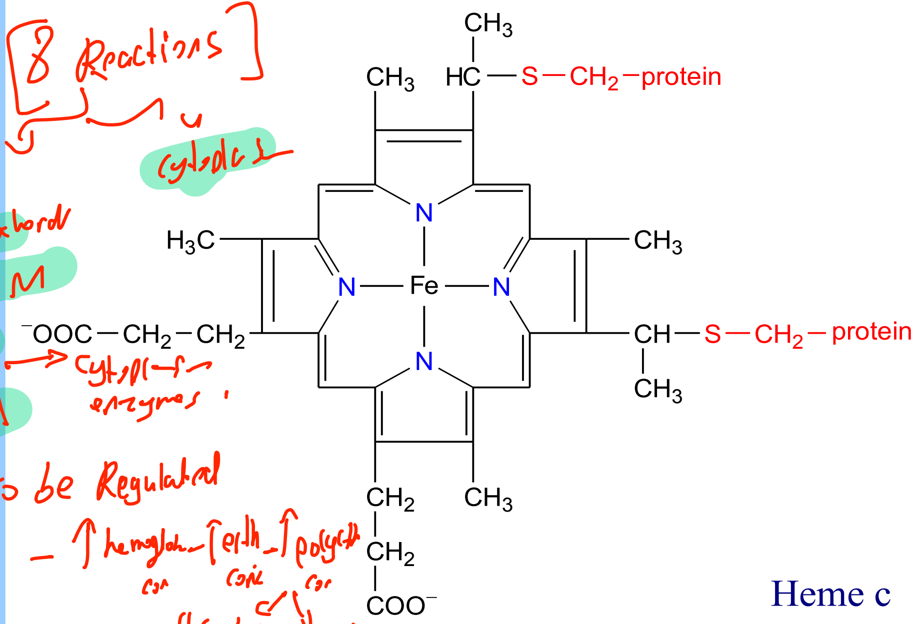
Hemoglobin synthesis

- Heme is the prosthetic group of hemoglobin, myoglobin, & cytochromes.
- Heme is an asymmetric molecule.



Heme c

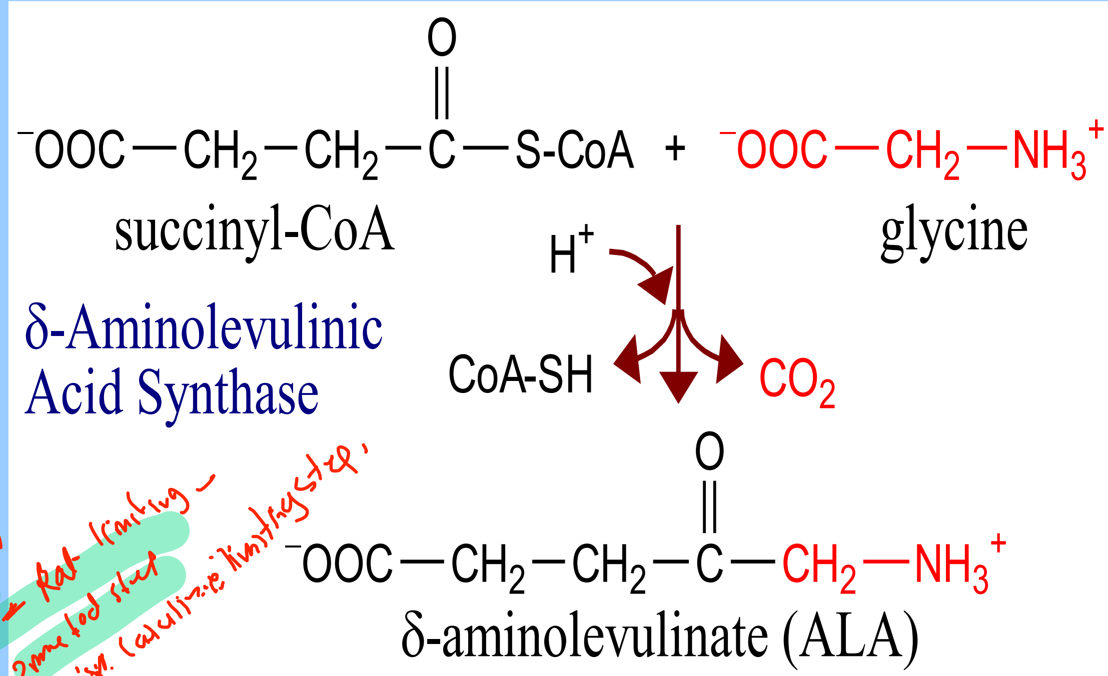
Heme synthesis (in Mitochondria)

