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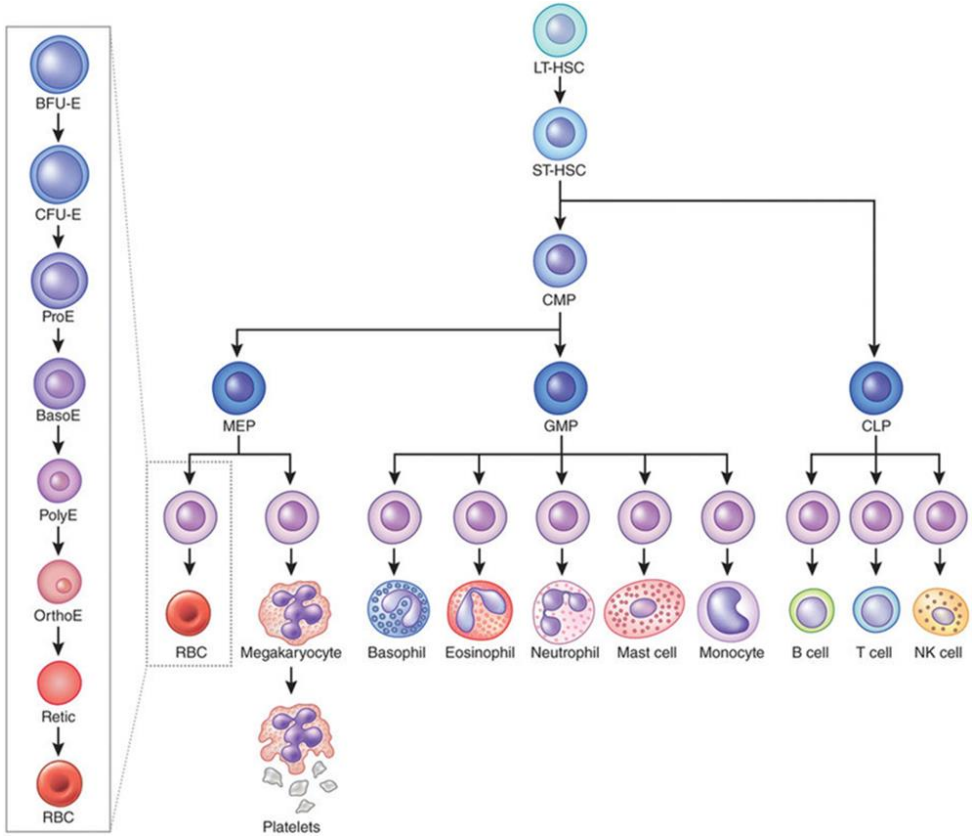
Anemia

Hematopoesis

- erythroid differentiation in the bone marrow takes 5-7 days

- the lifespan of an erythrocyte in the blood is 120 days
  - decreased in hemolytic anemias possibility of compensation by increased production of erythrocytes (8 – 10x)
- reticulocytes
  - normally in blood 1-1.5% within 1-2 days of maturation into erythrocytes



Hemopoietic growth factors

glycoproteins

- act on the cytokine-receptor superfamily

stimulating factors

- erythropoietin
- IL-3, 6, 7, 11, 12
- thrombopoietin
  - produced in the kidney and liver
  - controls platelet production

inhibiting factors

- TNF-α, TGF-β

use in treatment

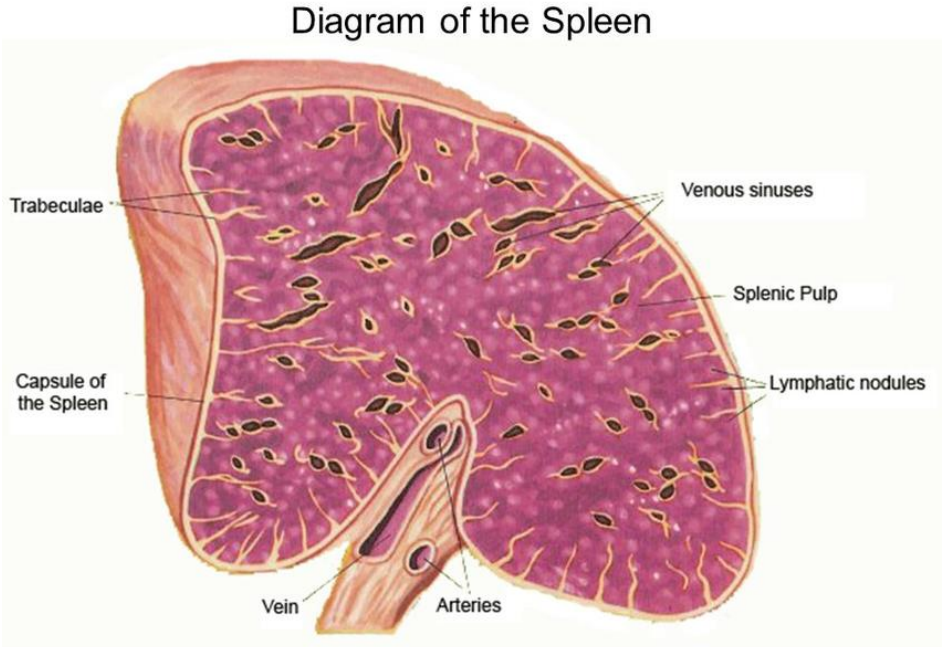
– G-CSF

- accelerate recovery after chemotherapy and hemopoietic cell transplantation
- EPO
- thrombopoietin receptor agonist
- treatment of immune thrombocytopenic purpura

Spleen

contains approximately 5% of blood

- function
  - remodelling of the erythrocyte membrane uptake and destruction of old and damaged erythrocytes
- splenomegaly
  - enlargement of the spleen due to increased destruction of erythrocytes in some pathological conditions (e.g. spherocytosis)
- removal of the spleen (=splenectomy) can correct anemia and relieve symptoms



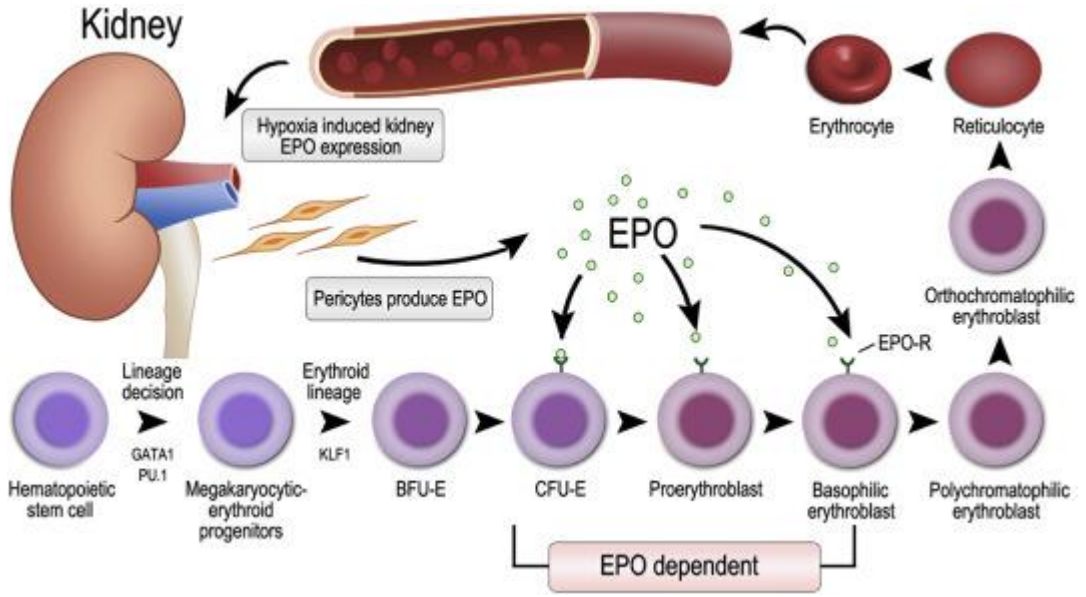
Kidneys and erythropoiesis

the main regulator of erythropoiesis is erythropoietin (EPO)

- produced by the peritubular cells of the kidney

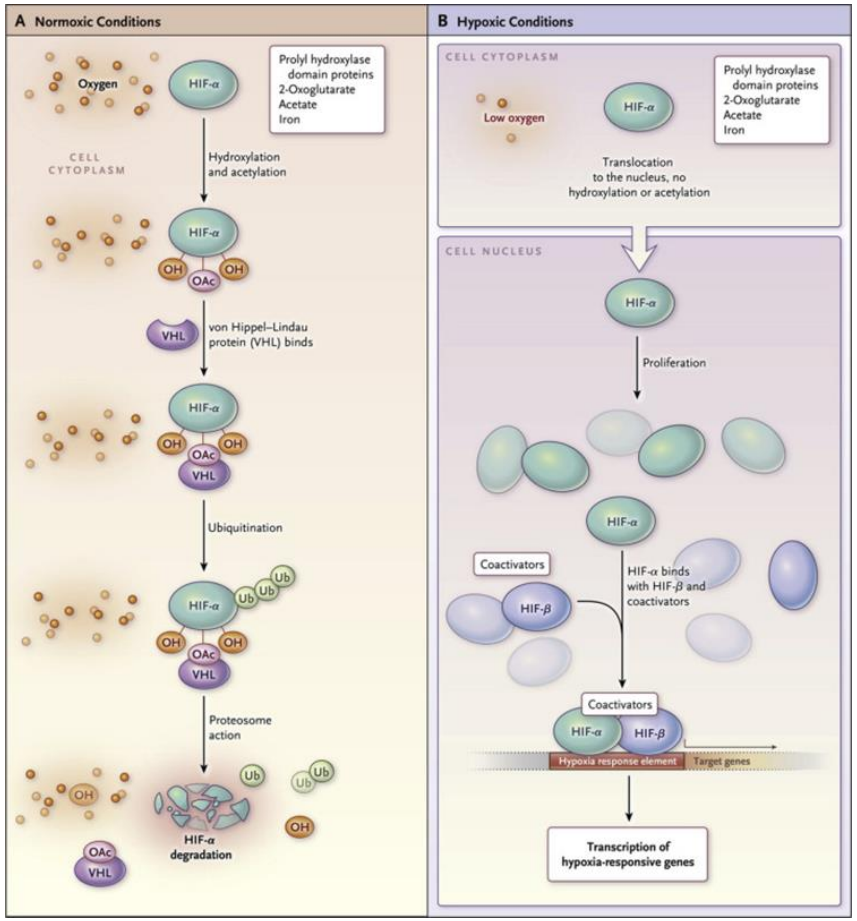
reduce the production of erythropoietin

- kidney disease
- antibodies against EPO



Journal of the Formosan Medical Association, Volume 117, Issue 11, 2018

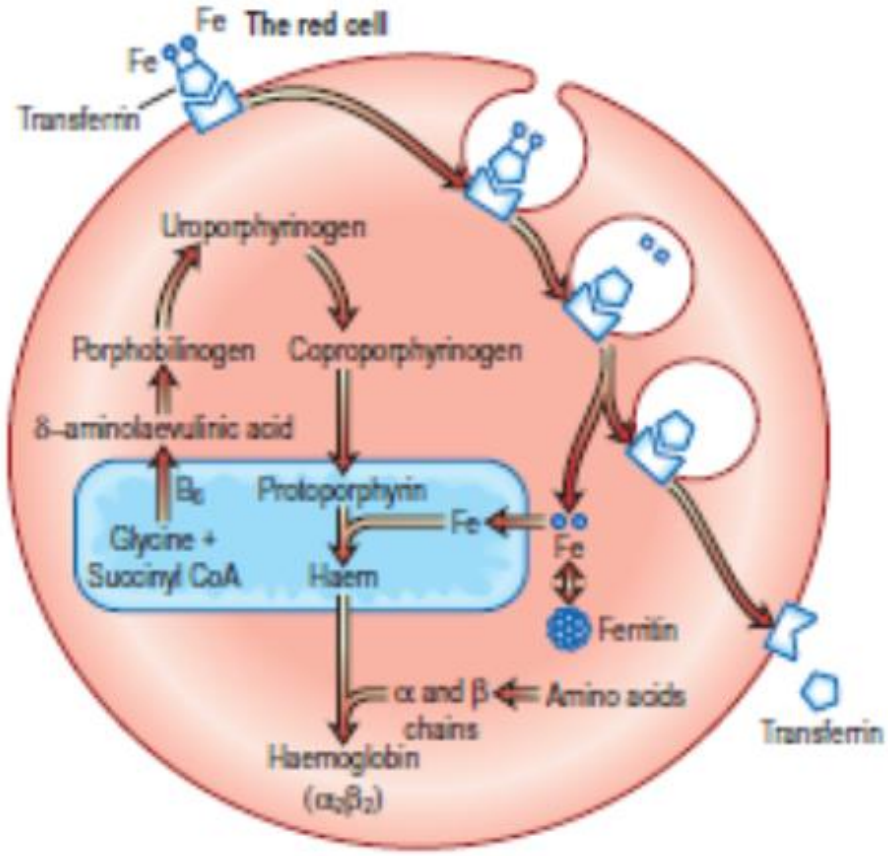
Oxygen sensor of the cell



- transcription factor HIF (hypoxia-inducible factor)
  - subunit α
    - „oxygen-dependent“
    - in normoxia - HIF-1α prolix is hydroxylated
      - degradation in proteasomes using von Hippel-Lindau protein
    - in hypoxia – inhibition of hydroxylation and activation of HIF signalling
  - subunit β
    - stable
- activation of gene expression and regulation of multiple processes
  - erythropoiesis and iron metabolism
  - anaerobic glucose metabolism
  - angiogenesis
    - e.g. VEGF – increased vascularisation of tissues
  - growth, proliferation

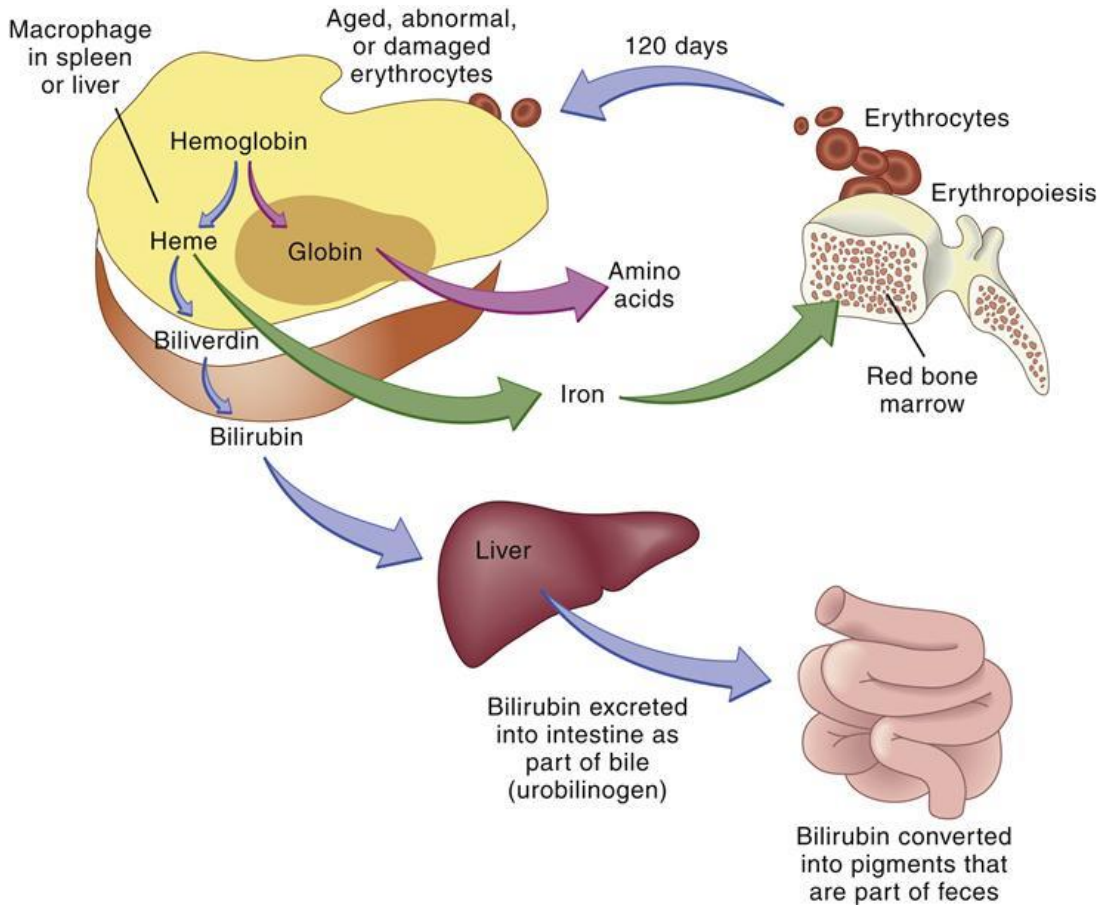
Hemoglobin synthesis

- performs main function of RBC
- adult Hb molecule (HbA)
  - 2 α chains, 2 β chains ($\alpha_2\beta_2$)
  - 97 % of the Hb in adults
- other types
  - HbA2 ($\alpha_2\delta_2$): 1.5 – 3.2 %
  - HbF ($\alpha_2\gamma_2$): < 1 %
- synthesis in the mitochondria
  - production of aminolevulinic acid
    - ALA synthase
    - rate-limiting step
    - coenzyme vitamin B_6
    - inhibited by heme
    - stimulated by EPO



Degradation of erythrocytes

- hemolysis may occur
  - extravascularly
    - spleen, bone marrow, liver
    - aggravated leads to jaundice
    - hemoglobin is reused
  - intravascularly
    - serum haptoglobin is decreased
    - hemoglobin is filtered in the kidneys
      - appears in the urine
      - precipitation in the tubules – up to acute kidney failure



