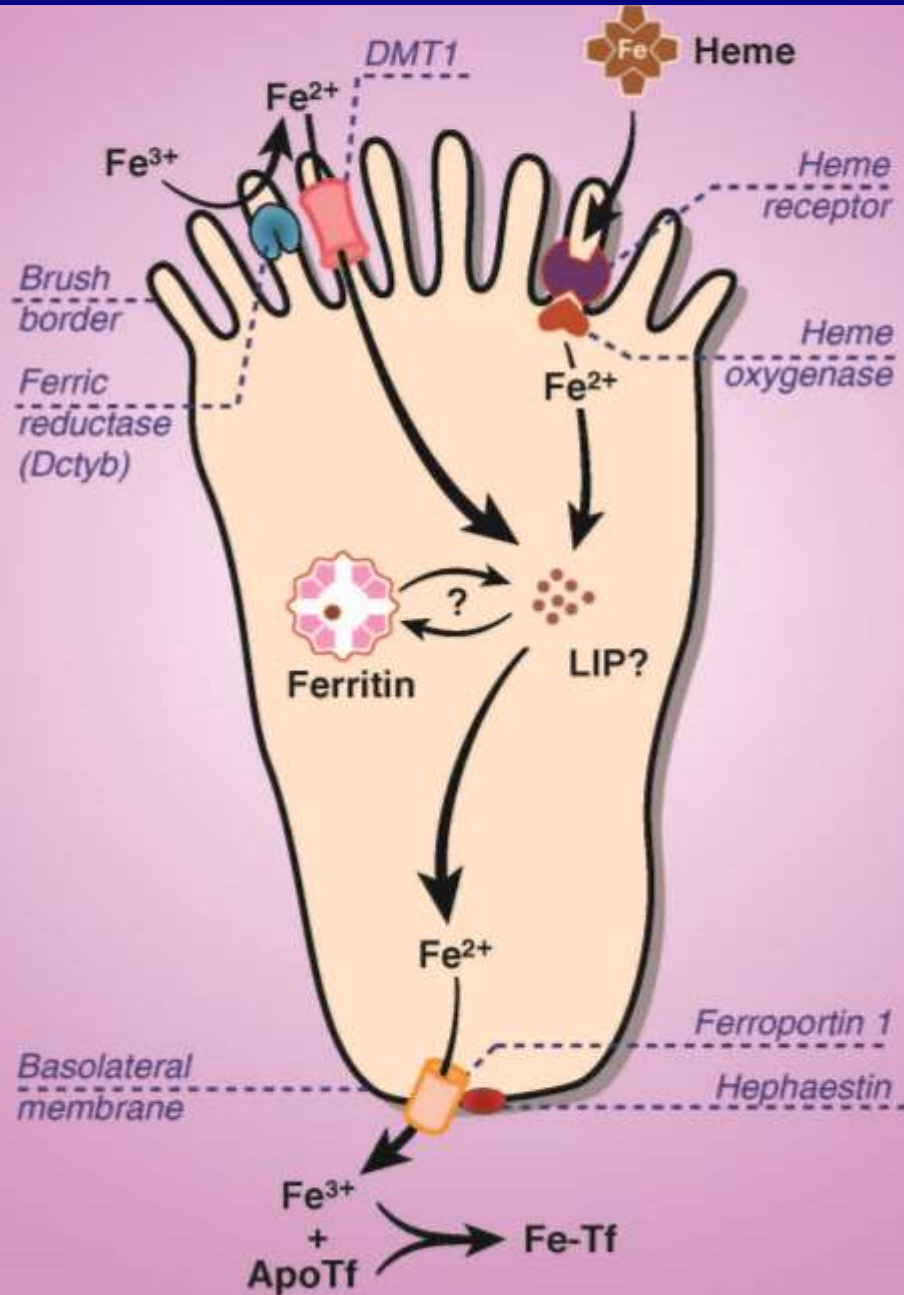
The Mammalian Iron Cycle



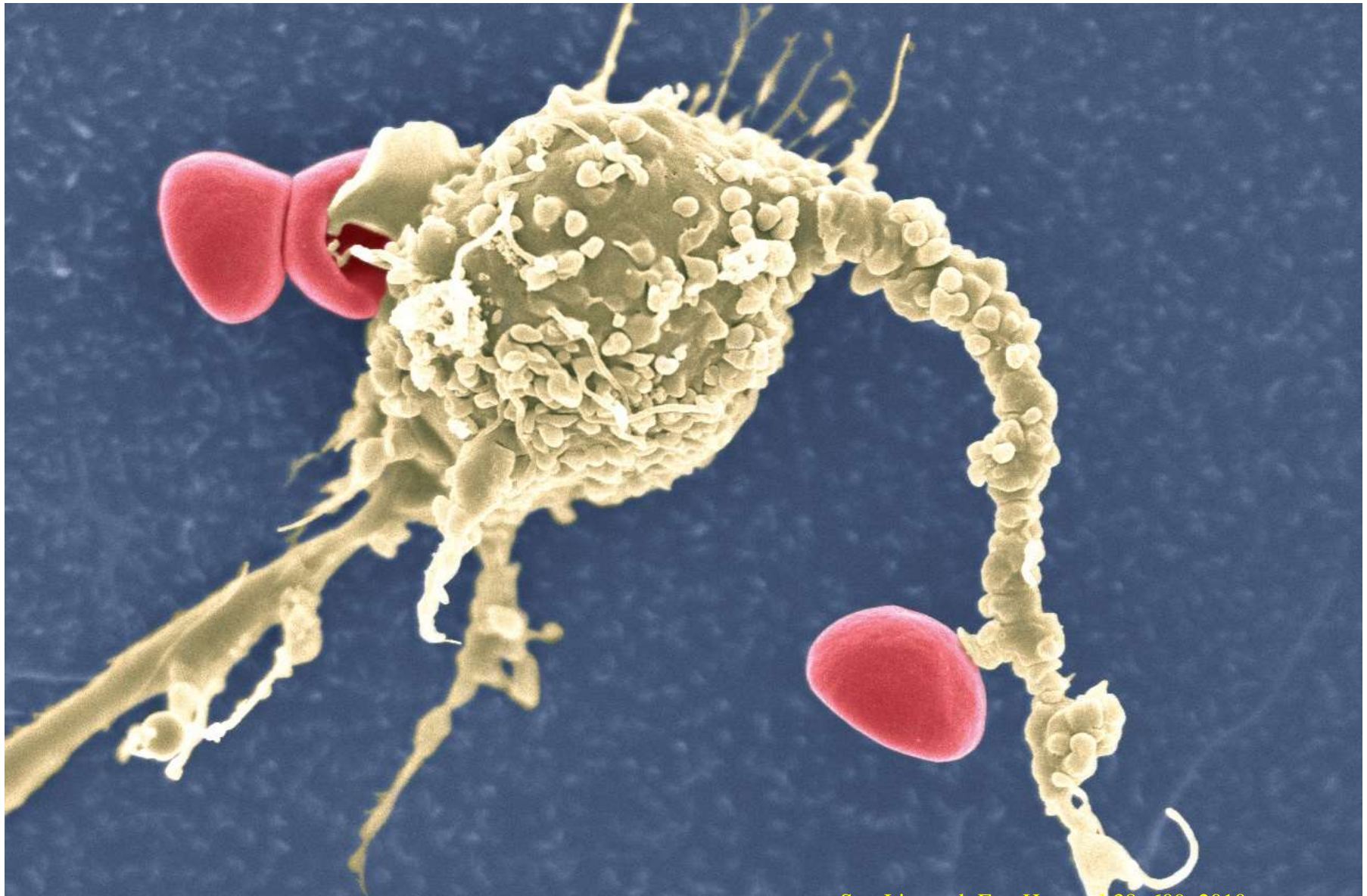
Proteins of iron metabolism

PROTEIN	FUNCTION
ALAS2/eALAS	1 st enzyme of heme synthesis; deficiency leads to x-linked sideroblastic anemia
Ceruloplasmin (Cp)	Plasma protein with ferroxidase activity; cellular export
DMT1/DCT1/Nramp2	Membrane Fe ²⁺ transporter; cellular uptake
Duodenal cytochrome b (Dcytb)	Membrane ferric reductase; cellular uptake
Erythroferrone	Produced by erythroblasts, inhibits the action of hepcidin; it increases the amount of Fe available for Hb synthesis