- Heme synthesis begins with condensation of glycine & succinyl-CoA, with decarboxylation, to form δ-aminolevulinic acid (ALA).

→ to cytoplasm

- Pyridoxal phosphate (PLP) serves as coenzyme for δ- aminolevulinate synthase (ALA synthase), an enzyme related to transaminases.

key Regulatory enzyme in turn rate limiting committed step
+ commit (catalyzes irreversible step)



Hemoglobin synthesis

ملحوظة : التبييض يشمل اللون الأزرق و الأخضر.

Hemoglobin synthesis :

Consist of 8 reactions , 4 of them are mitochondrial and 4 reactions are cytosolic (1 mitochondrial , followed by 4 cytosolic reactions , followed by 3 mitochondrial reactions) . So intermediates of hemoglobin synthesis reactions are going from and to mitochondria through the mitochondrial bilayer membrane .

Why don't you react to what happened in one place?

It's a way of enzyme activity regulation, called Compartmentation or Compartemetalization Which means that not all reactions happen at the same siteinside the cell, so adding more regulatory factors. double layer mitochondrial membrane

***if all heme synthesis step are done in the cytoplasm NO control over production ofHeme increase the production of globin more hemoglobin more erythrocytes (polycythemia)**

1. **Increase the blood viscosity**
2. **Slow blood flow**
3. **Thrombi -> stagnation of blood**
4. **Adding more load on the cardiac muscle & may be heart failure**

The treatment of polycythemia are transfusion of blood (التبرع بالدم ونقله) .... Because if we want to treat it medically we have to inhibit the secreation of EPO .

*** All cells that have mitochondria are able to synthesize heme**

- CoA~SH & the glycine carboxyl are lost following the condensation.

Gene expression

- ALA synthase is catalyzing the committed step of the heme synthesis pathway, & is usually rate-limiting for the overall pathway.

Amino acid Not produced

- Regulation occurs through control of gene expression.

enzyme found, Activity enzyme inhibited

- Heme functions as a feedback inhibitor, repressing the transcription of ALA synthase gene in most cells.