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Anemia

criteria

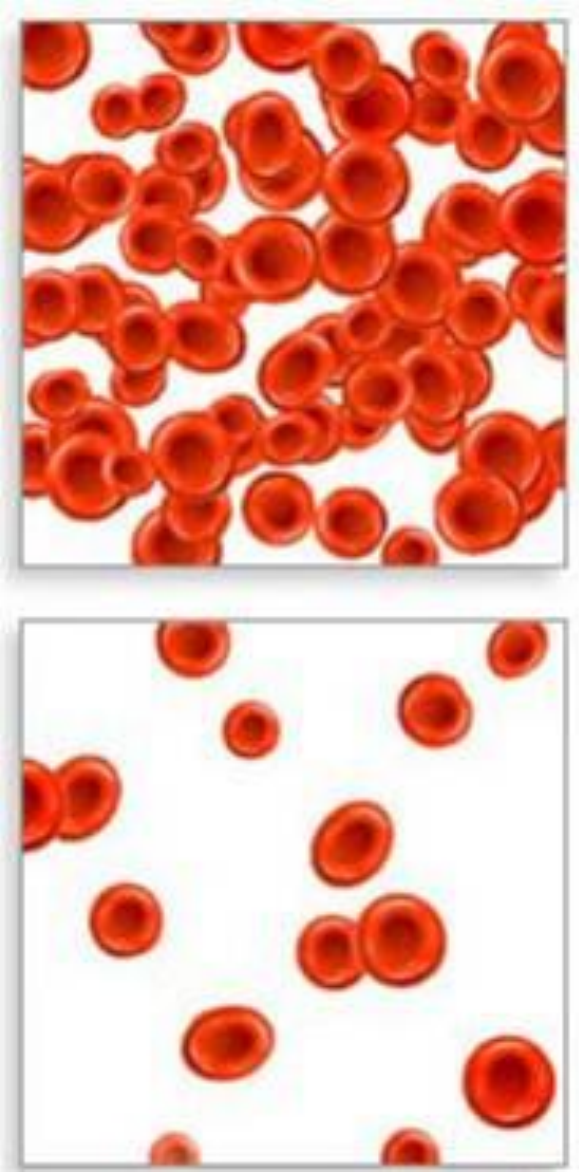
- ↓ the amount of **hemoglobin** - a basic criterion
  - the transport capacity of the blood for oxygen depends on the amount of hemoglobin !!!
- ↓ haematocrit
  - cave megaloblastic anemia
- ↓ the number of erythrocytes in a unit volume of blood
  - cave hypochromic anemia

- the reference level for the age and sex of the individual

- anemia
  - light (Hb 110 – 90 g/l)
  - moderate (Hb 90 - 60 g/l)
  - serious (Hb <60 g/l)

Pathogenesis of anemia

- regulation of erythropoiesis
  - [Hb]/O2 → pO2 in kidney → erythropoietin → marrow erythropoiesis
- Ery v circulation ~120 days
  - daily turnover 0.8% (~2×1011, =20ml erymass)
- anemia is the result of a production/destruction imbalance of Ery
  - (1) reduced production
  - (2) increased destruction
  - (3) a combination of both mechanisms



Symptoms and Signs

Symptoms

- Fatigue
- Dizziness
- ↓ exercise tolerance
- Shortness of breath
- Weakness
- Palpitations
- Vertigo
- Pica (with iron deficiency)
- Irritability

Signs

- Tachycardia
- Pale appearance
- ↓ mental acuity
- Neurological symptoms (with vitamin B12 deficiency)

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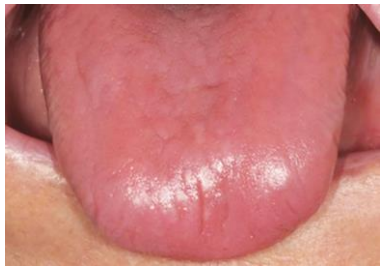
Anemia symptoms

symptoms of anemia

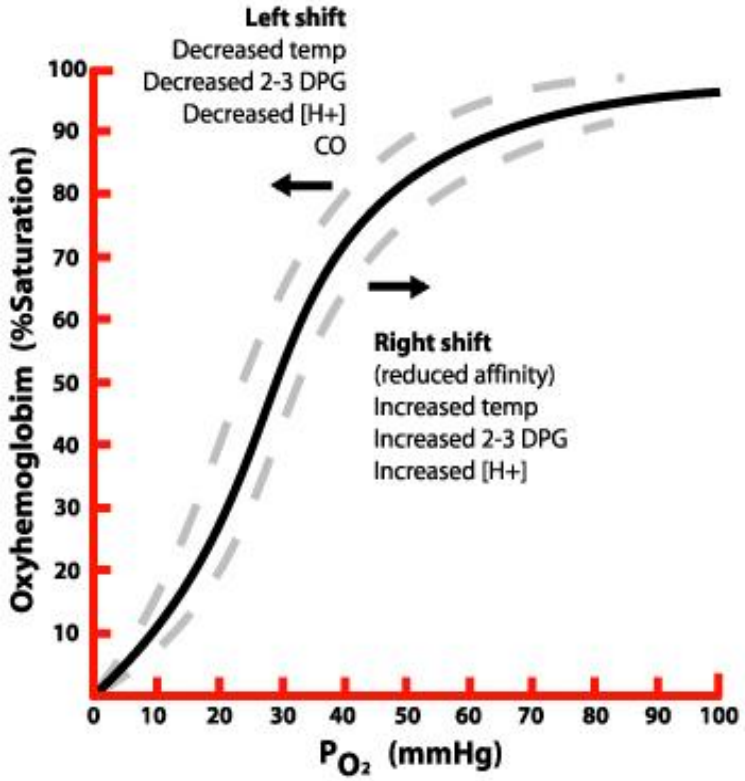
subjective
- nonspecific
- weakness, fatigue
- disturbances of sleep and performance
- emotional lability
- headache

objective
- depends on ethiology and pathogenesis
- paleness, jaundice, petechia, hematomas
- Hunter glositis
  - smoothed tongue
- albuminuria
- nervous system



Anemic syndrome - compensatory mechanisms

- compensation mechanisms
  - ↑ erythropoesis (+/-)
  - shift of the Hb dissociation curve to the right
  - increase in cardiac output
  - ↓ viscosity - hyperkinetic circulation
- due to the half-life and speed of recovery of leukocytes and platelets, the manifestation of post-hemorrhagic anemia is mainly due to changes in the erythrocyte line



- Acute loss of 30% volume (~1500 ml) → circulatory collapse, shock (> 50% → death)
  - no "emergency" RBC pool, only the release of reticulocytes is possible
  - medullary RBC production can increase up to 8-fold provided there is sufficient Fe supply
- symptomatology depends very much on the speed with which the anemia arose!!!

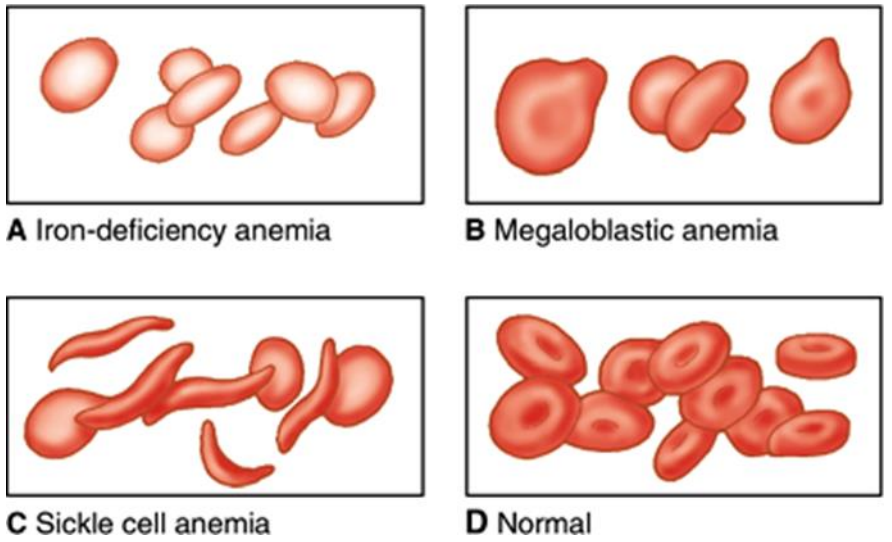
Anemia classification

pathogenetic

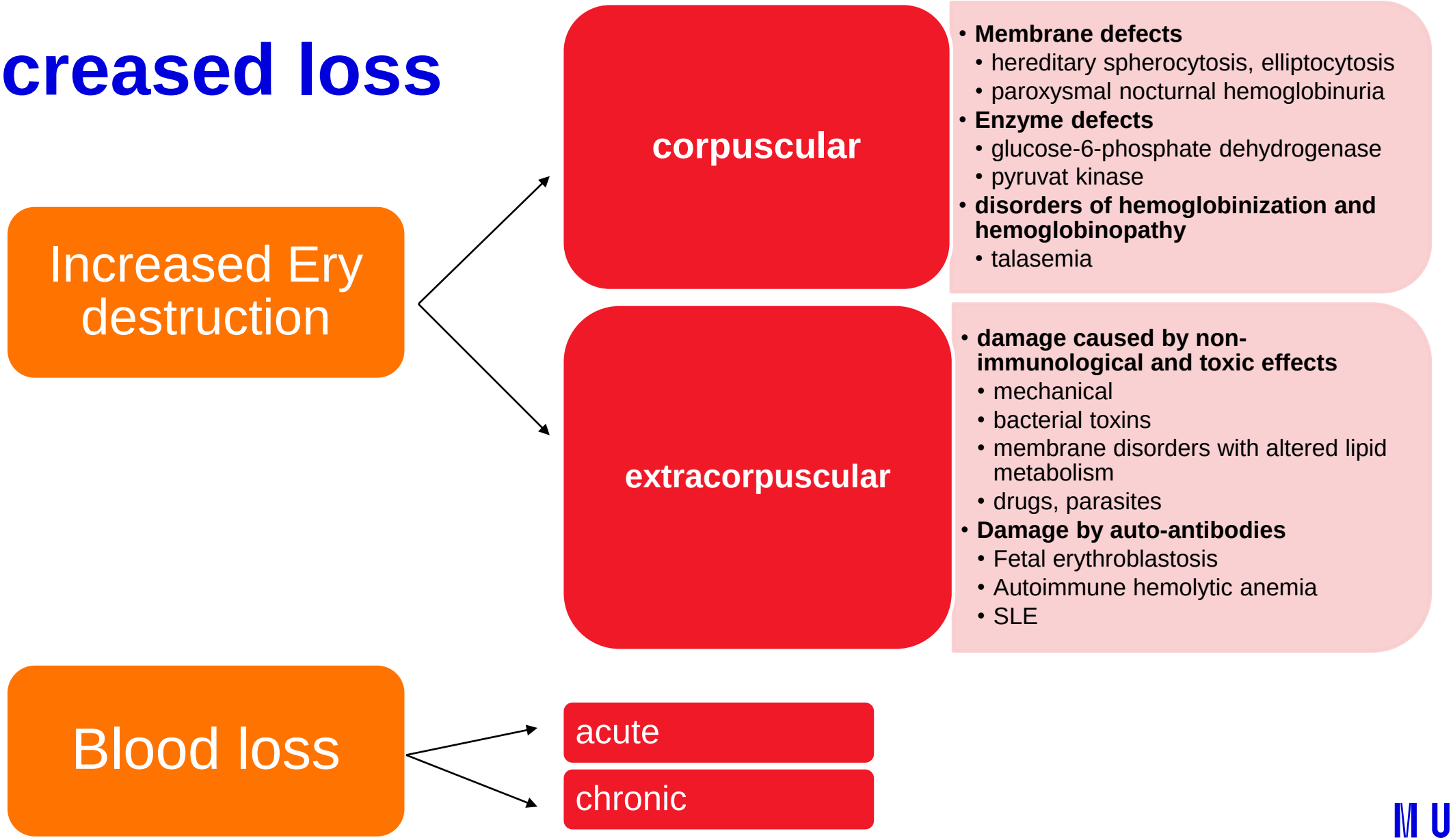
- increased RBC loss
  - bleeding
  - haemolytic anaemia
    - **corpuscular**
      - membrane
      - hemoglobinopathy
      - enzymopathy
    - **extracorpuscular**
      - toxic
      - autoimmune
- insufficient RBC production
  - lack of erythropoietin
  - lack of essential factors
  - bone marrow disorder

morphologic

- RBC size
- haemoglobin content
- pathologic morphology



Increased loss



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Anemia due to blood loss

- acute
  - intravascular volume loss
    - amount is important
    - cardiovascular collapse, shock, death
  - volume repletion
    - water shift, ↓ haematocrite
  - ↑ EPO production
  - iron loss
  - blood pressure decrease
    - epinephrine release
    - granulocytes mobilization
      - leukocytosis
  - reticulocytosis
    - 10 – 15 % after 15 days
  - thrombocytosis
- chronic
  - less activated erythropoiesis
  - losses may exceed regeneration capacity of bone marrow
  - iron stores depletion

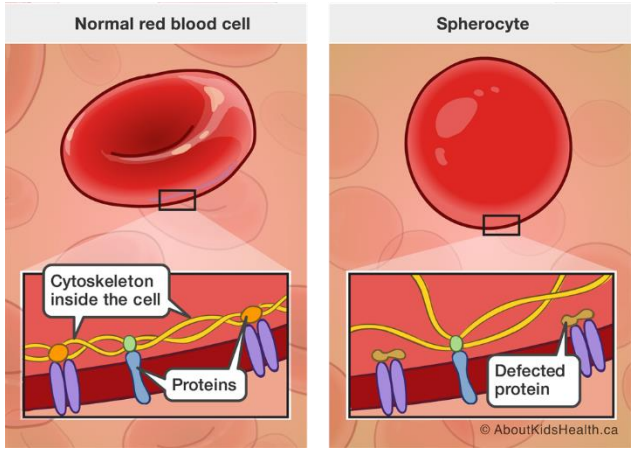
Hemolytic anemias

- common signs
  - premature RBC destruction
    - normally in mononuclear phagocytes
    - usually extravascular
      - phagocytes hyperplasia
        - splenomegaly
  - increased EPO and stimulation of erythropoiesis
  - accumulation of haemoglobin degradation products
  - iron deficit is not present

- clinical signs
  - anaemia
  - splenomegaly
  - jaundice
- intravascular haemolysis
  - hemoglobinemia
  - hemoglobinuria
  - hemosiderinuria
  - splenomegaly is missing
  - ↓ haptoglobin

Hereditary spherocytosis

- most common inherited hemolytic anemia in Northern Europeans (1:5000)
- autosomal dominant - one defect (75 %)
- in 75 % neither parent is affected
  - spontaneous mutation
  - recessive?
- defect in RBC membrane
  - deficit of structural proteins
    - ankyrin
    - spectrin
  - mutations
    - reading frame shift or premature stop codon
  - RBC lifespan 10 – 20 days
- changes
  - young RBC – normal shape
    - ↓ membrane stability with aging
    - ↓ deformability – trapping in the spleen
  - splenectomy
    - spherocytes remain
    - correction of anaemia
- clinical features
  - possible jaundice at birth
  - onset can be delayed for many years
  - some patients - without symptoms



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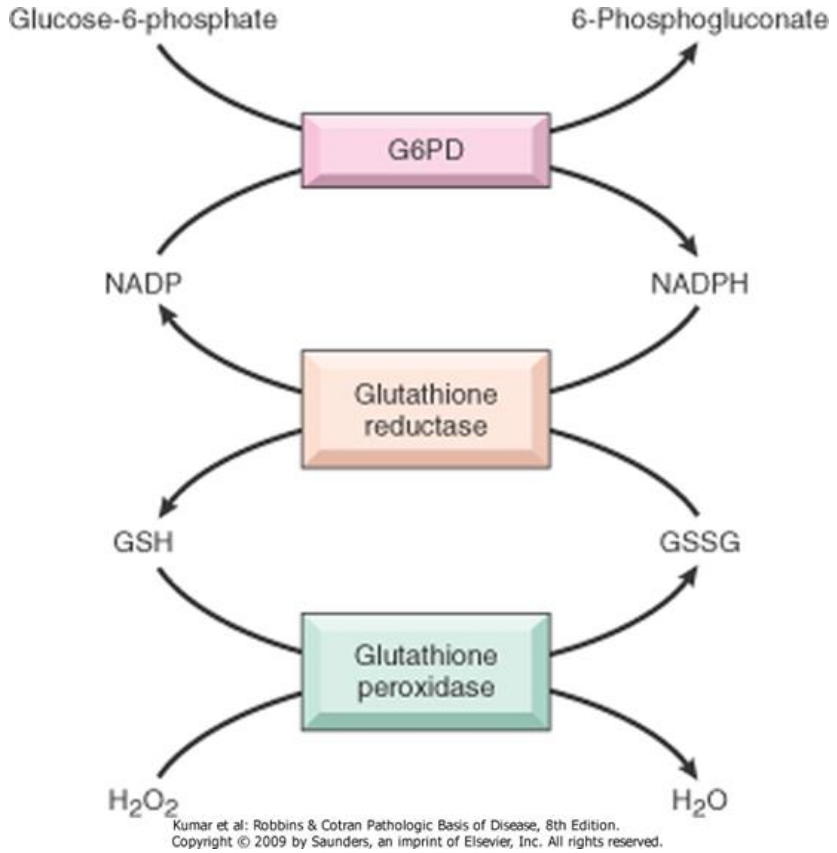
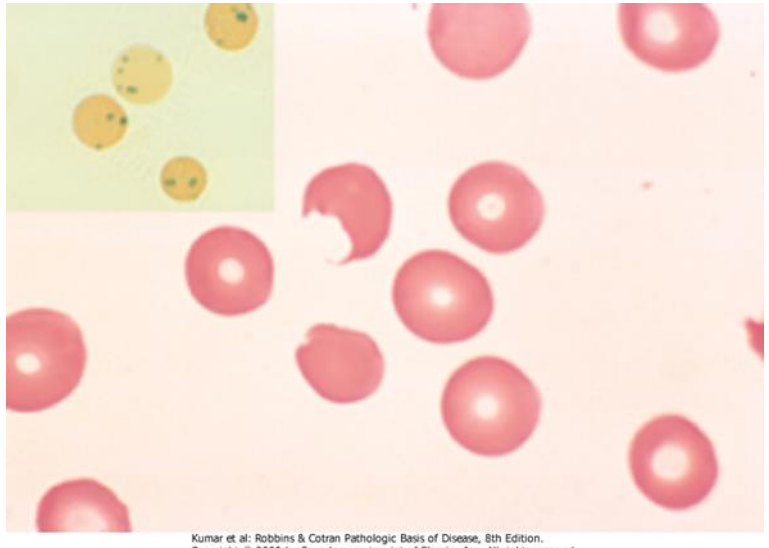
Glucose-6-phosphate dehydrogenase (G6PD) deficiency

- recessive X-linked disease (Xq28)
  - more common in males
  - affects millions of people
    - Africa, Mediterranean, Middle East (20 %)
    - South-East Asia (up to 40 % in certain areas)
- G6PD function
  - oxidation of G6P to 6-phosphoglycerate
    - production of NADPH
      - the only source of RBC
      - regeneration of glutathione
        - protection of oxidative damage