Ferritin (Ft; H and L)	Cytosolic Fe storage protein
Ferrochelatase	Mitochondrial protein; insert Fe into protoporphyrin IX ring to form heme
Ferroportin1/Reg1/MTP1	Membrane Fe ²⁺ transporter; cellular export
Fratxin	Involved in mitochondrial iron export
Heme oxygenase 1	Microsomal protein; recycle Hb iron
Hepcidin	Plasma peptide; deficiency leads to iron hyperabsorption
Hephaestin	Membrane Cp homolog; enterocyte export
HFE	Unknown; binds TfR; mutated in >85% of hereditary hemochromatosis
IRP (-1 and -2)	Cytosolic iron sensors; post-transcriptional regulation
Mitochondrial ferritin	Mitochondrial Fe storage; H-Ft homolog
Mitoferrin/Mrs3/4	Mitochondrial inner membrane Fe transporter
Sec151/Sec15	Mutated in "haemoglobin deficit mouse"; yeast homolog is part of exocyst pathway
Steap3	Possible (?) endosomal ferrireductase
Transferrin (Tf)	Plasma Fe ³⁺ carrier
Tf Receptor	Cognate membrane receptor for Tf
Tf Receptor 2	Unknown; similar to "classical" Tf receptor

Duodenal Enterocytes



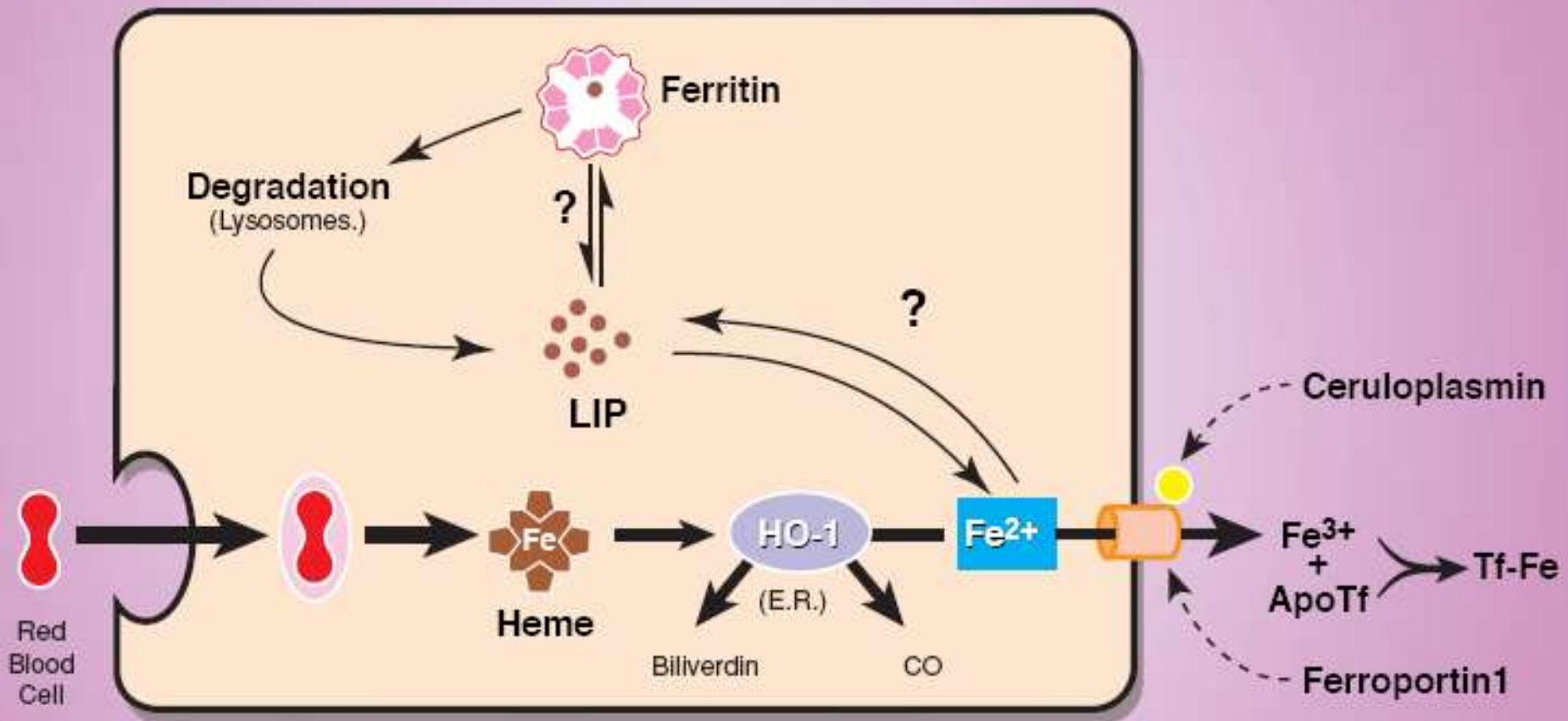
Macrophages Attach to and Begin Engulfing RBC