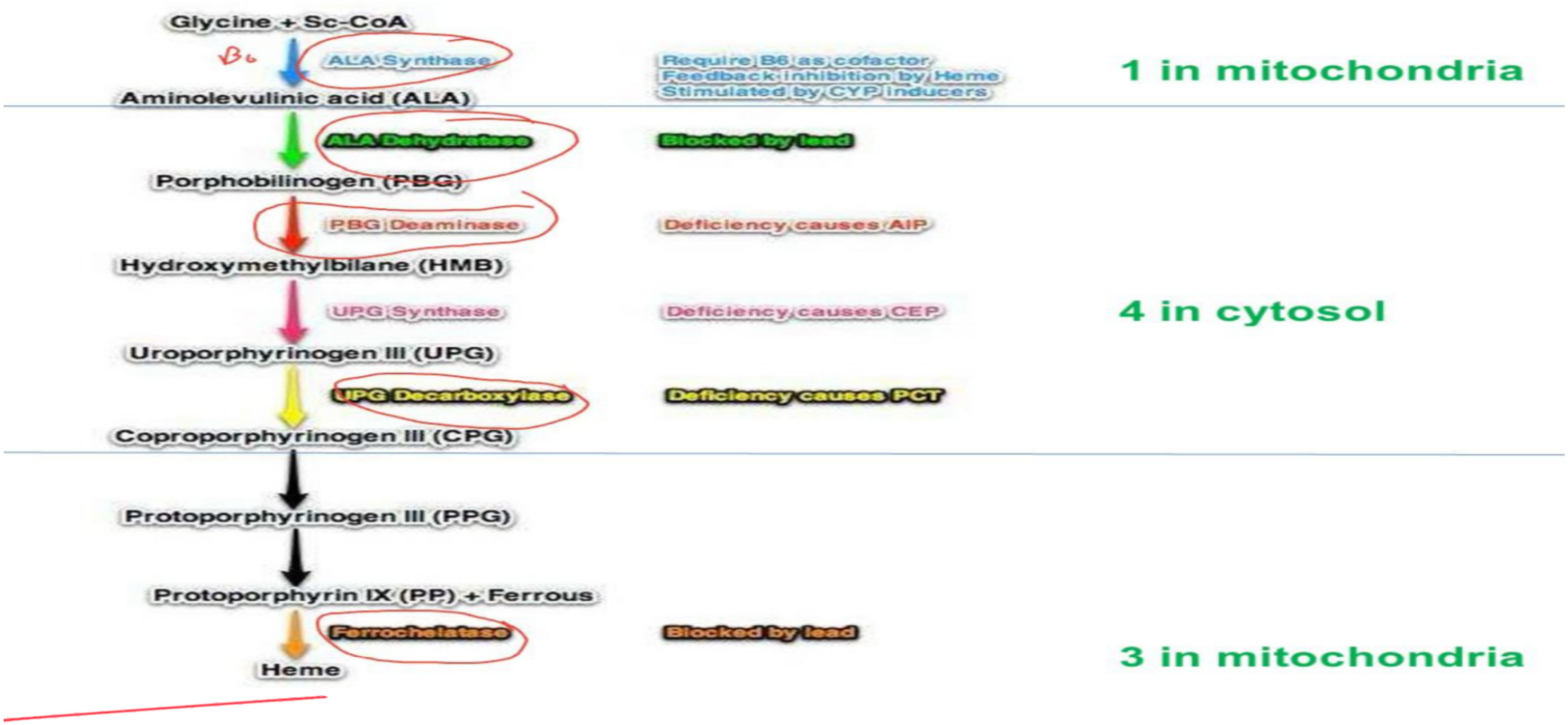
- A variant of ALA synthase expressed only in developing erythrocytes is regulated instead by availability of iron in the form of iron-sulfur clusters.

<u>There are two forms of ALAS</u>:

Small amount - All time

1-ALAS1 is considered a house-keeping gene and is expressed in all cells (located on chromosome 3).

2-ALAS2 is an erythroid-specific form of the enzyme, expressed only in fetal liver and adult bone marrow (located on the X chromosome).



Mnemonic for steps in heme synthesis

- S – SOME - Succinyl CoA
- G – GOOD -Glycine
- D – DOCTORS -Delta-Amino Levulinic Acid
- P – PALPATE -Porphobilinogen
- H – HEART - Hydroxymethylbelane
- U – UNDER -Uroporphobilinogen 3
- C – COVER -Coproporphyrinogen 3