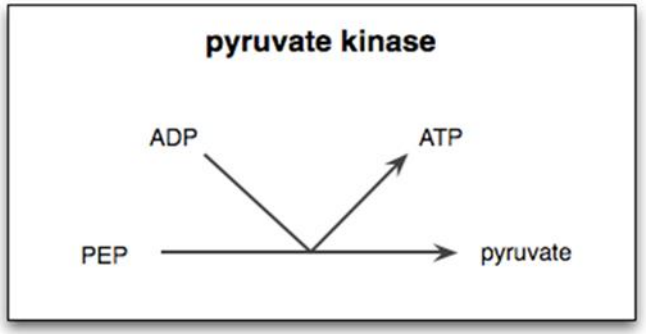
G6PD deficiency

- episodic hemolysis
  - ↑ oxidative stress
    - infection
      - viral hepatitis, pneumonia
    - drugs
      - antimalarics, sulfonamids
    - ingestion of fava beans
      - favism
  - denaturation of globin chains
    - binding of sulfhydryl groups
    - precipitates bound to membrane
      - Heinz bodies
        - ↓ deformability
        - intravascular haemolysis
  - clinical features
    - anemia
    - jaundice
    - hemoglobinuria



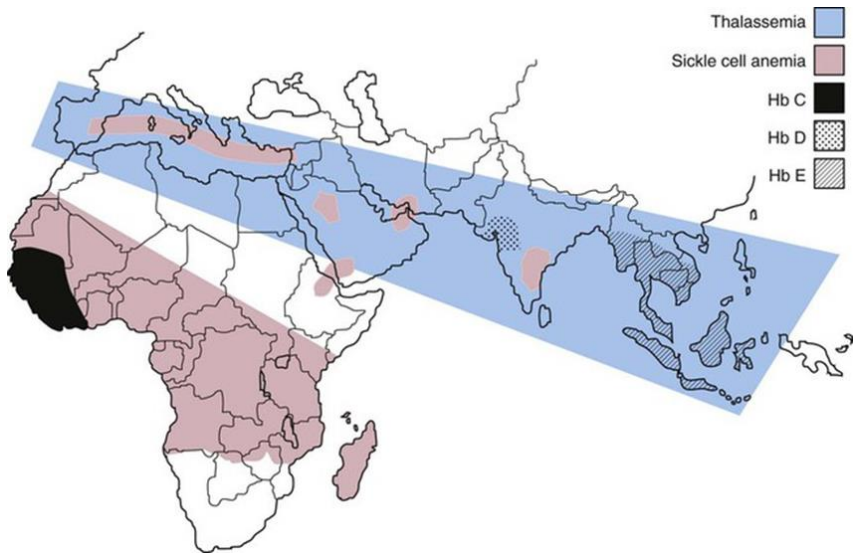
Pyruvate kinase deficiency

- the most common defect of RBC metabolism after G6PD deficiency
  - affects thousands people
- autosomal recessive
  - variable severity
  - homozygotes have anemia and splenomegaly
- lower PK activity
  - reduced ATP production
  - energy deficit
    - ↓ resistance of membrane – rigid RBC
- diagnostics
  - lower enzymatic activity
    - 5 – 20 % in affected homozygotes



Hemoglobinopathies

- abnormalities occur in
  - globin chain production
    - thalassemia
  - structure of the globin chain
    - sickle cell disease
- change of amino acid composition of globin chain or incorrect proportion of subunits
- highly variable clinical manifestations
  - mild hypochromic anemia
  - moderate hematological disease
  - severe, lifelong, transfusion-dependent anemia with multiorgan involvement



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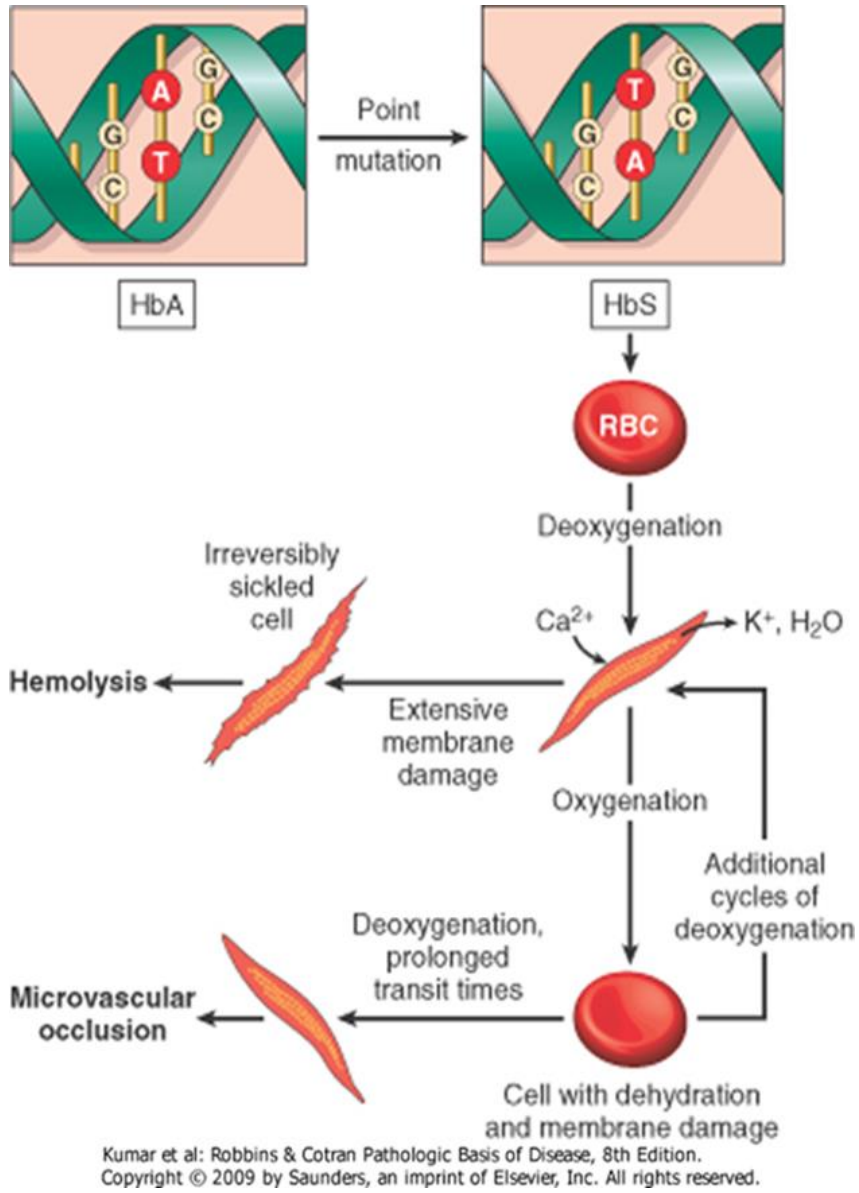
Sickle cell anemia

- common hereditary hemoglobinopathy
- point mutation in the codon 6
  - valin instead of glutamic acid
  - abnormal HbS
- 2 forms
  - homozygous
    - sickle cell anemia (HbSS)
  - heterozygous
    - sickle cell trait (HbAS)
- most common in
  - Africa
    - up to 25 % in some populations
  - India, Middle East, Southern Europe
- HbF synthesis is normal
  - manifestation when hbF decreases to adult levels
    - approx. 6 months of age



Sickle cell anemia

- deoxygenated HbS
  - polymerizes and becomes insoluble
  - flexibility of RBC is decreased
  - rigid, sickle appearance
  - change of shape
    - initially reversible
    - after repeated sickening membrane loses flexibility
      - irreversibly sick cell
      - due to dehydration
- sickling can produce
  - shortened RBC survival
  - impaired passage through microcirculation
- sickling precipitated by
  - infection, dehydration
  - cold, hypoxia

- clinical features
  - vaso-occlusive crisis
    - pain in the hands and feet
  - pulmonary hypertension
    - in 30 – 40 %
      - NO deficiency?
  - anemia
    - stable Hb 60 – 80 g/l
  - splenic sequestration
- long-term problems
  - growth and development
  - bones
  - infections
  - cardiac problems
  - neurological complications
  - liver
  - pregnancy

Thalassemias

- normally balanced production of α and β globin chains (1:1)
- defective synthesis of globin chains in thalassemia
  - imbalance
  - precipitation of globin chains
    - ineffective erythropoiesis
    - Hemolysis
- mutations causing ↓ synthesis of HbA
- heterogenous group
- endemic
  - Middle East, tropic Africa, India, Asia
  - one of the most common hereditary diseases
    - heterozygous forms
      - protection from malaria

- α-talassemia
  - deficit of α chain synthesis
- β-thalassemia
  - deficit of β chain
    - chromosome 11

Table 1. Features of the Thalassemias.*

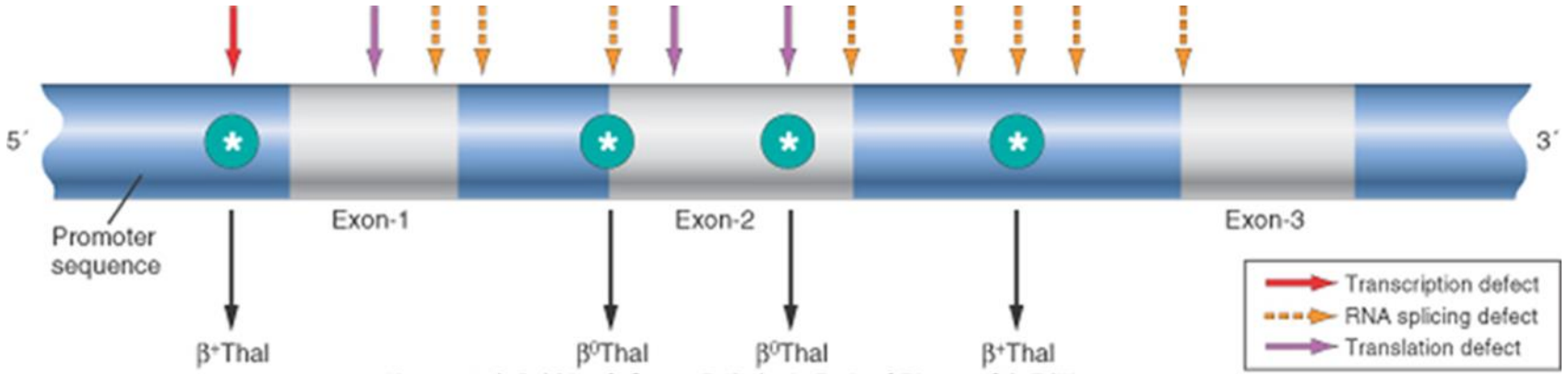
Type	Mean Corpuscular Volume (*fl*)	Hemoglobin (*g/dl*)	Findings on Electrophoresis	Other Features
β-Thalassemia				
Major	50–75	<7	Increased hemoglobin A_2	Severe anemia
Intermedia	50–75	<9	Increased hemoglobin A_2	Target cells on smear
Minor	65–75	9–10	Increased hemoglobin A_2	Target cells on smear
α-Thalassemia				
Trait 1 (α α/α–)	80–85	12–14	Normal	
Trait 2 (α–/α–) or (α α/–)	65–75	12–13	Normal	
Hemoglobin H disease (α–/–)	60–69	9–8	Hemoglobin H	Hemolysis, splenomegaly
Hemoglobin Bart's (– –/–)			Hemoglobin H, hemoglobin Bart's	Hydrops fetalis
Hemoglobin E disease				
Heterozygous	80–85	12	Hemoglobin E present	Rare target cells on smear
Homozygous	70–79	11–12	Hemoglobin E predominant	Target cells on smear

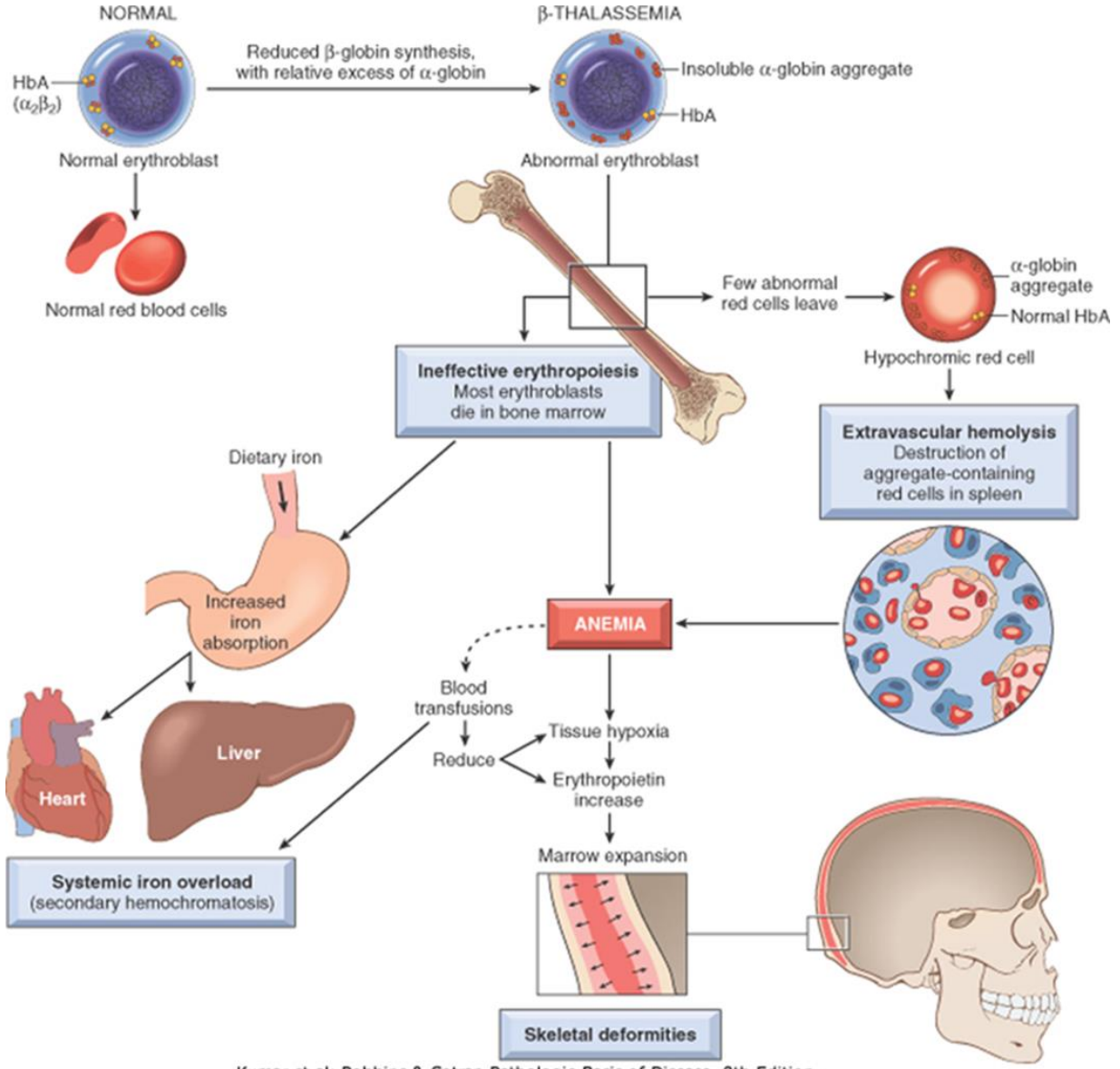
* The normal range for mean corpuscular volume is 80 to 100 fl. The normal range for hemoglobin level is 13.5 to 17.5 g per deciliter in men and 12 to 16 g per deciliter in women.

β-thalassemia

- homozygous β-thalassemia
  - β0 mutation
    - β-chain is missing
  - β+ mutation
    - β-chain production is reduced
- heterozygous β-thalassemia
  - usually symptomless
  - microcytosis with or without mild anemia

- ↓ lifespan of RBC and their precursors
- precipitation of α-chains – membrane damage
- ineffective erythropoiesis
  - destruction of some RBC in bone marrow
  - remaining RBC are prone to extravascular hemolysis





Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.