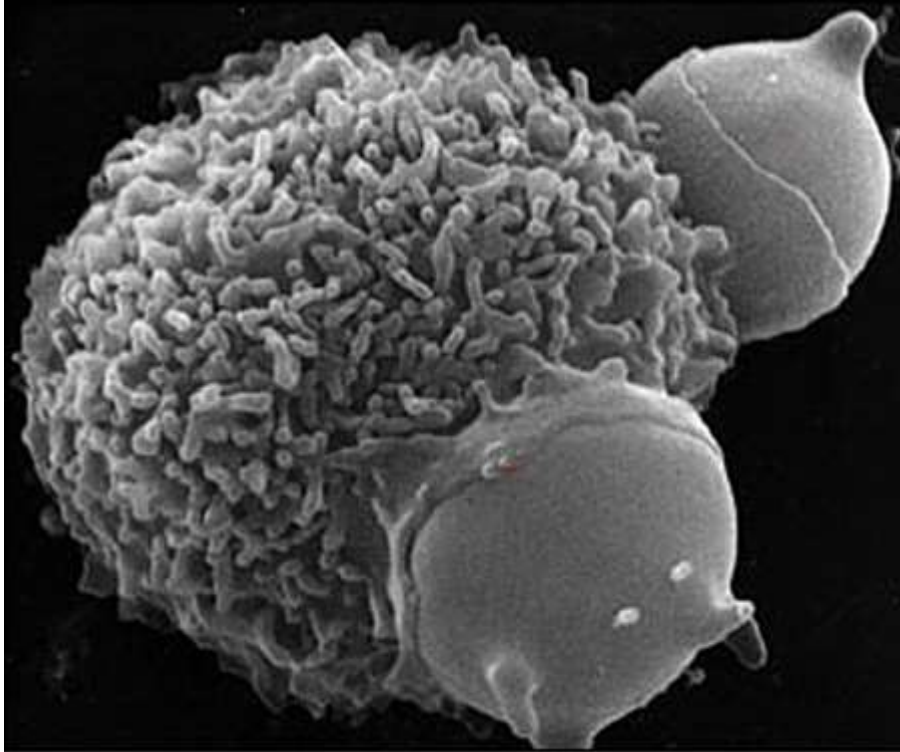
Soe-Lin et al. Exp Hematol 38: 609, 2010
Featured on the Frontpage