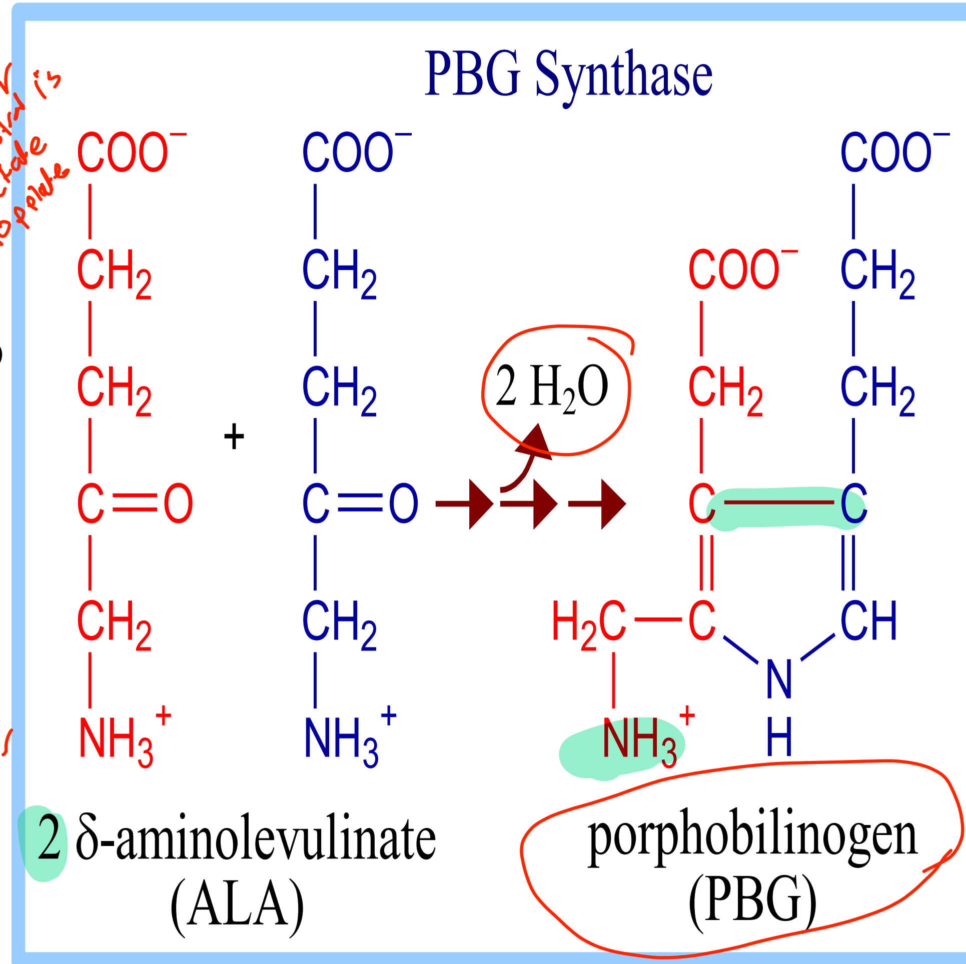
- PBG synthase (Ala + Ala) (porphobilinogen synthase), also called ALA dehydratase, catalyzes condensation of two molecules of δ- aminolevulinate to form the pyrrole ring of porphobilinogen (PBG).
- The Zn^{++} in the active of site mammalian porphobilinogen synthase, acting as binding sites for ligands including cysteine S, it can also bind Pb^{++} (lead).
- Inhibition of porphobilinogen synthase by Pb^{++} results in elevated blood ALA, as impaired heme synthesis leads to de-repression of the transcription of ALA synthase gene.

2 water
Final substrate is Acetate [propionate]

sulfur lead

sulfer

↑ Ala
Replace GaBa Receptor ← GABergic Receptor → excitatory [convulsion]



inhibition
Ala – GABA
similar 2 structure compound
GaBa [keto group]

[Keto group] → Similarity of structure هو Ala ال تكوينه زي اي *

- Dehydratase = remove water molecule

- The first pyrrole ring produced are (porphobilinogen)

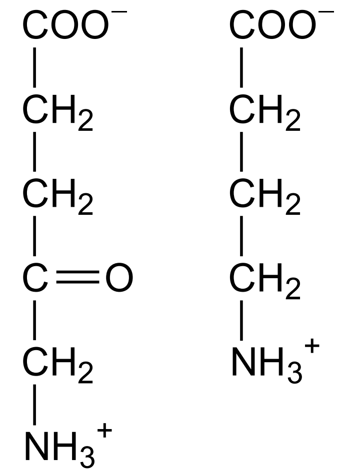
2. - the porphobilinogen which produced from reaction of PBG synthase enzyme (ALA dehydratase enzyme) , has different substitutions that bind to carbon atoms ... one with acetate and other with propionate , sothe heme is an asymmetric molecule .

If lead (Pb^{+2}) in high concentration binding to Zn^{+2} in the active sute of ALA dehydratase enzyme , it will inhibit the activity if this enzyme so only one step are done in pathway , so no production of hemoglobin , and the ALA which produced from first step will be acummulated because ALA has similar structure of GABA (which is the main inhibitory neurotransmitter) , the accumulated ALA will bind to GABA receptors , this will lead to loss of balance between excitatory & inhibitory neurotransmitter functions , so convulsions occur .