β-thalassemia

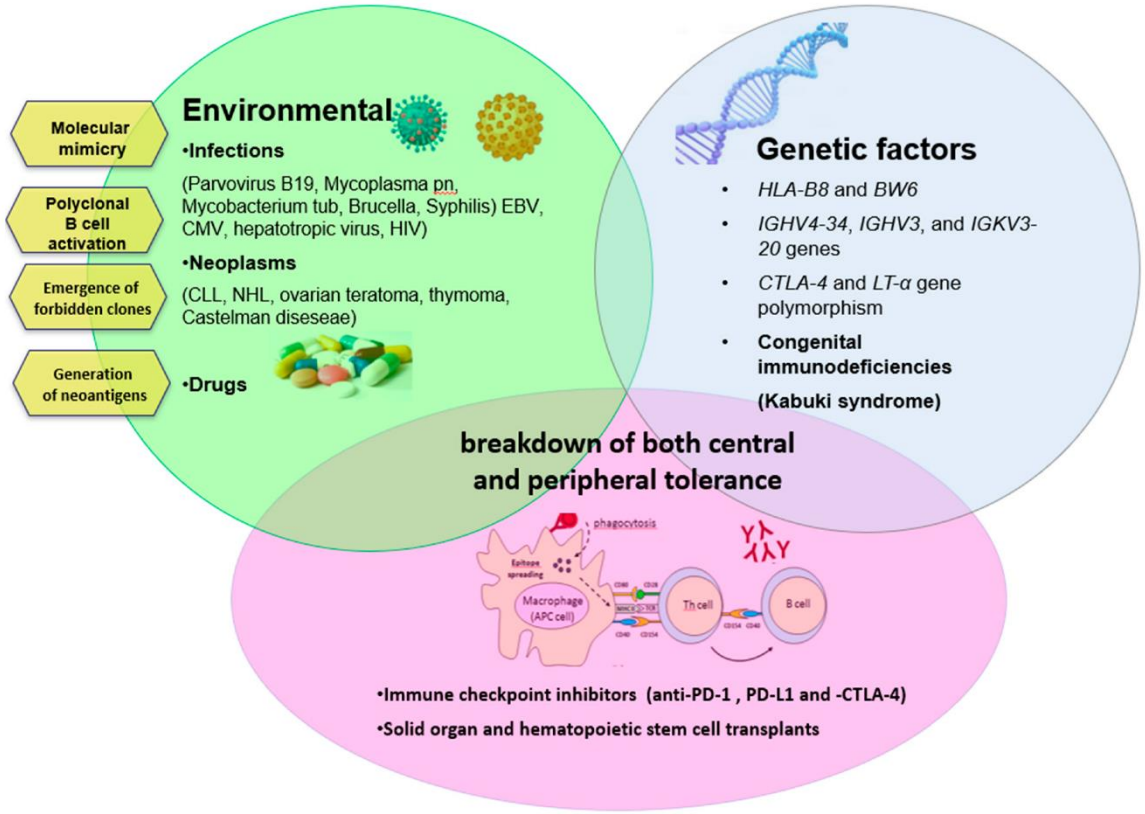
- > 200 genetic defects
  - mainly point mutations
  - highly unstable β-chain
- clinical classification
  - major
    - 2 alleles
    - severe anemia requiring regular transfusions
  - minor (thalasemia trait)
    - 1 allele, heterozygous carrier
    - without symptoms
  - intermedia
    - genetically heterogenous
    - moderate anemia not requiring regular transfusions
- serious β-thalassemia
  - erythroid hyperplasia, extramedullar hemopoiesis
  - bone damage
  - increased iron absorption
    - supressed hepcidin synthesis
    - iron from transfusions

α-thalassemia

- gene for α-globin chain is duplicated on both chromosomes 16
- normal person has 4 α-globin genes
  - deletion of 1 or both α-chain genes on each chromosome may occur
    - most common is deletion of 1
- decreased α-chain synthesis
  - excess of unmatched chains
- less severe than β-thalassemia

Autoimmune hemolytic anemia (AIHA)

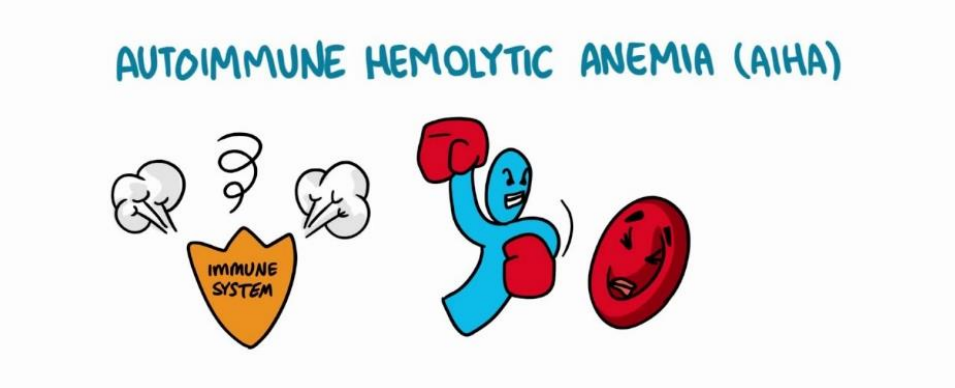
- Autoimmune hemolytic anemia (AIHA) is caused by auto-antibodies directed against self red blood cell (RBC) surface antigens
- intravascular hemolysis mediated by activated complement or extravascular hemolysis
  - By activating complement,
  - to the destruction of erythrocytes with bound antibody in the monocyte-macrophage system
- Classification
  - primary (idiopathic) and secondary
- According to the nature of the antibodies present
  - AIHA with warm antibodies,
  - AIHA with cold antibodies,
  - AIHA with mixed antibody type and
  - paroxysmal cold hemoglobinuria.

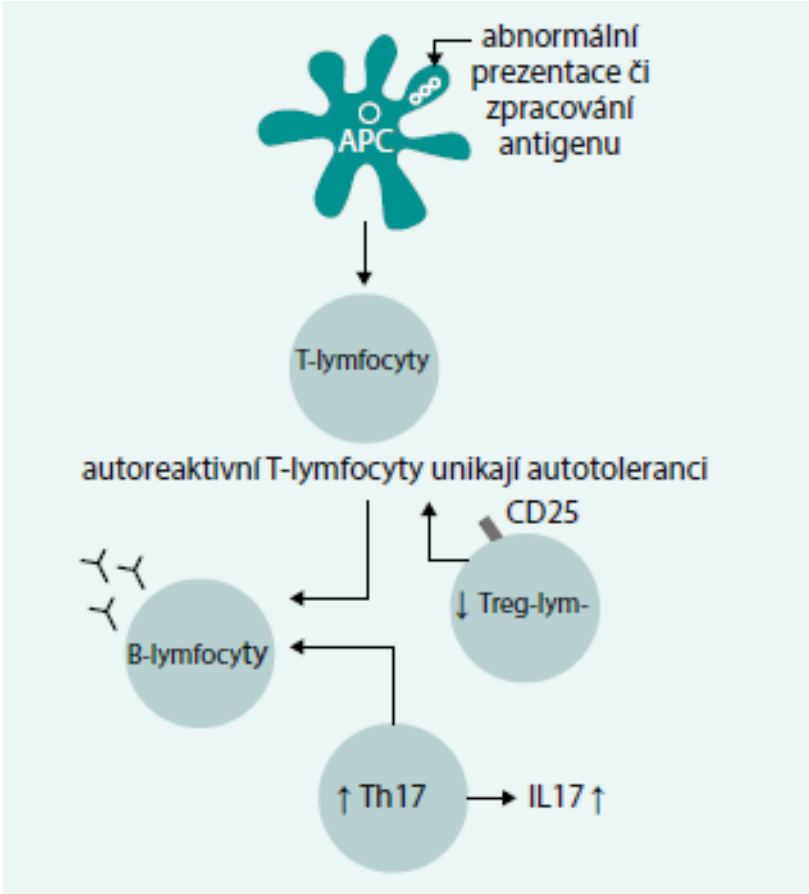


J. Clin. Med. 2020, 9(12), 3859; https://doi.org/10.3390/jcm9123859

Pathogenesis of AIHA

- consists of
  - a defective antigen presentation to immunocompetent cells,
  - insufficient process of T-lymphocyte tolerance to autoantigens and
  - induction of autoantibody production by B-lymphocytes
- Abnormal antigen presentation or processing leads to a defect in apoptotic signals





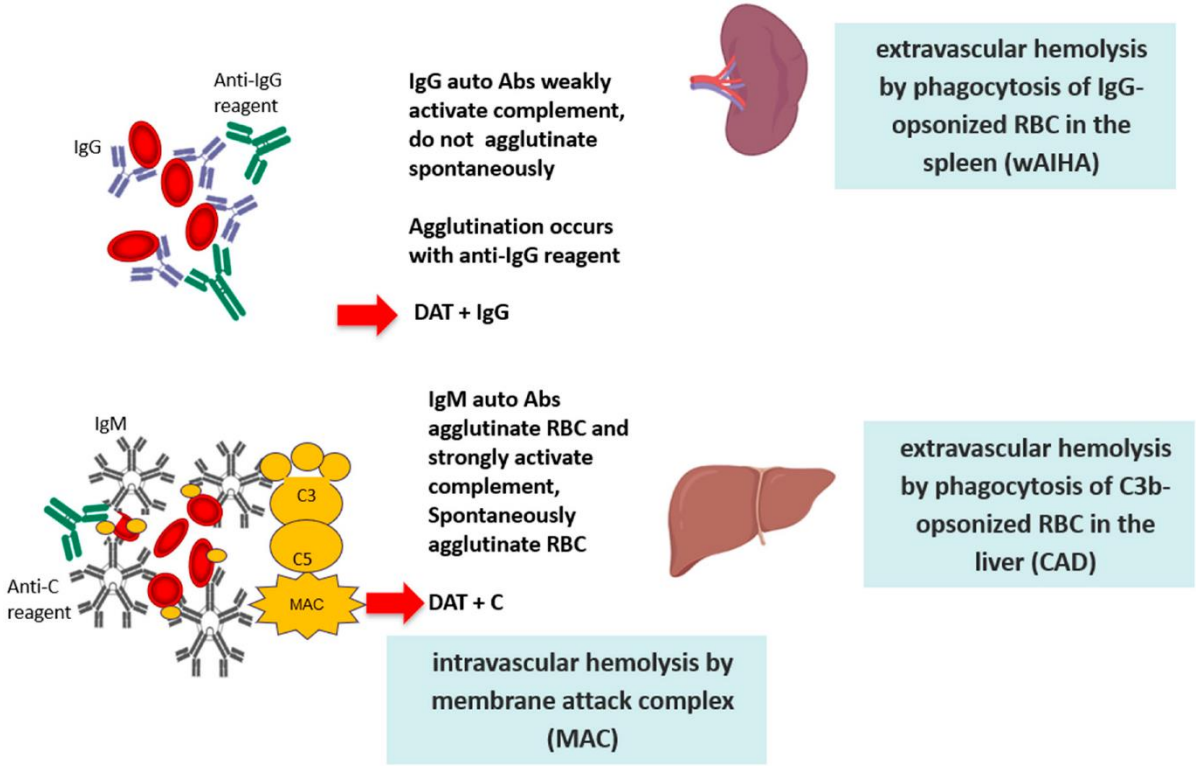
Vnitř Lék 2018; 64(5): 514–519

Autoimmune hemolytic anemia (AIHA): classification

	Autoantibody Characteristics			
	Class	**Optimal T of Reaction (Range)**	**Specificity**	**DAT Positivity**
Warm AIHA (wAIHA)	IgG (possible Complement fixation)	37 °C (0–40)	Rh system	IgG or IgG + C
Cold Agglutinin Disease (CAD)	IgM (common complement fixation)	4 °C (4–34)	I/i system	C
Mixed AIHA	warm IgG and cold IgM	4 °C and 37 °C	//	IgG + high titer cold IgM
Paroxysmal Cold Hemoglobinuria (PCH)	IgG (common complement fixation)	Reacts at 4 °C and hemolyzes at 37 °C	P Antigen	Positive Donath-Landsteiner Test

Dsetruction of Ery

- IgG autoantibodies are monomers - weakly fix the complement system;
  - they cause RBC destruction via the antibody-dependent cellular cytotoxicity (ADCC), -monocyte-macrophage system that phagocyte RBCs. (Activated lymphocytes that express receptors for the IgG Fc fragment and for C3b may also mediate an ADCC.)
  - Hemolysis is extravascular and occurs mostly in the spleen in the case of macrophage-mediated ADCC, and in the liver in the case of C3b-mediated ADCC.
  - Spleen represents also a lymphatic organ, and therefore able to contribute to autoantibody production.
- IgM autoantibodies are pentamers with high avidity and ability to activate the complement cascade until the final lytic complex (C5–C9).
  - The lysis of RBCs directly in the circulation (intravascular hemolysis) through the activation of “perforins” and other cytotoxic factors.
  - with a consequent greater clinical severity



J. Clin. Med. 2020, 9(12), 3859; https://doi.org/10.3390/jcm9123859

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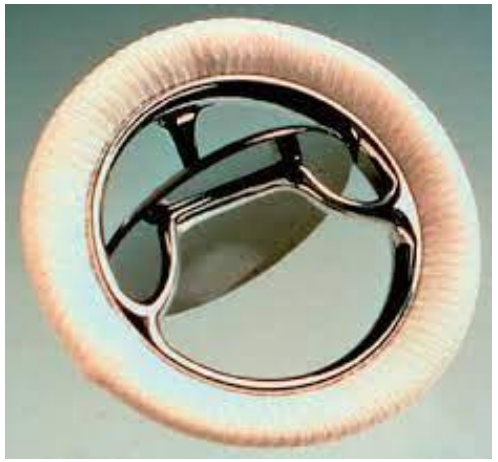
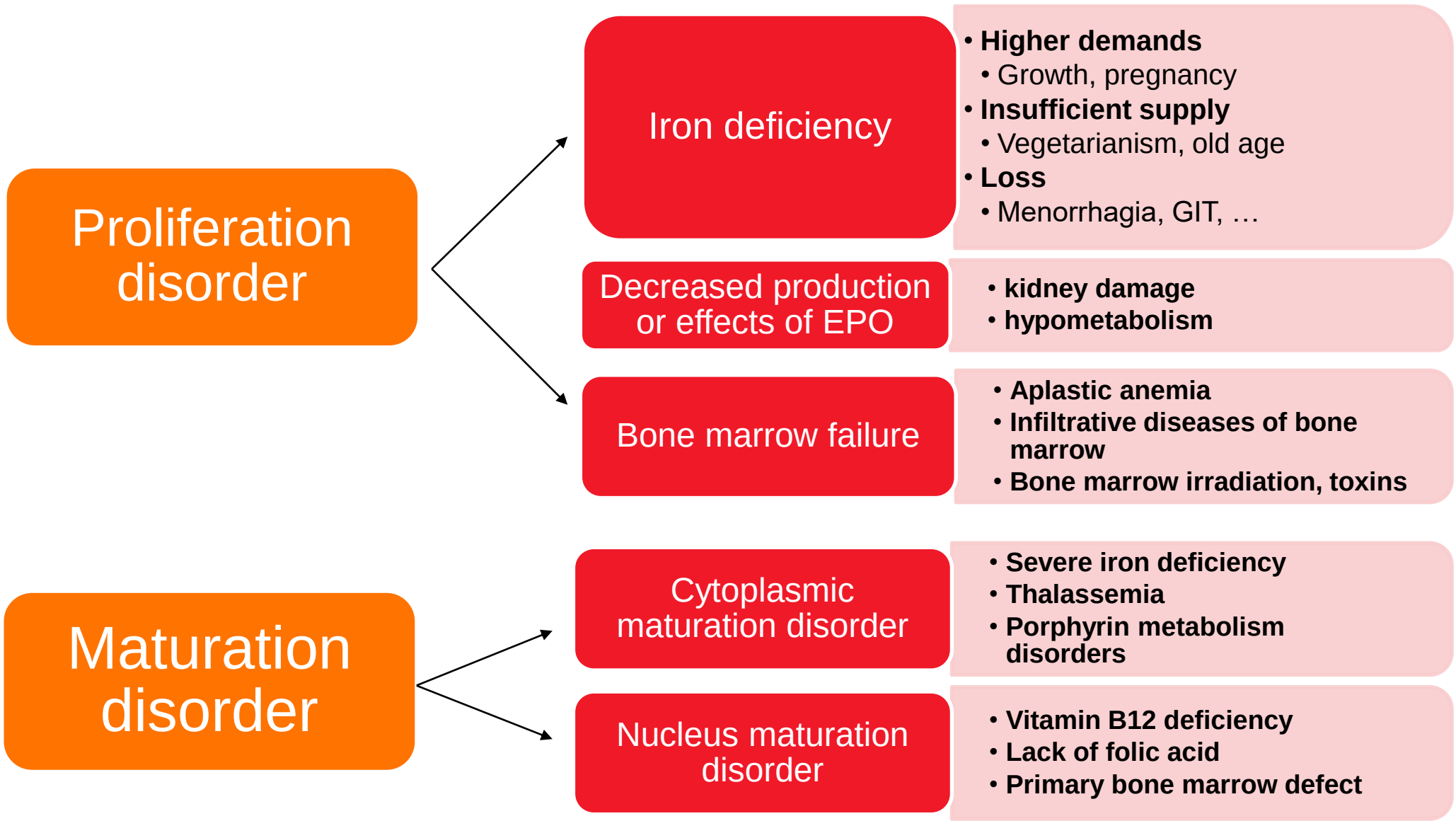
Extracorpuscular hemolytic anemia

- mechanical damage to erythrocytes
- damage by toxins or parasites
- antibody and complement damage
- damage by antibodies against blood group antigens



https://www.kardiochirurgie.cz/

Production failure



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Anemia of decreased RBC production

- nutritional deficiency
  - iron
  - vitamin B_{12}
  - folic acid
- aplastic anemia
- sideroblastic anermia

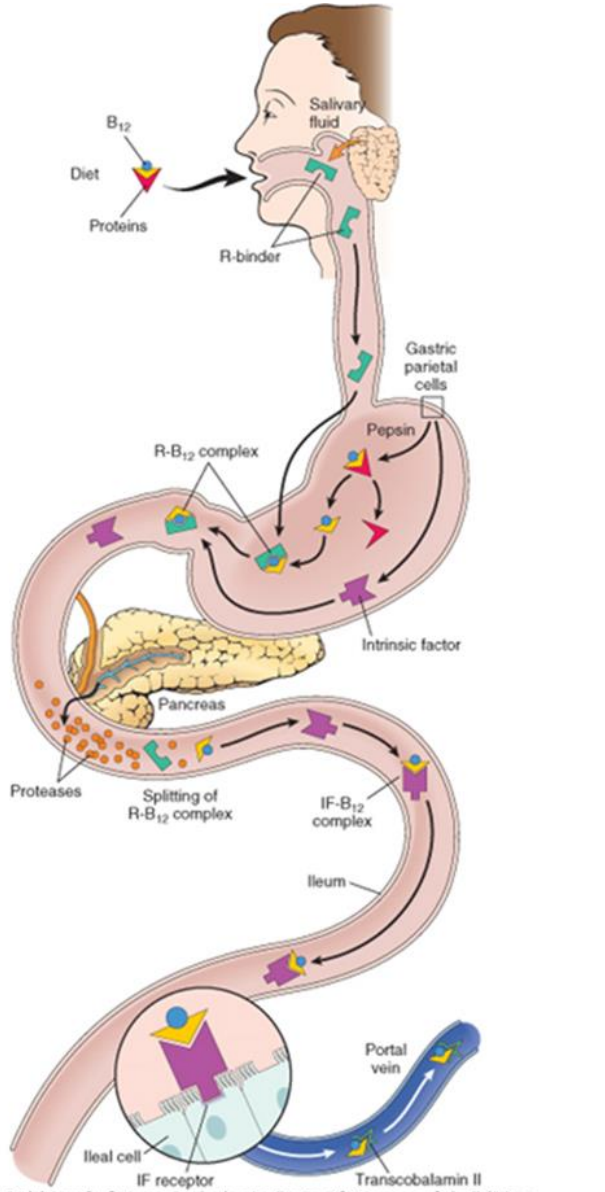
- secondary as a result of
  - kidney failure
  - chronic inflammation

Megaloblastic anemias

- erythroblasts with delayed nuclear maturation in the bone marrow
- defective DNA synthesis
  - abnormally large RBC and their precursors
  - immature nuclei
- deficit of vitamin B_{12} or folic acid
  - thymidine synthesis
  - defects in nucleus maturation
    - delay or blockade of cell division
- morphology
  - macrocytes or macroovalocytes
    - central brightening is missing but MCHC is not increased
    - anisocytosis, poikilocytosis
    - ↓ reticulocytes
    - neutrophils
      - larger and hypersegmented
    - hypercellular bone marrow
    - maturation of cytoplasm and Hb accumulation is normal
    - ↑ growth factors
      - apoptosis of precursors in the bone marrow
    - mild hemolysis