Hemoglobin Iron Recycling

Macrophage



Macrophages and Erythrophagocytosis

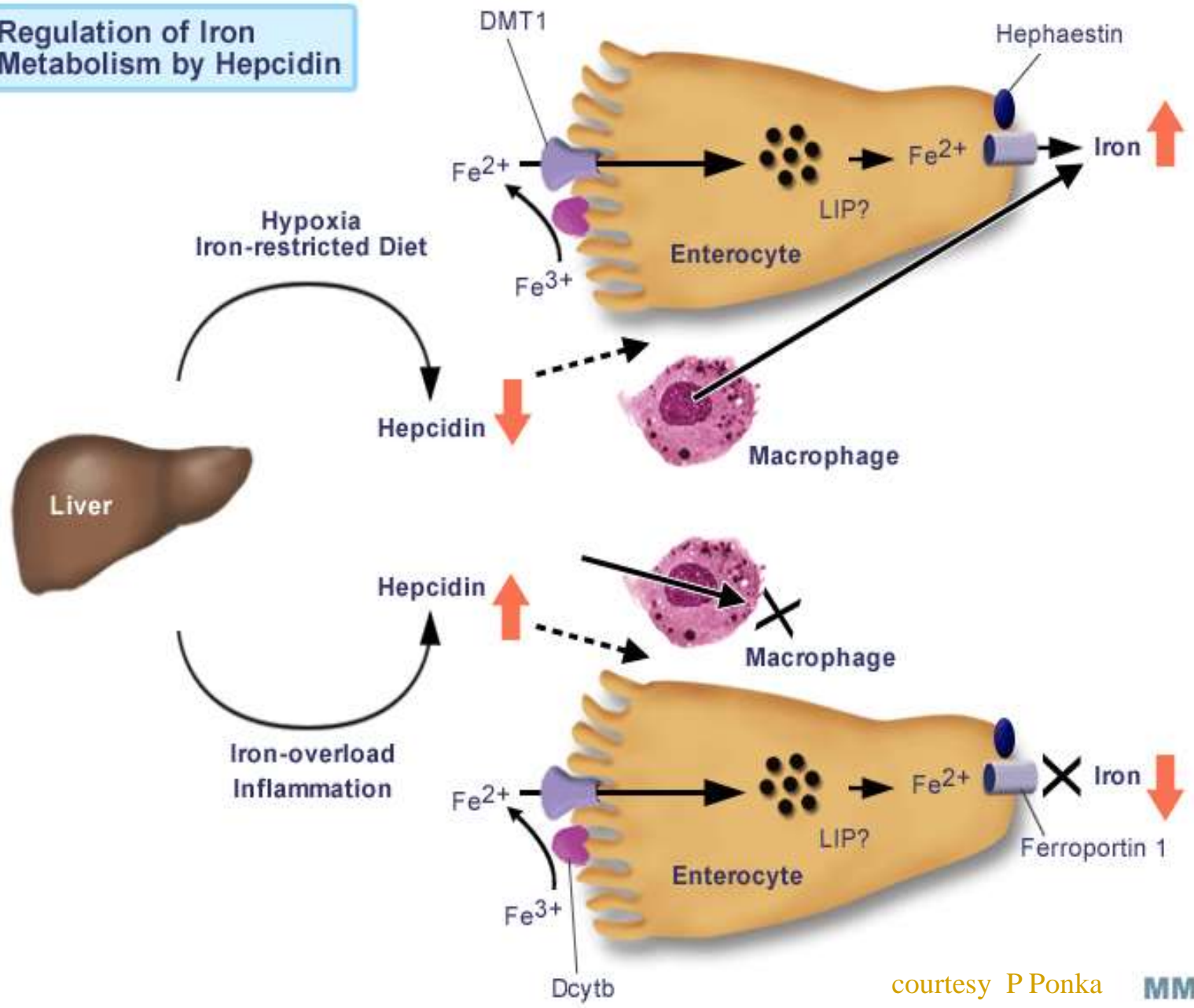


- 2 million red blood cells are ingested/s
- 24 mg of iron are recycled daily through macrophages with remarkable efficiency

HEPCIDIN

- **Expressed in hepatocytes**
- Induced by iron via an incompletely characterized pathway requiring bone morphogenic proteins (BMPs)
- Downregulated in response to increased erythropoietic demand or hypoxia
- Induced during inflammation by IL-6, involved in innate immune responses

Regulation of Iron Metabolism by Hepcidin



Fe Transport across Biological Membranes

II

ferroportin

aka MTP1 (metal transport protein 1) or Ireg1

- exports iron (Fe^{2+} ?) from “donor” cells
(**enterocytes, macrophages**)
to plasma **transferrin**

IRON DEFICIENCY ANEMIA

- Low MCV
- Low ferritin
- Low serum iron
- High transferrin (TIBC)
- Low Fe/transferrin saturation
- Absent marrow iron

- Serum zinc protoporphyrin
- Serum transferrin receptor
- Reticulocyte hemoglobin content
- Therapeutic trial

MICROCYTIC ANEMIA (low MCV)