*ALA Replace GABA

**** number of inhibitory neurotransmitters is much less than number of excitatory neurotransmetters so if there is an analogue of GABA that bind to its receptor, this results in loss of function of GABA and loss of balance between neurotransmitters = increase excitatory functions ends up with convulsions**

- High ALA is thought to cause some of the neurological effects of lead poisoning, although Pb^{++} also may directly affect the nervous system.
- ALA is toxic to the brain, perhaps due to:
  1- Similarity in the structures between ALA and GABA (γ- aminobutyric acid).
  2- ALA autoxidation generates reactive oxygen species (oxygen radicals).

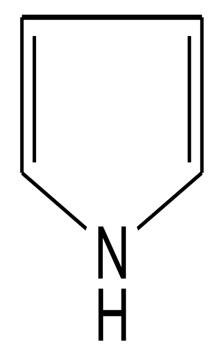


ALA GABA

- Porphobilinogen (PBG) is the first pathway intermediate that includes a pyrrole ring.
- The porphyrin ring is formed by condensation of 4 molecules of porphobilinogen.
- Porphobilinogen deaminase (hydroxymethylbilane synthase) catalyzes successive PBG condensations, initiated in each case by elimination of an amino group. it leads to the formation of the tetrapyrrole hydroxymethylbilane.

De Amination From 4 group

De Amination 4 pyrrol



pyrrole

Hydroxymethylbilane has two fates:

1- The most important is regulated, enzymatic conversion to uroporphyrinogen III, the next intermediate on the path to heme which is mediated by a holoenzyme comprised of uroporphyrinogen synthase plus a protein known as uroporphyrinogen III cosynthase. (1)