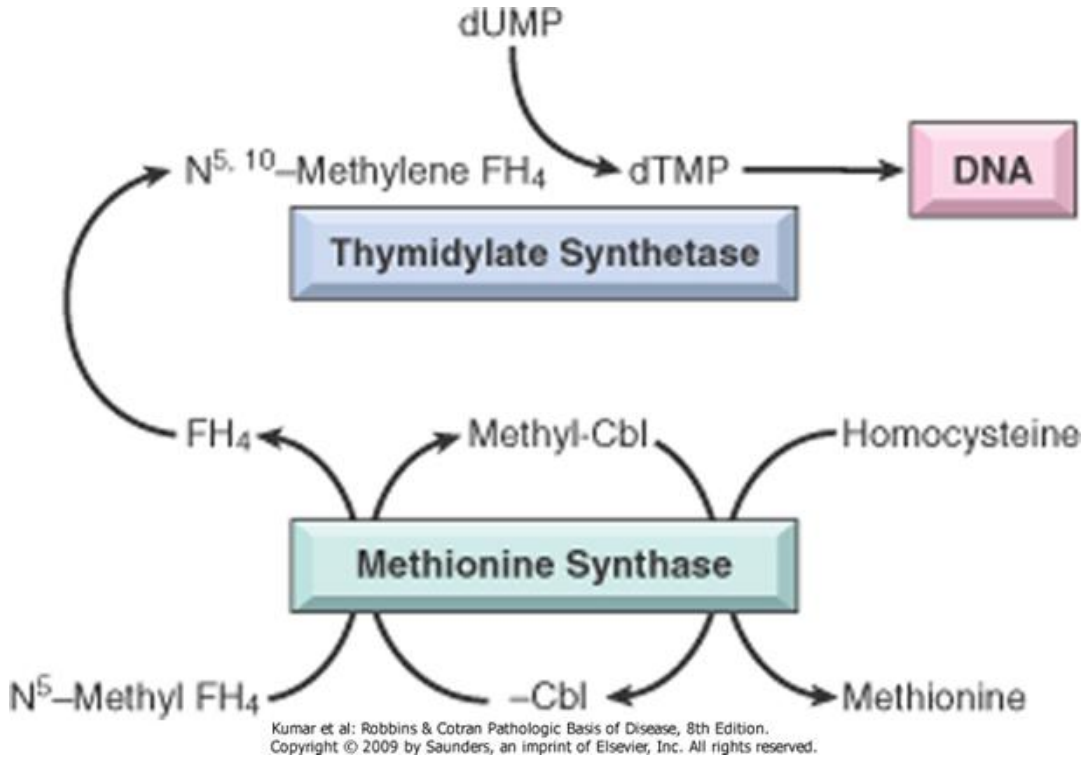
Metabolism of vitamin B_{12}

- vitamin B_{12} = cobalamin
- essential
- animal sources
  - meat, fish, egg, milk
  - not in plants
  - usually not destroyed by cooking
- stores in the liver
- alternative resorption
  - without IF
  - up to 1 % of its content in the diet



Functions of vitamin B_{12}

- 2 reactions dependent of B_{12}
  - methionine production
    - methyl group acceptor
    - formation of TH4
  - generation of sukcinyl CoA from methylmalonyl CoA
    - ↑ methylmalonyl acid in plasma and urine
    - abnormal fatty acids in neuronal lipids
    - neurologic complications



B_{12} deficit = pernicious anemia

- autoimmune gastritis
  - intrinsic factor deficit
- occurrence
  - all races
  - older people (median 60 years)
- pathogenesis
  - autoimmunity
    - chronic atrophic gastritis
      - parietal cells loss
      - autoantibodies are not specific
    - autoreactive T cells
  - achlorhydria, ↓ pepsine
  - gastrectomy
  - exocrine pankreas dysfunction
  - ileum resection
  - tapeworm
  - ↑ demands on B_{12}
    - relative deficit
- diagnostics
  - megaloblasts
  - leucopenia
    - hypersegmented granulocytes
  - ↓ level of B_{12}
  - ↑ homocysteine and methylmalonyl acid
  - gastritis
    - ↑ risk of gastric carcinoma
  - homocysteine

Folic acid deficiency anemia

- tetrahydrofolate (FH4)
  - transfer of 1 C groups
    - methyl, formyl
  - processes dependent on these transfers
    - purines synthesis
    - homocysteine → methionine
    - synthesis of deoxythimidylate monophosphate

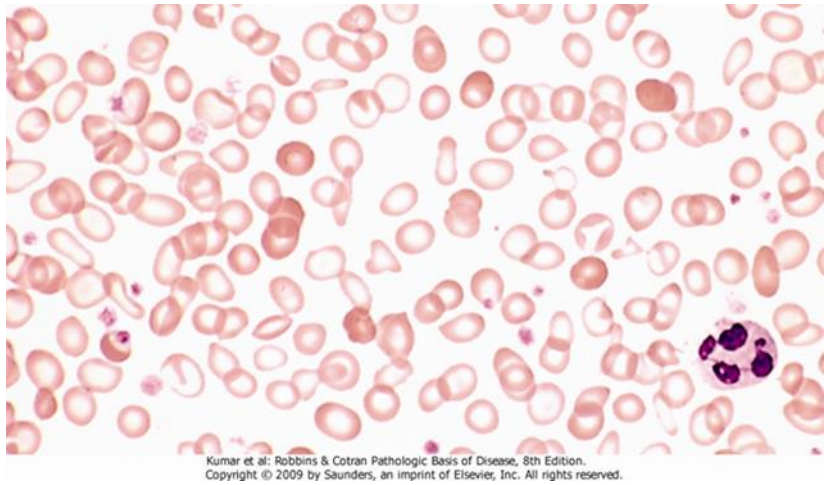
- etiology
  - decreased intake
    - essential, heat inactivation
    - small stores (weeks)
  - increased demands
    - pregnancy, growth, cancer
  - disturbed utilization
    - methotrexate
      - folic acid antagonist
        - dihydrofolate reductase
- distinction from pernicious anemia
  - ↓ folates in the blood
  - ↑ homocysteine but not methylmalonic acid

Iron deficiency anemia

- inadequate iron for haemoglobin synthesis
- cause
  - blood loss
  - increased demands
    - growth, pregnancy
  - decreased absorption
    - post-gastrectomy
  - poor intake
- etiology
  - food deficiency
    - infants
    - developing countries
  - ↓ absorption
    - absorption is supported by
      - ascorbic acid
    - supressed by
      - oxalates, phosphates, tanins
    - malabsorption syndrome
    - diarrhea
    - gastrectomy
  - ↑ demands
    - growth, pregnancy
  - ↑ losses
    - chronic
      - GIT bleeding

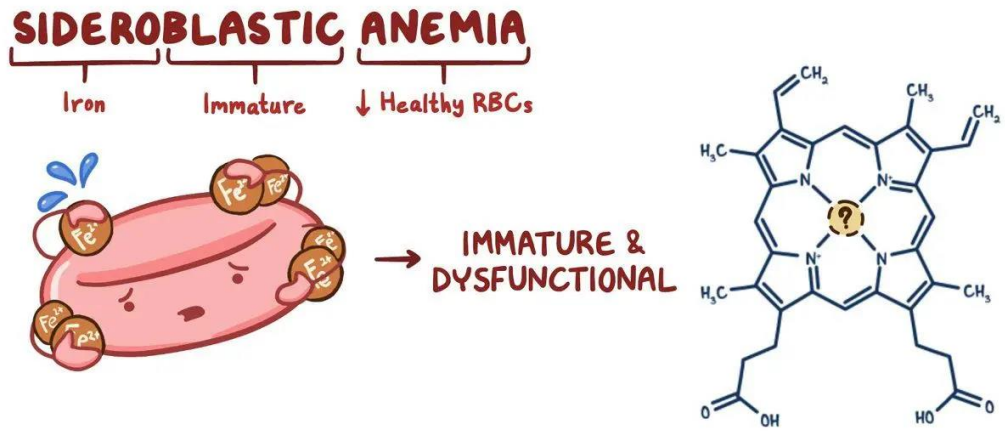
Iron deficiency anemia

- hypochromic microcytic anemia
  - after depletion of stores
    - ↓ serum iron, ferritin and transferin saturation
    - absence of stainable iron in the macrophages from bone marrow
- diagnostics
  - ↓ hemoglobin, hematocrit
  - ↓ iron, ferritin and transferrin saturation (< 15 %)
- iron supplementation
  - ↑ reticulocyte count after 5 – 7 days

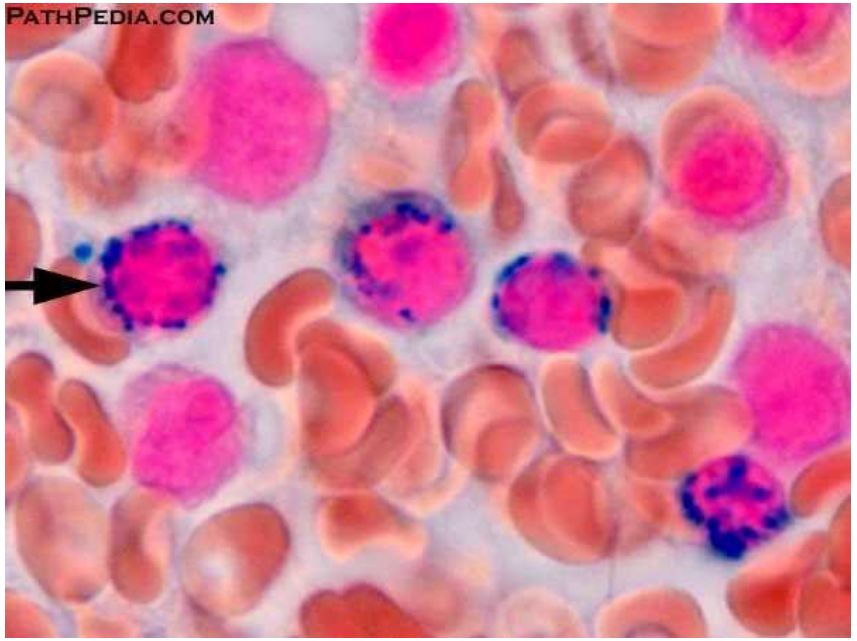


Sideroblastic anemia

- inherited or acquired disorder
- inadequate use of iron
  - accumulation in mitochondria of erythroblasts
    - ring sideroblast
      - an erythroblast with stainable iron granules in its cytoplasm
  - defect of ALA-synthase
    - inherited form
  - excess iron in bone marrow
- acquired
  - alcohol, drugs
- mutations
  - protoporphyrine production is slow
- variable number of hypochromic microcytes



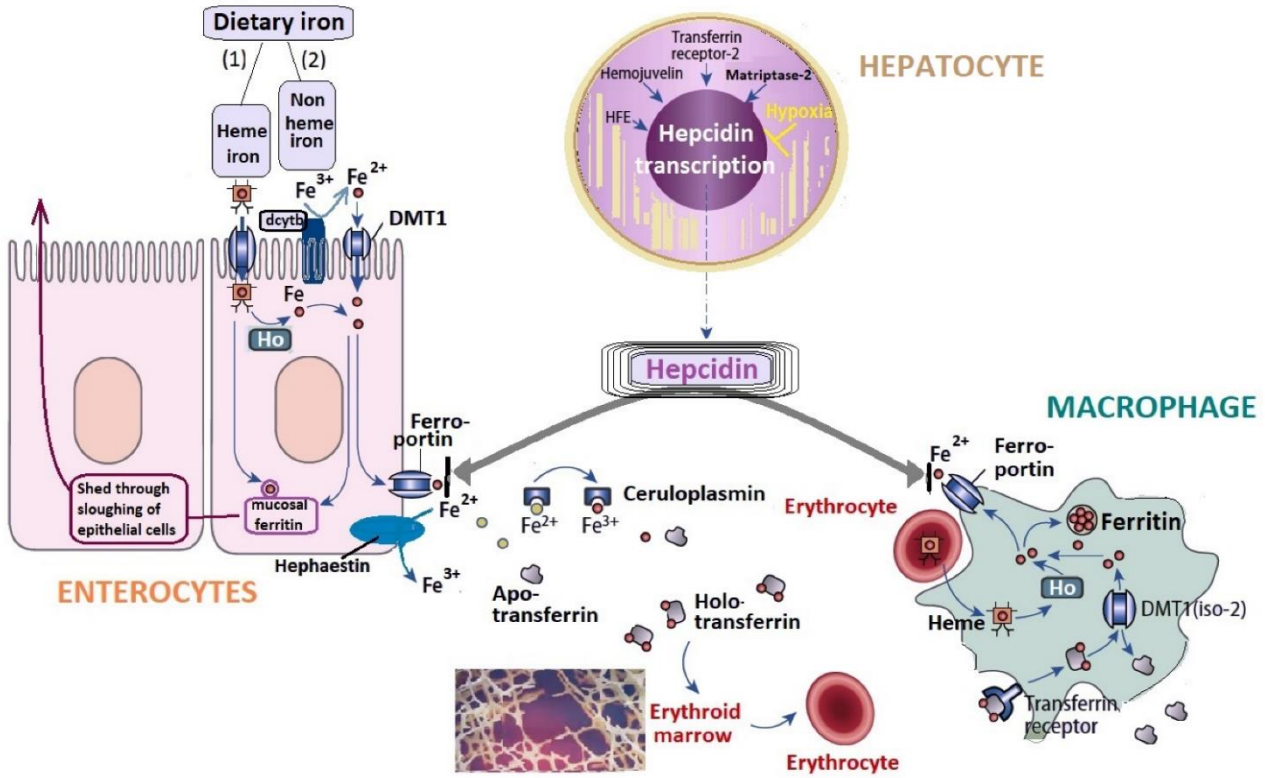
https://www.osmosis.org/learn/Sideroblastic_anemia



Causes of Iron Deficiency Anemia	
1. Anemia due to martial deficiency	
(a) insufficient reserves:	prematurity, twinship, neonatal hemorrhages, maternal anemia
(b) insufficient food intake:	diet with excess flour, exclusive diet with goat's milk, protein and vitamin deficiencies, vegetarian diet
(c) deficient absorption:	presence of inhibitory factors (phytate, phosphates, carbonates), lack of reducing factors (vitamin C, hydrochloric acid, bile acids), celiac disease, gastrectomy, Helicobacter Pylori infection, intestinal resections, bacterial overgrowths
2. Iron-loss anemia	
(a) gastro-intestinal hemorrhages:	esophageal varices (liver cirrhosis), diaphragmatic hernia, esophagitis, gastro-duodenal ulcer, cancer of the digestive tract (esophageal, gastric, colonic cancer), tumors of the small intestine, Vaterian ampulloma, hemorrhoids, rectal polyps, intestinal parasites, celiac disease, Crohn's disease, ulcerative colitis, colonic angiodysplasia, bariatric surgery, NSAIDs consumption
(b) hemorrhages of respiratory origin:	epistaxis, pulmonary tuberculosis, lung cancer, bronchiectasis, pulmonary microinfarcts, alveolar hemorrhage
(c) genito-urinary hemorrhages:	prolonged menstrual cycle, metrorrhagia, renal tuberculosis, renovesical cancer, hemorrhagic nephritis, hemodialysis
(d) hemorrhagic diathesis:	alteration of the capillary wall, alteration of platelets, combined alterations
(f) hypersplenism:	
(g) genetic causes:	iron-refractory iron deficiency anemia
(h) mechanical fragmentation of RBCs:	prosthetic valves
(i) endocrine diseases:	hypothyroidism, pituitary insufficiency, autoimmune polyglandular syndromes
(j) autoimmune diseases:	scleroderma, rheumatoid arthritis, lupus
(k) drugs:	anticoagulants, antiaggregants, NSAIDs
(l) CHF, CKD.	

Iron metabolism

- The iron metabolism involves absorption from the duodenal enterocytes, usage in the erythroid precursors, and storage and reutilization in the hepatocytes and tissue macrophages
- Hepcidin is the key regulator of iron homeostasis, as its synthesis is inhibited to facilitate iron efflux in the circulation during increased erythropoiesis
- Hepcidin is produced in the liver and degrades the ferroportin transport channel, reducing the ability of macrophages to recycle the iron and thus iron availability
- Nevertheless, hepcidin expression is increased by stress and inflammation
- Exercise-induced changes in hepcidin and IL-6 are similar in resistance and endurance training



Life 2021, 11(9), 987; https://doi.org/10.3390/life11090987

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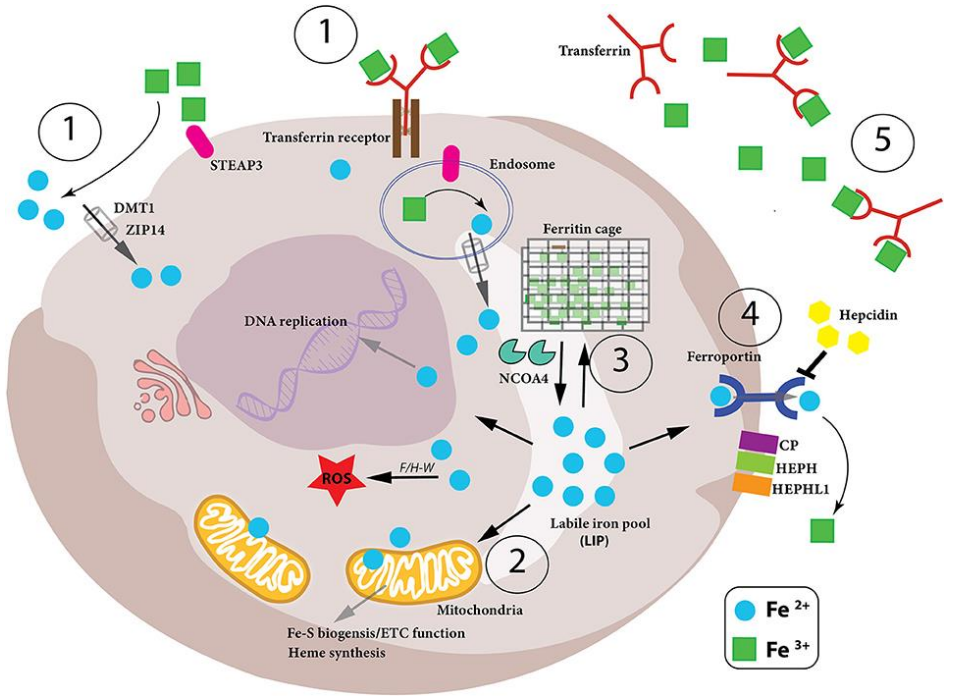
Iron metabolism in the cell

- (1)-iron uptake - Iron-bound transferrin (TF-Fe^{3+}) and NTBI (non-transferrin-bound iron) are taken up into the cell by the iron importers DMT1 and ZIP14. STEAP3 is a ferrireductase which reduces Fe^{3+} to Fe^{2+}, which can then be imported.