Differential diagnosis:

- Hemoglobinopathies
 - Thalassemia trait (alpha, beta, beta/delta)
 - Thalassemia major beta, Hemoglobin H disease
 - Hemoglobin E disease
 - Hemoglobin Lepore trait, Hemoglobin E trait
- Anemia of inflammation
- Blockade of heme synthesis (lead, INH)
- Sideroblastic anemia

MICROCYTIC ANEMIA (low MCV)

iron deficiency versus thalassemia trait

- Iron deficiency anemia
 - low MCV / high RDW
- Thalassemia trait
 - low MCV / normal or mildly increased RDW
- Compound cases
 - (frequent in pregnancy)

IRON DEFICIENCY ANEMIA

Symptoms:

Symptoms of anemia

Decreased work performance

Hair loss

Pica

Delayed infant and child development

IRON DEFICIENCY ANEMIA

- There is an obligatory iron loss (1 mg/day) due to shedding of cells of mucosae, skin and small amount of blood
- In majority of subjects iron losses and iron intake are perfectly balanced
- **Diagnosis of iron deficiency obliges us to identify the cause of iron loss, that is of hemorrhage**

IRON DEFICIENCY ANEMIA

Causes of hemorrhage:

- **GI**
- **GU**
- **GYN**
- Respiratory tract
- Biliary tract
- Falcious anemia
- Iatrogenic anemia
- Vascular disorders

IRON DEFICIENCY ANEMIA

Treatment: must be calculated to rectify anemia **and**
replenish iron stores

Oral iron preparations

many !

- use the cheapest, non-enterocoated

(IM iron)

painful, leaves stains

Intravenous iron

succrose or dextran

- possible anaphylactoid reaction

IRON DEFICIENCY ANEMIA

Useful numbers 1 :

- Obligatory blood loss 1mg
- 1 gm of red cell mass 1mg
- Average menstrual blood loss 40 mls (20 mg of Fe)
- 1 unit blood donation 200 mg
- 1 unit blood transfusion 200 mg
- Iron given to the baby and peripartum blood loss 300 – 900 mg
- daily iron requirement 1mg
 - young women 1.7 – 2mg
 - pregnancy 3 mg
 - breast feeding 2 mg

IRON DEFICIENCY ANEMIA

Useful numbers 2 :

Fe content of standard diet 20 mg

Absorption of ingested oral iron 6 – 10 %

Usual iron oral tbl 50-60 mg of elemental iron

Duration of oral iron therapy:

time to correct anemia

plus

6 to 12 months

IRON DEFICIENCY ANEMIA

ANEMIA OF INFLAMMATION

1. Anemia of chronic disease

develops over weeks, months

2. Anemia of critical illness

develops within days (ICU)

ANEMIA OF INFLAMMATION

- mild to moderate anemia
- normocytic to microcytic
- low serum iron
- low TIBC (transferrin)
- high ferritin
- high sed rate and or CRP
- presence of an underlying illness

- high hepcitidin
- high IL-6 and or other cytokines
- low transferrin receptor

ANEMIA OF INFLAMMATION

- Principal cause is restriction of erythropoiesis due to **non-availability of iron**
- Additional minor causes:
 - decrease life span of rbc
 - decrease synthesis of erythropoietin

ANEMIA OF INFLAMMATION

Treatment:

- Treatment of underlying disease
- If not possible or not completely satisfactory:
 - transfusion
 - erythropoietin
 - iron therapy (IV infusion) usually to supplement epo therapy

TAKE HOME MESSAGE

- when Hb low, check MCV, then RDW
- do Iron studies, or Hb electrophoresis, or both
- try to fully diagnose pts' anemia
- (if you cannot , refer)
- **ALWAYS** identify the site and cause of bleeding (IDA)
- treat **COMPLETELY** with oral iron preps (IDA)
- identify and treat underlying disorder (AI)

Iron Deprivation Anemia

- THANK YOU

IRON DEFICIENCY ANEMIA

- Iron depletion

low ferritin, normal serum iron/TIBC

- Iron deficiency without anemia

low ferritin, low serum iron/TIBC, normal Hb

- Iron deficiency anaemia

low ferritin, low serum iron, low Hb