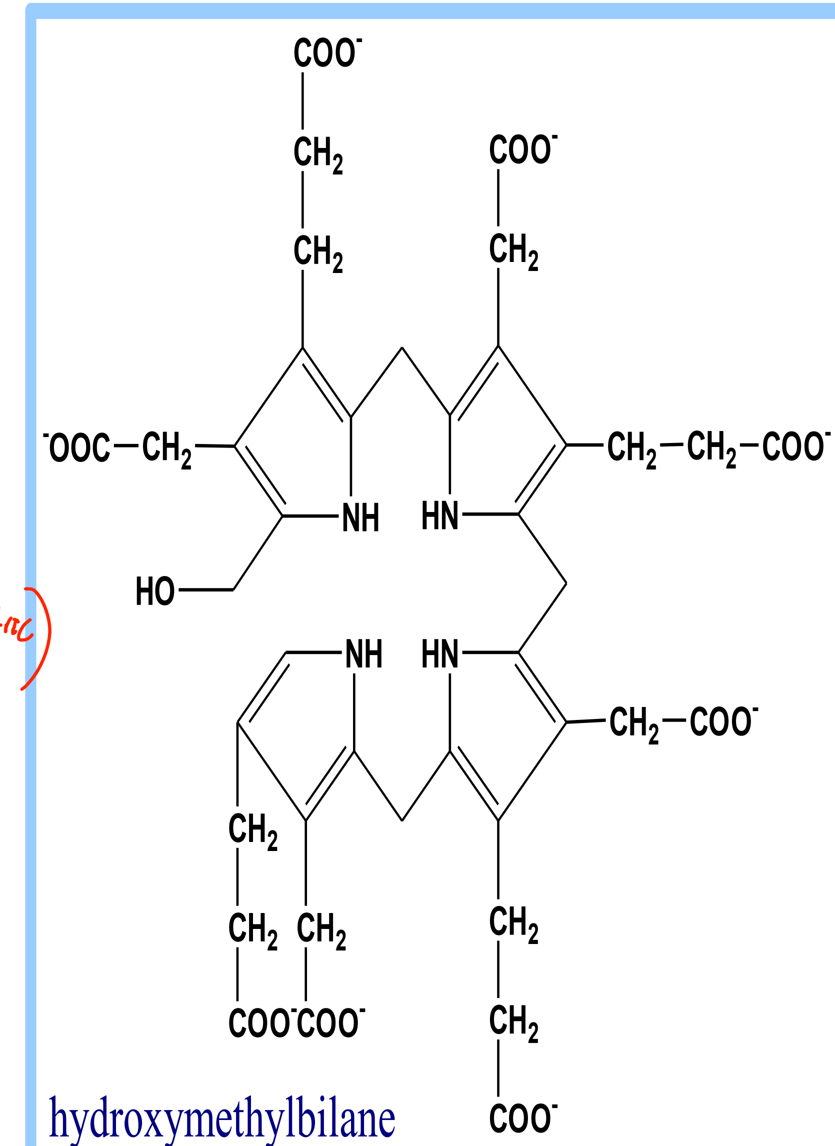
Ring 1 — Ring 4 Rotation

Ring 4 Symmetric (Asymmetric Ring 4)

2- Hydroxymethylbilane can also non – enzymatically cyclize forming uroporphyrinogen I. (2)

Non enzymatically

without Rotation


hydroxymethylbilane

4 Actions in Cytoplasm are:-
1. ALA Dehydratase
2. Hydroxy Methyl bilane synthase.
3. Uroporphyrinogen synthase 3
4. URoporphyrin Dicarboxylase

Iydroxymethylebilane molecule :

t is a molecule which is produced from reaction between 4 PBG molecules
y deamination of its amino groups and linearization of it by

Hydroxymethylebilane is cyclized .. which mean ring number 1 will binding ringnumber 4 by an enzyme known as (Uroporphyrinogen synthase)

This enzyme has two states :

- Non - enzymatically ... it will bind 1 & 4 rings in the same substitution (acetate / propionate ---- acetate propionate ----- acetate propionate ----- acetate propionate)
This will form structure called (Uroporphyrinogen I) 5%.

*All enzymes will complete Action in

- Enzymatically in the presence of special co- factors called (Uroporphyrinogen III co-synthase)........during binding of 1&4 rings , ring number 4 will turn around itself so give more assymetry in the structure of heme .. the binding will be as (acetate / propionate ----- acetate / propionate ------ acetate / propionate ------- *propionate / acetate*)
The diffrence in ring number 4 because of flipping over or rotation of this ringaround itself .

95%.

**** only Uroporphyrinogen III will continue in heme synthesis .

Uroporphyrinogen I has no function , this because there are no enzyme can actupon it or react with it → cyclization without enzyme

Decarboxylase

Uropophyrinogen decarboxylase enzyme will go on last reacrion inside thecytosole , which is decarboxylation reaction , by removing CO2 from each acetate group so it converts to methyl group (acetate = CH3-COO ..... methyle = CH3 **** so decarboxylated acetate = methyl)

The molecule produced are known as (Coproporphyrinogen) .... which has substitution as follow (methyl/ propionate ---- methyl / propionate ----- methyln/ propionate ----- propionate methyl)

① ALA

Copropophyrinogen will go in the mitochondria to give the rest of reactions in hemoglobin synthesise .

→ Rotation Ring 4.

It will go in oxidative decarboxylation reaction of two of protionate groups on ring 1& 2 to convert it to vinylgroups by enzyme called (coproporphyrinogen oxidase) , so the substitution of the new molecule are as follow (methyle / vinyl ---- methyle / vinyl ----- methyle / propionate -- propionate / methyle)

This structure is known as (protopophyrinogen) which will go into oxidation by (protopophyrinogen oxidase) to convert it into (protopophyrine) , which has double bond .... because the bonds which link the pyrrole rings with each other are not methyline bonds , it is methynele so this enzyme form double bonds in the methyline groups that link the 4 pyrrole rings together .