- (2)-utilization - bioavailable and more soluble Fe^{2+} is used for various biological processes– DNA replication, ROS production via Fenton/Haber-Weiss (F/H-W) chemistry, mitochondrial bioenergetics, Fe-S and heme biosynthesis, as well as a plethora of proteins which utilize the metal to carry out their functions.

- (3)-storage - Excess Fe^{2+} iron is dangerous - it needs to be stored but, at the same time, be readily available for use: ferritin proteins designated the “ferritin cage” which stores the more inert, insoluble Fe^{3+} form of iron.
- (4)-export - If intracellular iron levels are saturated. This is achieved by the iron exporter ferroportin (FPN). Once outside the cell the Fe^{2+} iron is oxidized to Fe^{3+}.

- (5)-Fe^{3+} iron is then bound to transferrin (Tf-Fe^{3+}) and enters the circulation to begin the cycle again.



Front. Mol. Biosci., 22 November 2019

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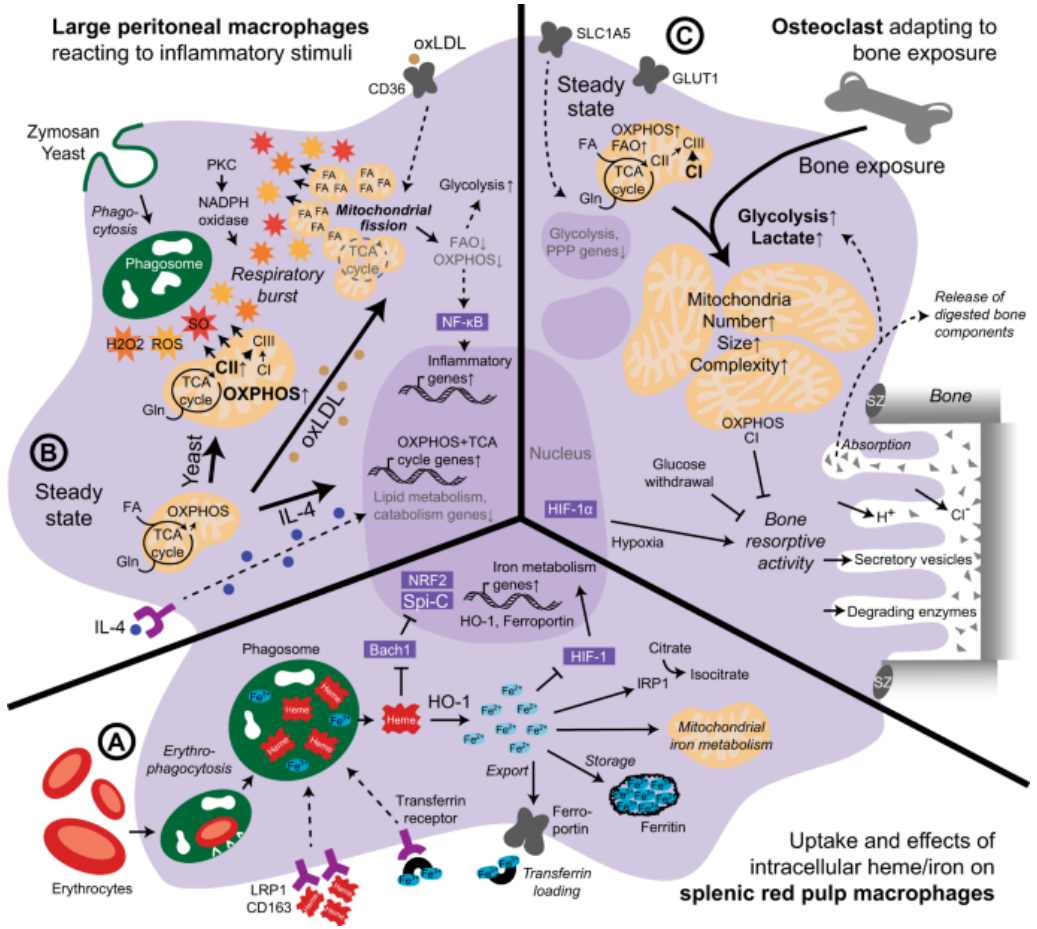
Tissue macrophage metabolism

- **A** Splenic red pulp macrophages scavenge defective erythrocytes for iron recycling.
- **B** Large peritoneal macrophages adapt their bioenergetics after detection of different microenvironmental factors, such as yeast, oxLDL or IL-4, to facilitate the respiratory burst.
- **C** Osteoclasts shift their cellular metabolism when exposed to bone, promoting bone resorptive activity.

- CI-III, complex I-III; FA, fatty acid; Gln, glutamine; IRP1, iron-responsive element-binding protein; PKC, protein kinase C; SO, superoxide; SZ, sealing zone. Solid lines: direct relationships; dashed lines: indirect relationships. Purple circles: cytokines; brown circles: bound holesterol/LDL/oxLDL; red and orange stars: ROS, SO and H_2O_2



Cellular & Molecular Immunology **volume 19**, pages384–408 (2022)

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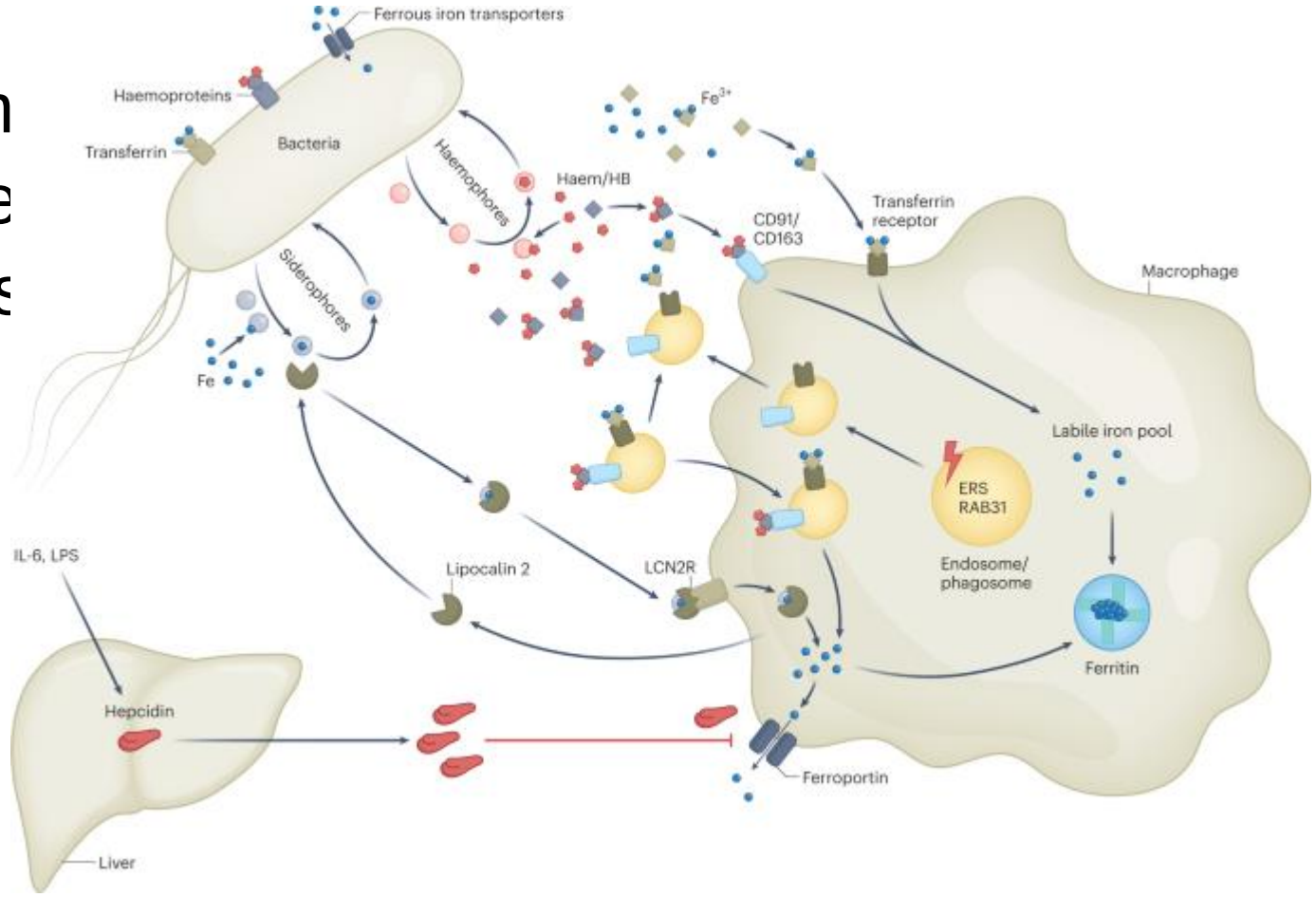
Iron macropahge

- Iron is a growth factor for m
  critical for the course of infe
- Extracellular vesicles releas
  from the blood, limiting iron
  outcomes from sepsis.



Nature Metabolism volume 5, pages10–12 (2023)

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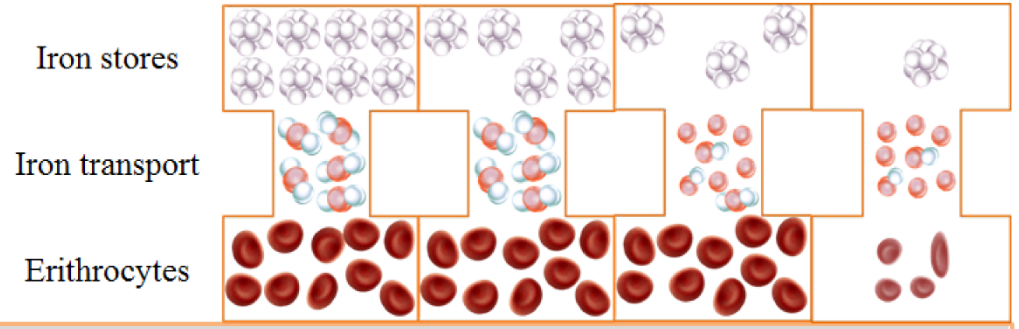
Assessing iron status

- Serum iron
  - Measures ferric iron (Fe^{3+}), subject diurnal variation
- Total iron-binding capacity (TIBC)
  - TIBC measures the amount of iron binding sites available on serum transferrin.
- Transferrin saturation (TSAT)
  - Generally reflects iron available for transport to the bone marrow
  - Calculated as serum iron/TIBC x 100 = TSAT
- Serum ferritin
  - Ferritin in the liver reflects stored iron, however, serum ferritin may not be as robust in reflecting stored iron
  - Acute phase reactant and will be elevated in acute & chronic inflammation



	Normal	Iron depletion	Iron deficiency	Iron deficiency anemia
Hemoglobin (g/dL)	N	N	N	↓
Hematocrit (%)	N	N	N	↓
Mean corpuscular volume (MCV) (fL)	N	N	N	↓
Red cell distribution width (RDW) (%)	N	N	N	↑
Ferritin (ng/dL)	N	↓	↓↓	↓↓
Serum Iron (µg/dL)	N	N	↓	↓
Transferrin saturation (%)	N	N	↓	↓
Transferrin (mg/L)	N	N	↑	↑
Soluble transferrin receptor (sTfR) (mg/L)	N	N	↑	↑

Nutrients 2015, 7(4), 2324-2344

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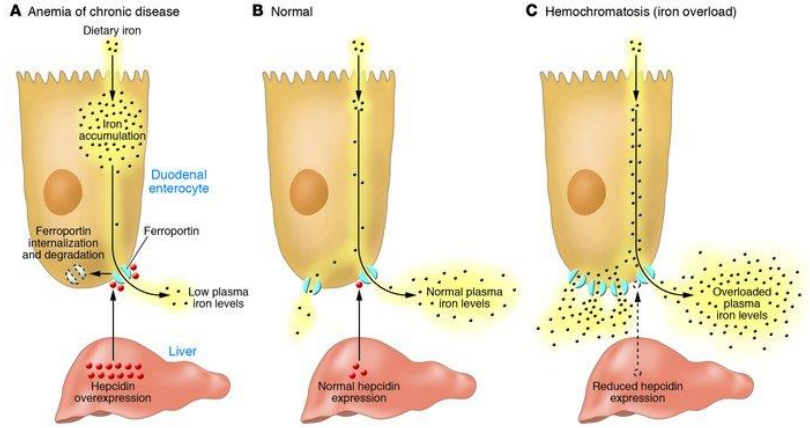
Anemia of chronic disease vs. iron deficiency anemia



J Clin Invest. 2007;117(7):1755-1758. https://doi.org/10.1172/JCI32701.

	Anemia of chronic disease	Iron deficiency anemia
Serum Iron	Reduced	Reduced
Transferrin	Reduced to normal	Increased
Transferrin Saturation	Reduced	Reduced
Ferritin	Normal to increased	Reduced
Soluble transferrin receptor	Normal	Increased
Cytokine level	Increased	Normal
Hepcidin	Increased	Reduced
Bone marrow iron stores	Normal to increased	Reduced
Erythrocytes	Normal, microcytes	Microcytes

Anemia of chronic disease

- common
- ↓ proliferation of RBC precursors
- deteriorated utilization of iron
- causes
  - chronic microbial infection
  - autoimmune disease
    rheumatoid arthritis
  - cancer
    lung cancer
- systemic inflammation
  - hepcidin stimulation (IL-6)
    suppression of iron release from macrophages
    ↓ supplementation of RBC precursors
    defence from bacteria that utilize iron (H. influenza)
    structural similarity between hepcidin and defensins
  - production of EPO is supressed

anemia
mild
normochromic and normocytic or hypochromic
microcytic
↑ serum ferritin,
↑ iron in macrophages
treatment
correction of the cause
possibly EPO

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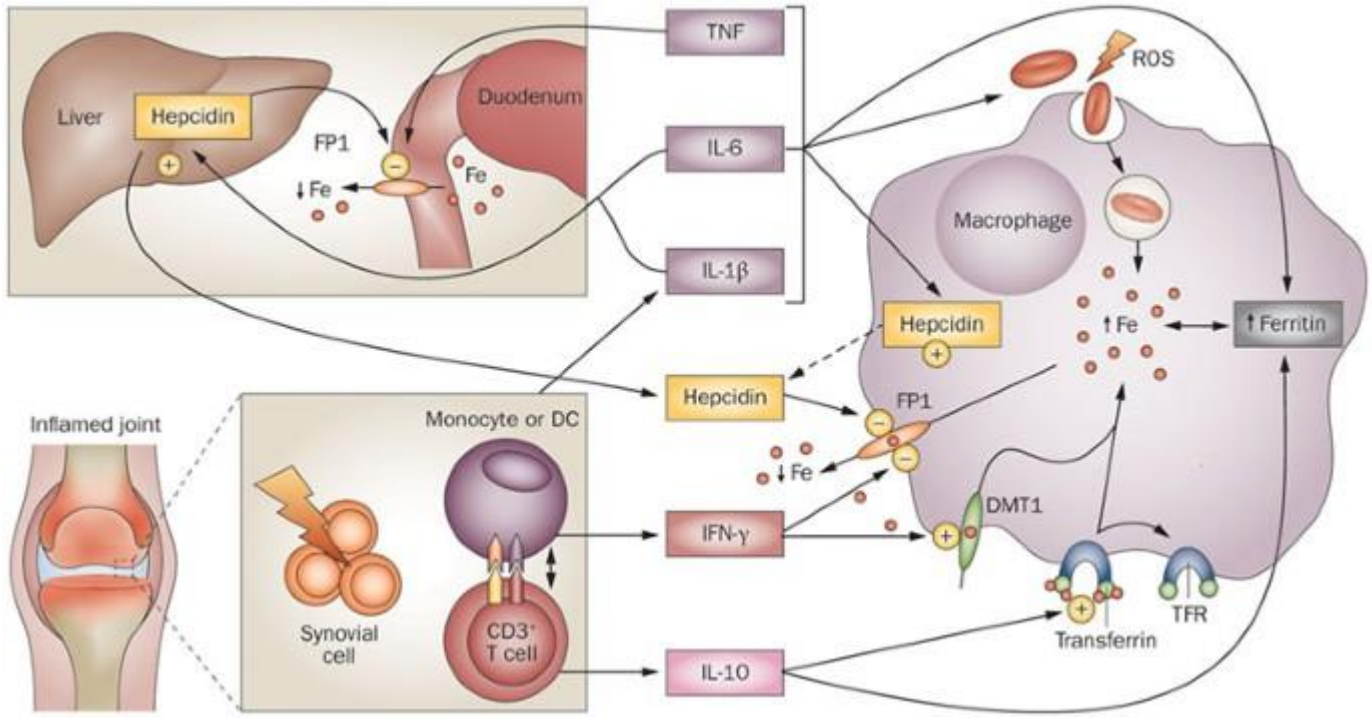
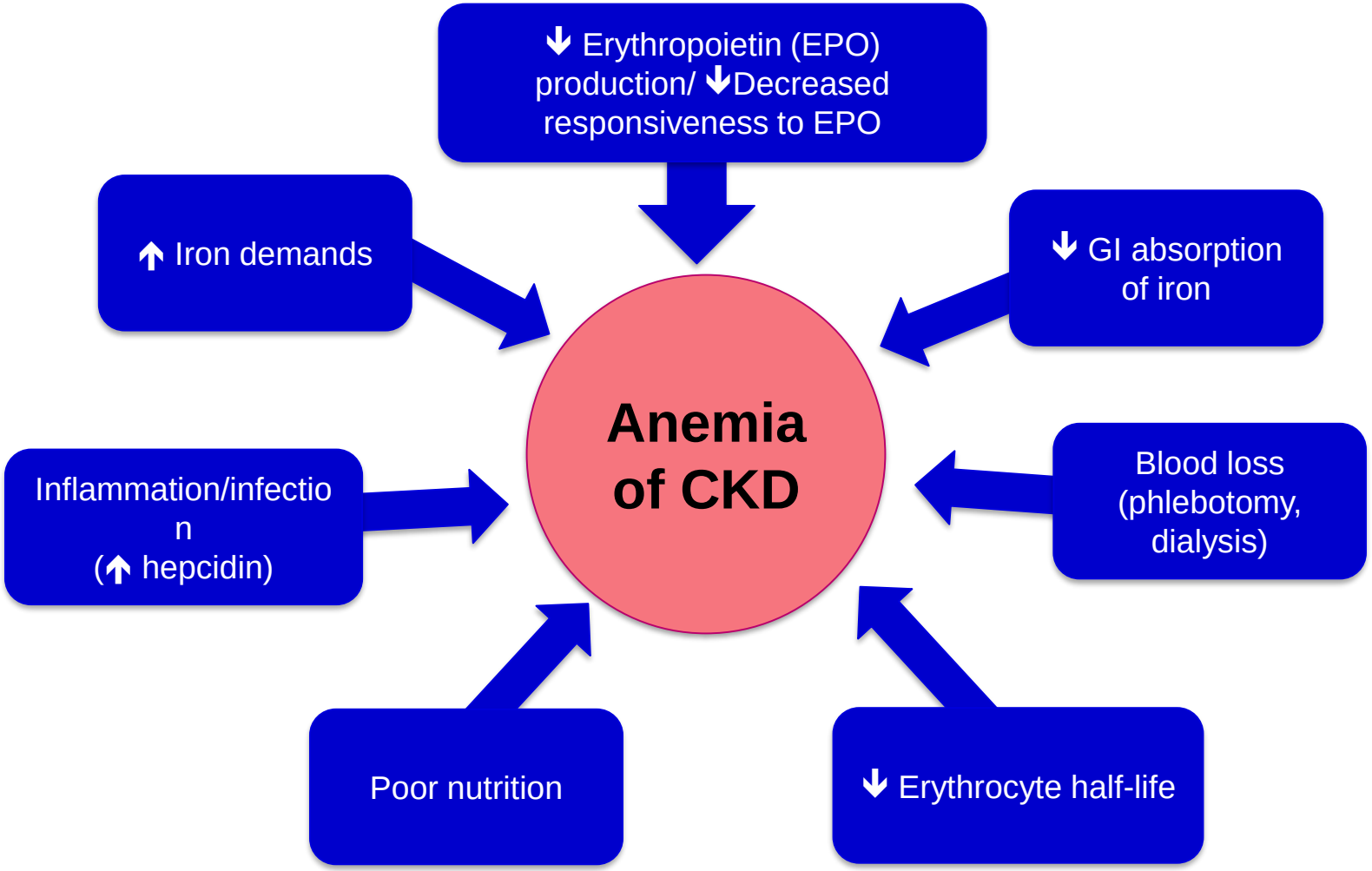
Anemia in RA

- mostly immune-driven,
- typical features that include
  - iron retention in the reticuloendothelial system,
  - impaired erythropoiesis,
  - shortened erythrocyte half-life and
  - blunted erythropoietin activity



Nature Reviews Rheumatology volume 9, pages205–215 (2013)

Anemia in CKD



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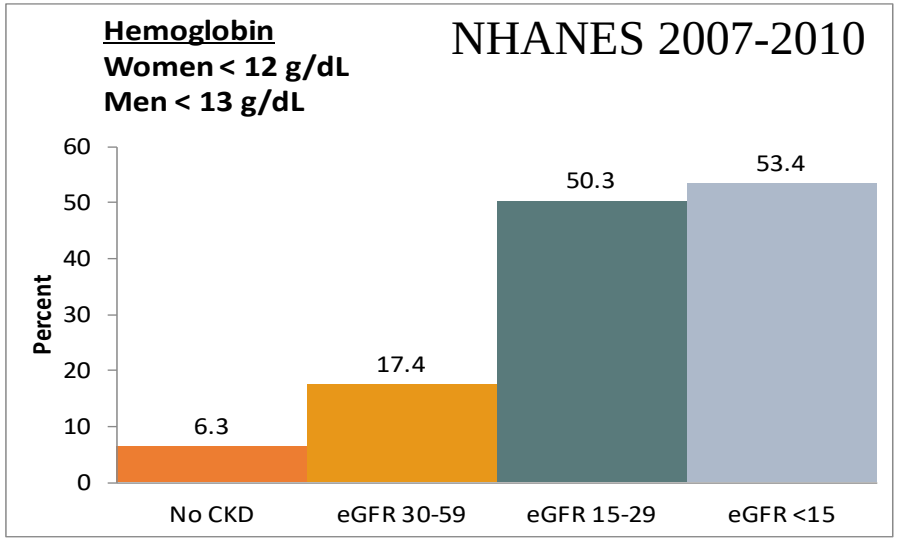
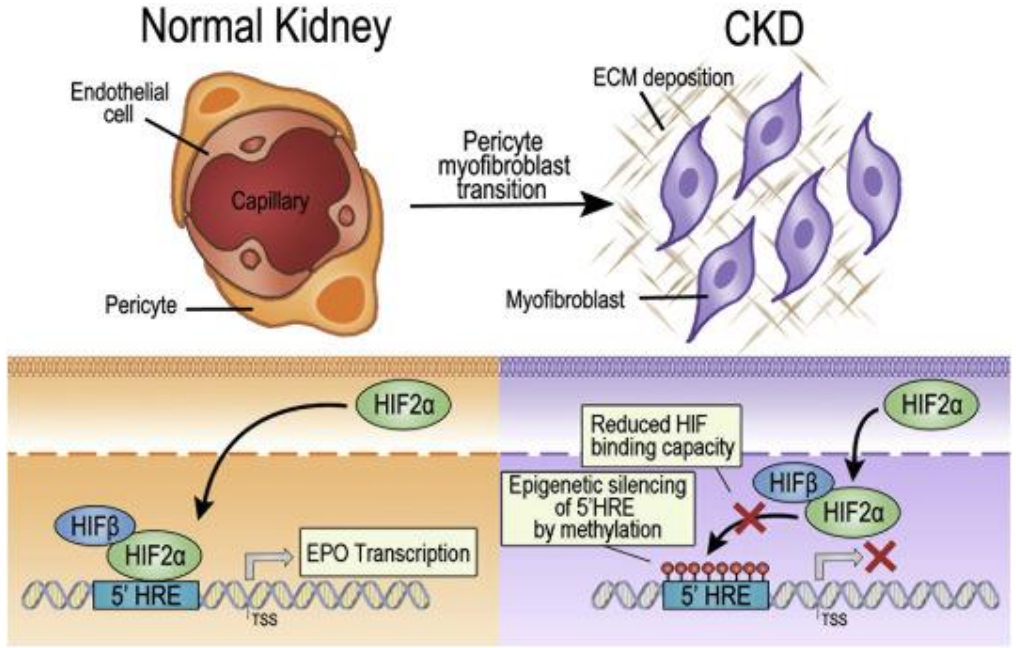
Anemia may develop as eGFR declines

Anemia in CKD may:

- Result from inadequate erythropoietin synthesis.
- Develop early and worsen as CKD progresses.
- Occur earlier in people with diabetes.
- Involve inadequate iron intake, impaired iron absorption and chronic inflammation.



Adapted from Stauffer PLoS ONE 2014



Journal of the Formosan Medical Association, Volume 117, Issue 11, 2018

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A 66 year old patient with an eGFR of 20 mL/min/1.73m^2 presents with symptoms of anemia. The patient has been taking ferrous sulfate orally and currently has a diabetic foot infection being treated with antibiotics. Which of the following is likely contributing to the patient's anemia?

a) Decrease in EPO production
b) Decrease in iron absorption in GI tract
c) Infection
d) All of the above

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A 66 year old patient with an eGFR of 20 mL/min/1.73m^2 presents with symptoms of anemia. The patient has been taking ferrous sulfate orally and currently has a diabetic foot infection being treated with antibiotics. Which of the following is likely contributing to the patient's anemia?

a) Decrease in EPO production
b) Decrease in iron absorption in GI tract
c) Infection
d) All of the above

Answer: D
Anemia in CKD is often multi-factorial. The principal cause of anemia in CKD is decreased EPO production but, in this patient decreased iron absorption in GI tract and current infection are also contributors.

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Anemia and Iron Deficiency in Heart Failure

- Iron deficiency is present in approximately 30% of heart failure patients, usually classified as chronic normocytic anemia. Functional iron deficiency occurs in about one third of patients
- a negative prognostic factor

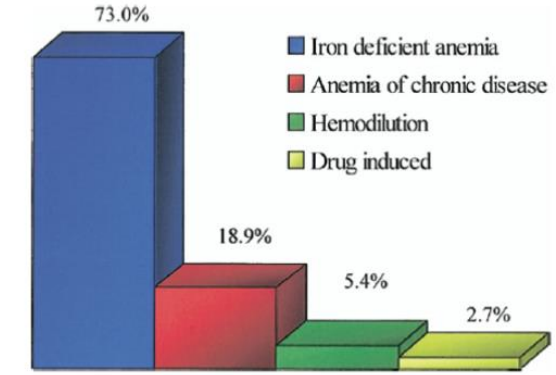
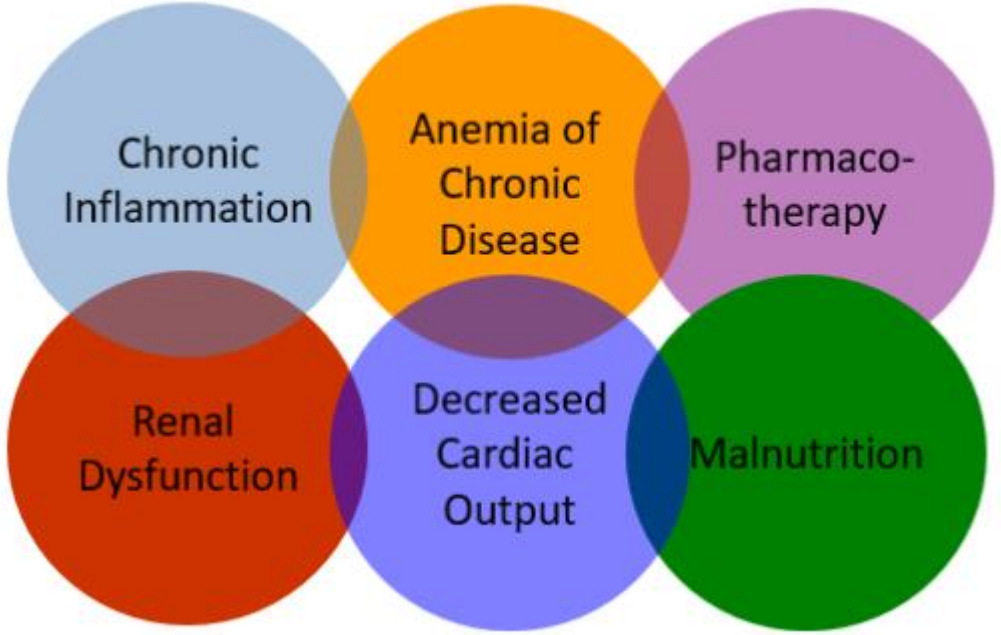


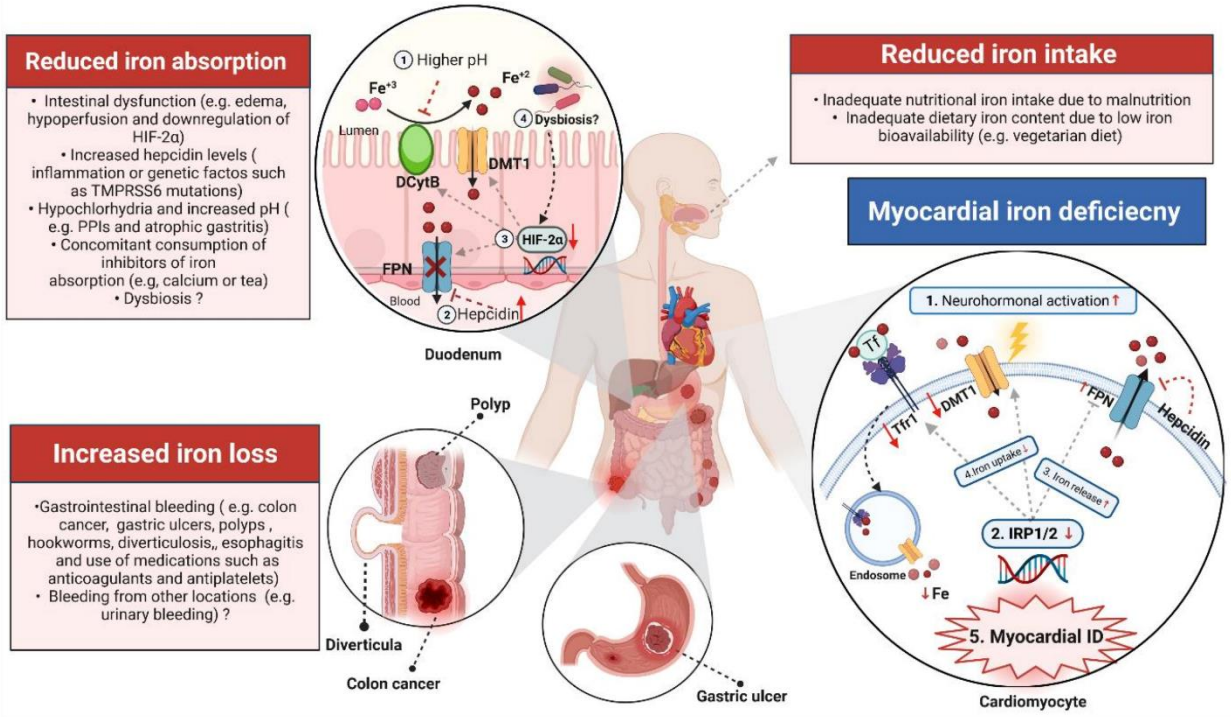
Figure 1. Distribution of various etiologies of anemia among 37 patients with advanced congestive heart failure.

Nanas et al, J Am Coll Cardiol 2006



Causes and Etiopathogenic Mechanisms of Iron Deficiency and Anemia in Chronic Heart Failure

- iron deficiency,
- excessive secretion of cytokines,
- hemodilution by sodium retention,
- cardiac cachexia,
- the use of angiotensin II converting enzyme inhibitor (ACEI) drugs,
- chronic kidney pathology associated with decreased levels of EPO, which characterizes the anemic cardio-renal syndrome, in which failure of a single organ (heart or kidneys) determines the alteration of the function of the other



Life 2021, 11(9), 987; https://doi.org/10.3390/life11090987

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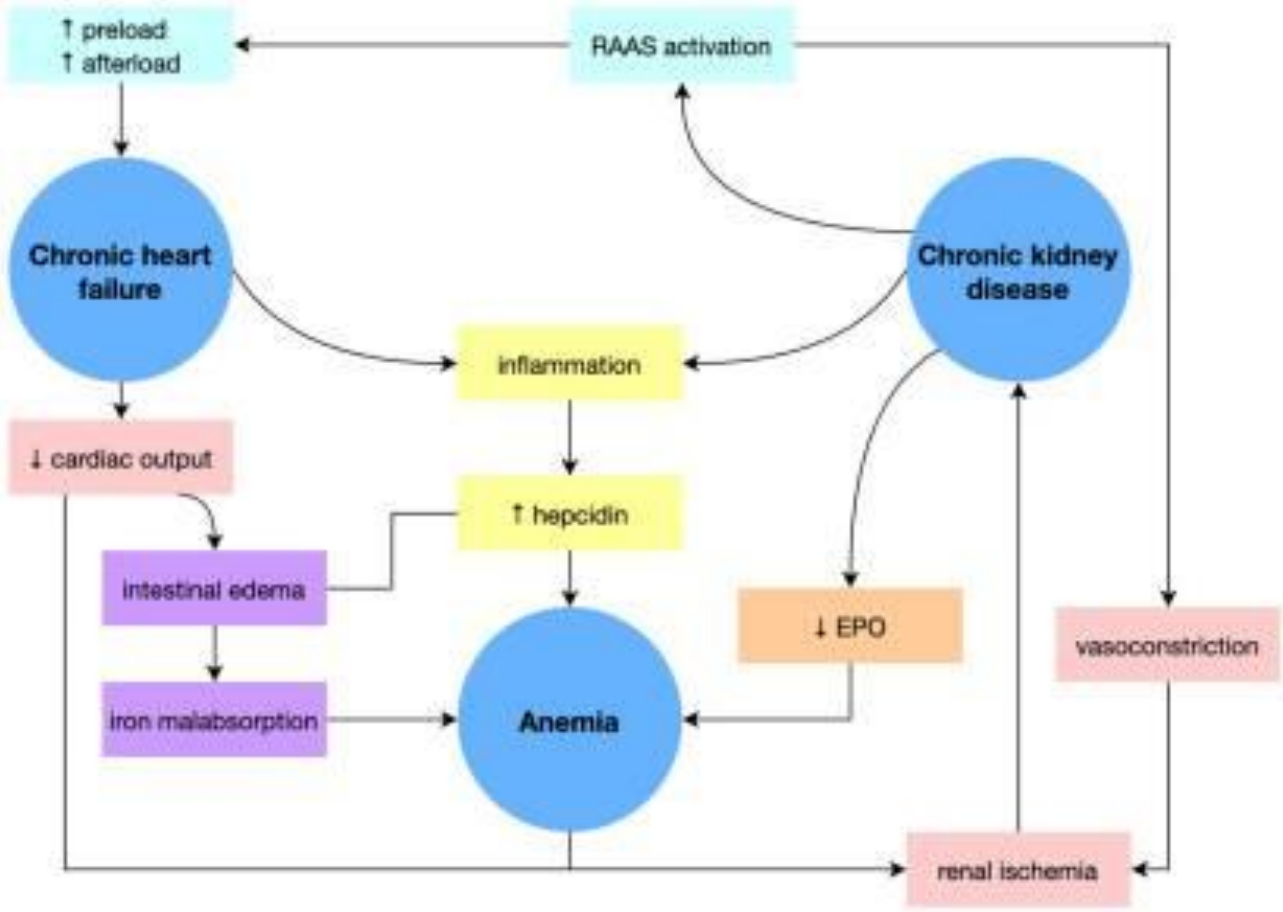
Physiopathology of cardio-renal anemia syndrome

- cardio-renal syndrome - failure of one organ (heart or kidneys) determines a change in the function of another



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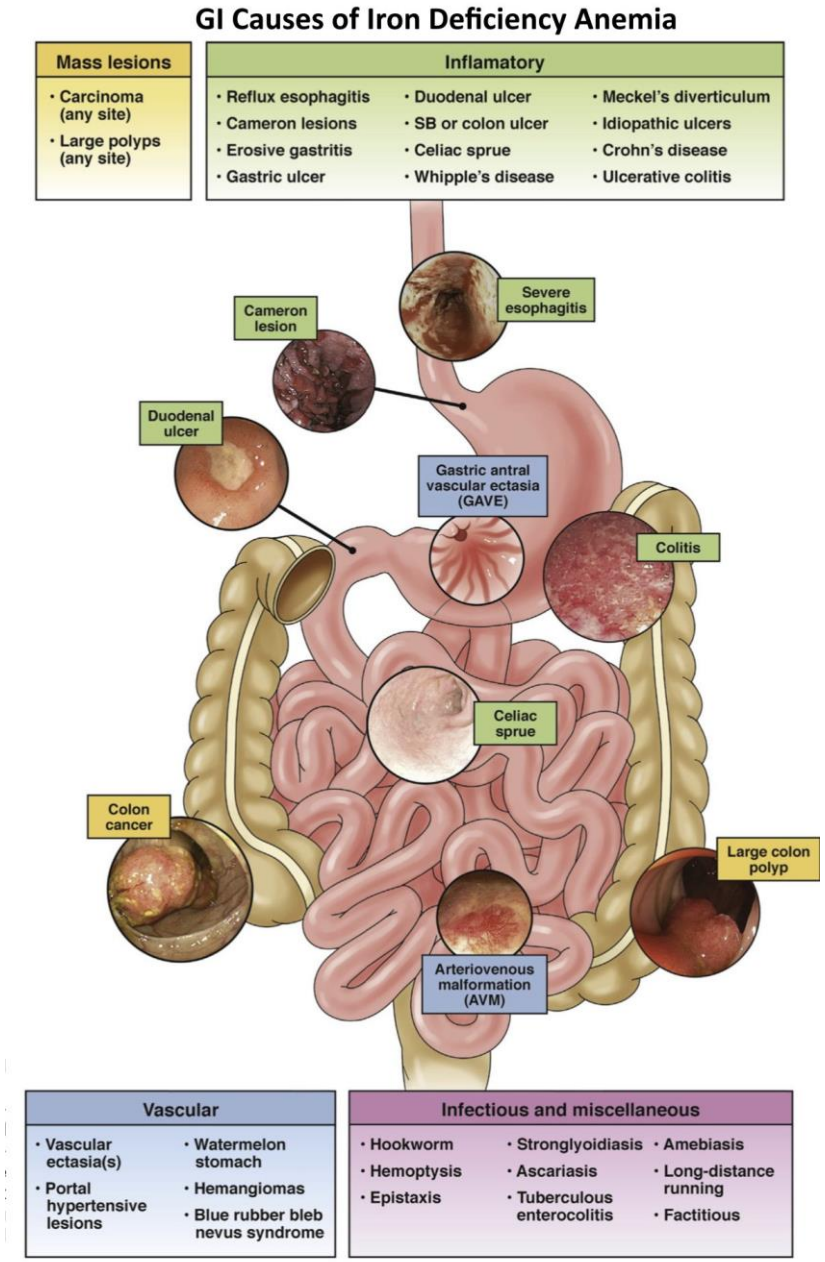
GIT

- HF patients have an altered intestinal morphology, permeability and absorption
- HF patients with venous congestion have reduced blood to the intestine, causing intestinal hypoperfusion and consequently nonocclusive bowel ischemia, increased mucosal permeability, bowel edema, cachexia and altered composition of mucosal bacteria
- Collectively, all of this might culminate in the malabsorption of micronutrients, including iron



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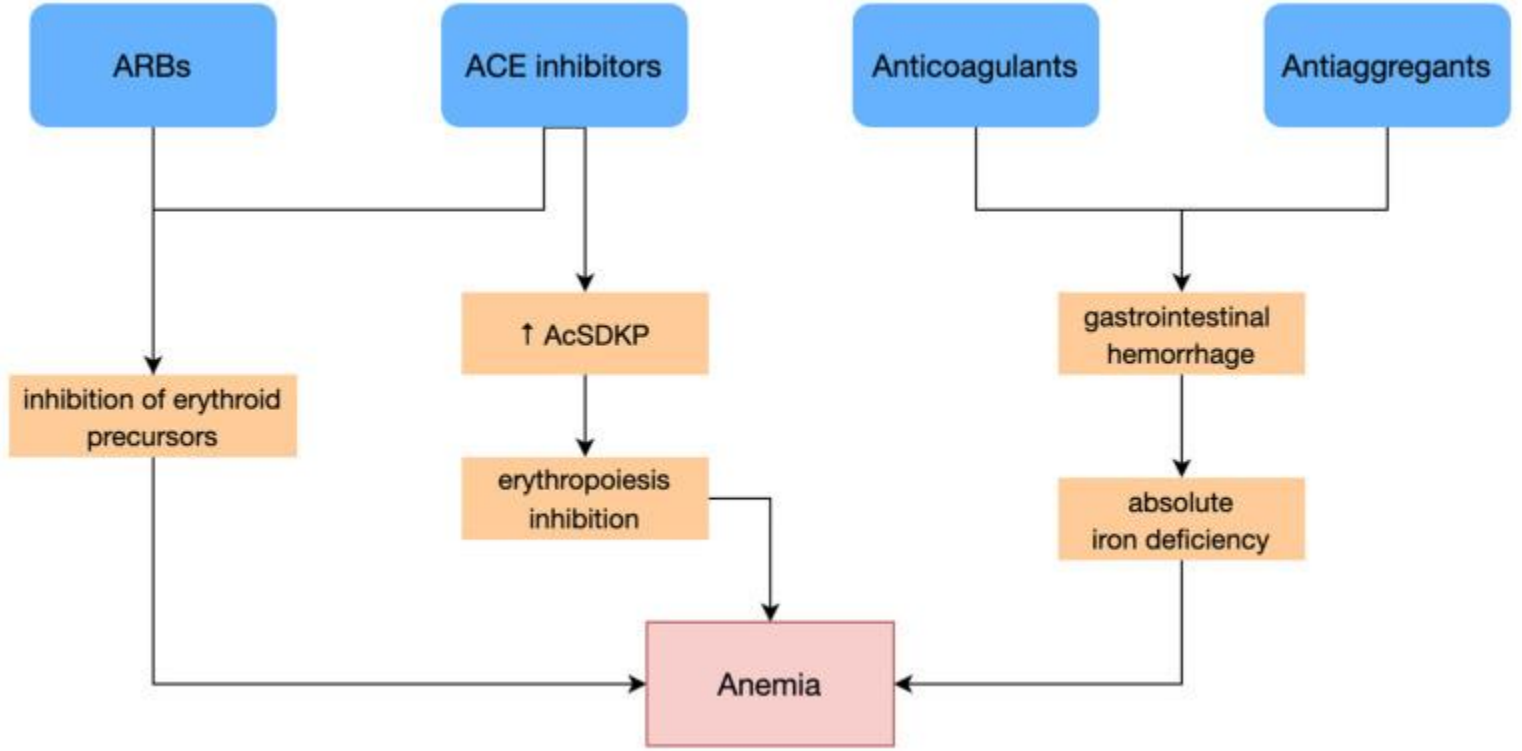
HF therapy

- Therapeutical agents used in CHF management and their pathogenic mechanisms.
- ARB, angiotensin receptor blockers. ACE, angiotensin-converting enzyme. AcSDKP, N-Acetyl-Seryl-Aspartyl-Lysyl-Proline.



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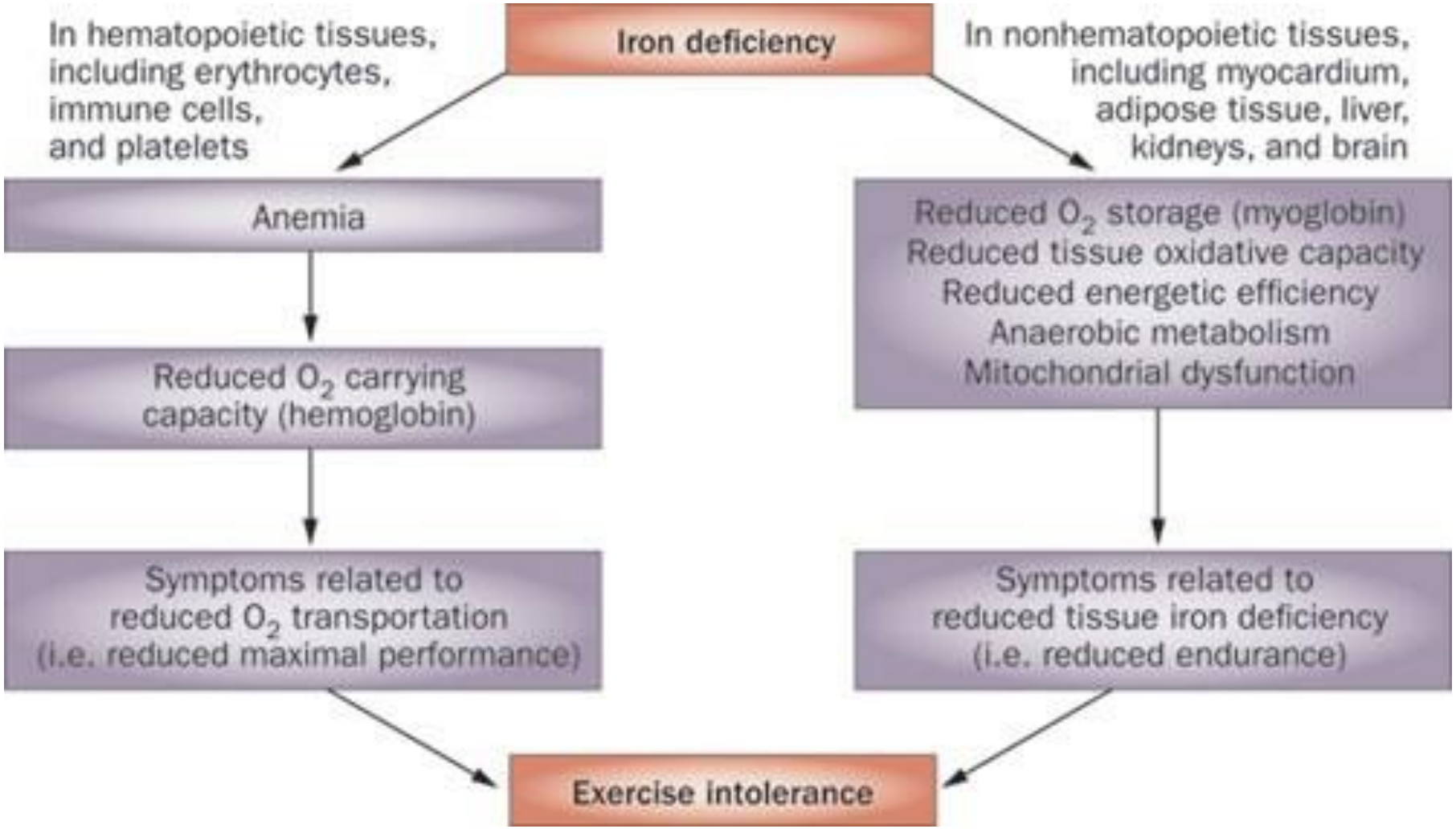
Iron deficiency



Nature Reviews Cardiology **volume 8**, pages485–493 (2011)

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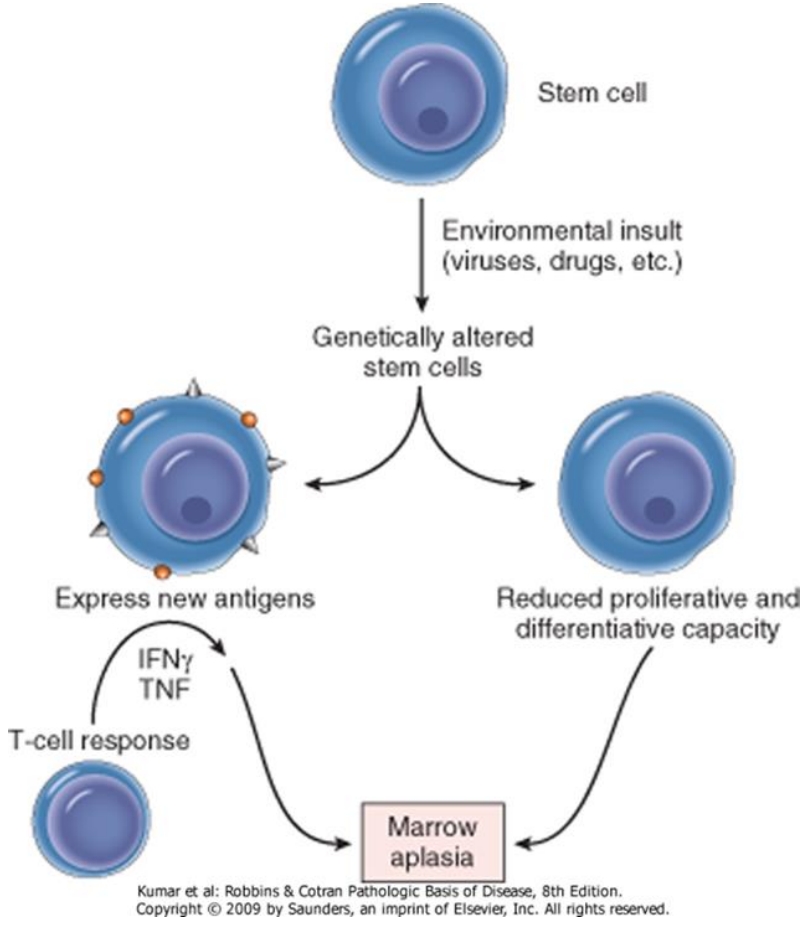
Aplastic anemia

- chronic failure of hematopoiesis
- etiology
  - idiopathic (65 %)
  - chemicals
    - benzene
    - alkylation agents
    - antimetabolites
  - viral infection
    - hepatitis, CMV, EBV
  - radiation
  - hereditary defects
  - Fanconi anemia
    - DNA reparation disorder
    - defects of telomerase



Aplastic anemia

- pathogenesis
  - extrinsic cause
    - change of stem cells‘ antigens
    - activation of Th1
      - cytokines, destruction of progenitors
    - up-regulation of proapoptotic genes
    - immunosuppressive therapy
  - intrinsic cause
    - karyotype changes
    - short telomeres
- morphology
  - hypocellular bone marrow
  - common infection, bleeding
- signs
  - pancytopenia
    - anaemia, petechia, infection
    - reticulocytopenia
- treatment
  - transplantation

Anemia in cancer

- Anemia occurs in more than 50% of cancer patients
- It is therefore considered a "paraneoplastic symptom"

Direct effects of disease
Bone marrow infiltration by malignant cells or fibrosis
Blunted erythropoietin response
Blood loss
Hemorrhage
Surgery
Phlebotomy
Effects of treatment
Myelosuppression by chemotherapy or radiotherapy
Hemolytic anemia
Nephrotoxicity
Thrombocytopenia or bleeding
Neutropenia or infection
Iron, folate, or vitamin B_{12} deficiency
Inflammation or activation of the immune system, anemia of chronic disease
Autoimmune hemolysis

KLENER P. - Anémie u nádorových onemocnění a jejich léčba. Remedia 2011; 22.

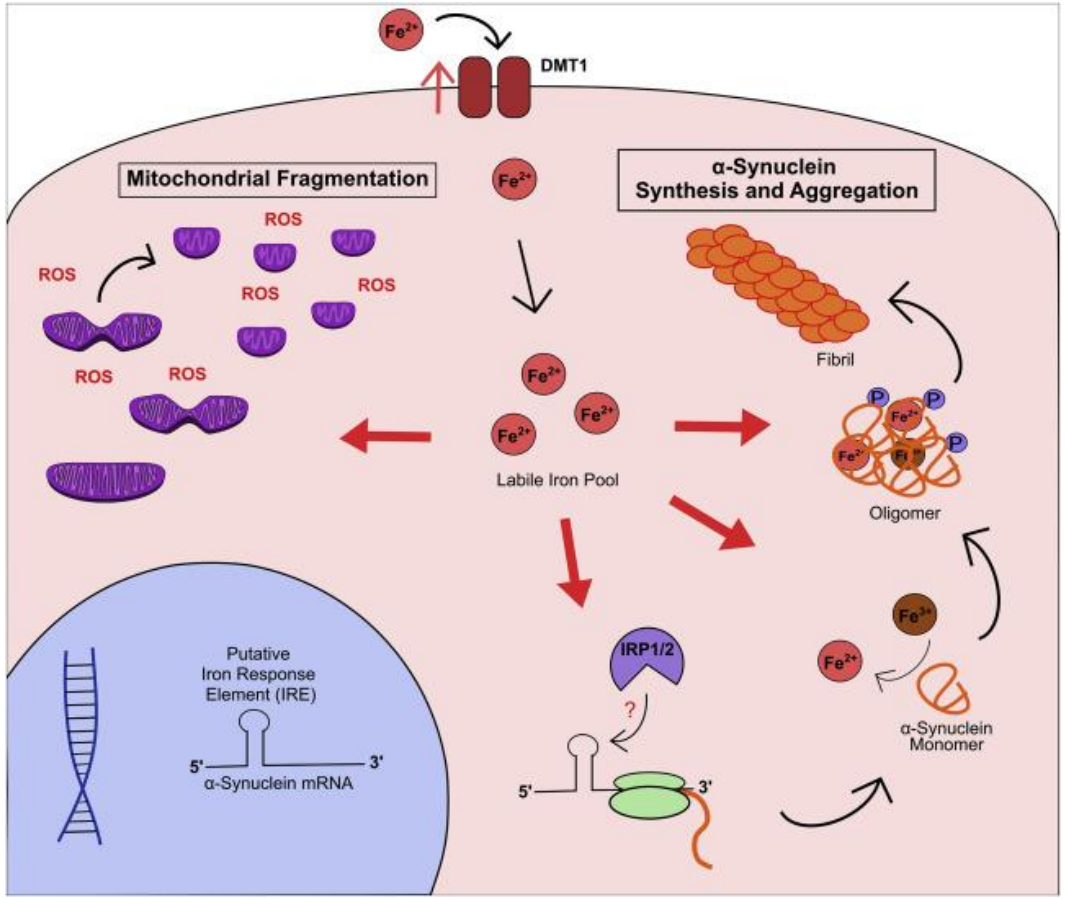
MUNI MED

Thank you for attention

Iron metabolism in the CNS

The role of iron in Parkinson's disease.

- Iron accumulation is found in the substantia nigra (SN). With PD, divalent metal transporter 1 (DMT1) expression is increased in the SN contributing to the increased iron uptake into the cell.
- Iron also directly interacts with α-synuclein, which acts as a ferrireductase converting Fe^{3+} to Fe^{2+}.
- Furthermore, excess iron has been shown to promote aggregation of α-synuclein by promoting post-translational modifications.
- Mitochondrial dysfunction is another key feature of PD pathology. Iron overload promotes mitochondrial fragmentation and disrupt mitochondrial fission.



Molecular Aspects of Medicine, Volume 75, 2020, 100867

MUNI MED