→ highest molecule of Asymmetry

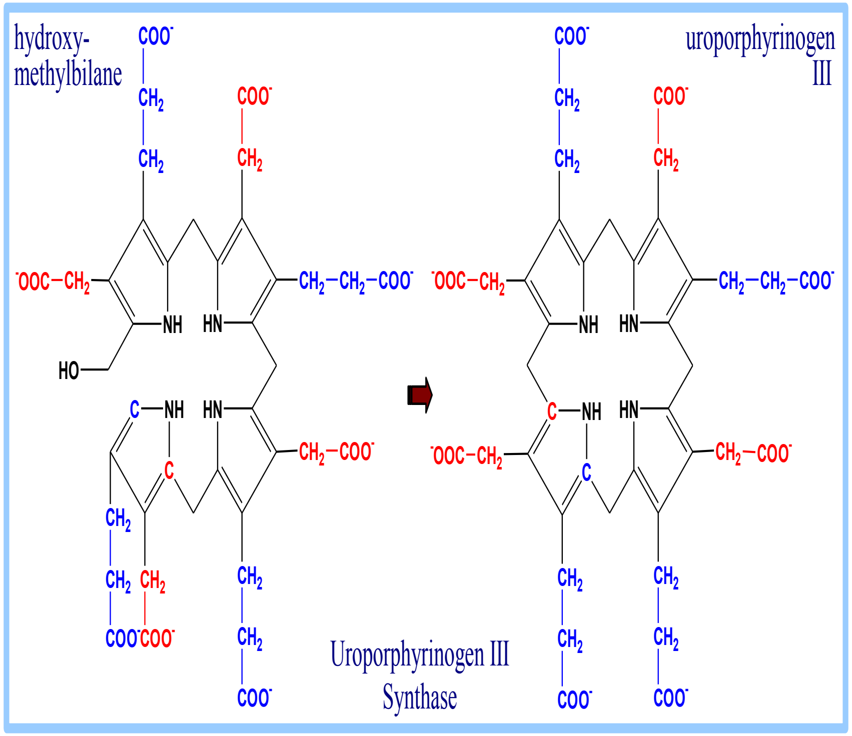
the final asymmetry of hemoglobin is attributed to :

1. Acetate propionate on each ring
2. More asymmetry on ring 4 by its rotation around itself .
3. Another asymmetry by decarboxylation of all acetate groups to convert it to methyle groups .
4. More asymmetry by oxidative decarboxylation of propionate groups on the 1&2 pyrrole

- Uroporphyrinogen III synthase converts the linear tetrapyrrole hydroxymethylbilane to the macrocyclic uroporphyrinogen III.
- Uroporphyrinogen III synthase catalyzes ring closure & flipping over of one pyrrole to yield an asymmetric tetrapyrrole.

-The distribution of acetyl & propionyl side chains, as flipping over of one pyrrole yields an asymmetric tetrapyrrole.

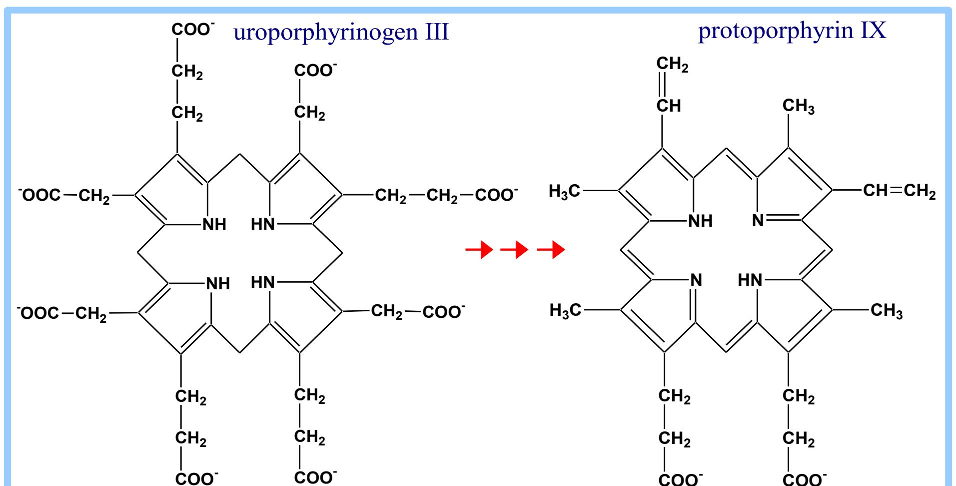
- Uroporphyrinogen III is the precursor for synthesis of vitamin B12, chlorophyll, and heme, in organisms that produce these compounds.

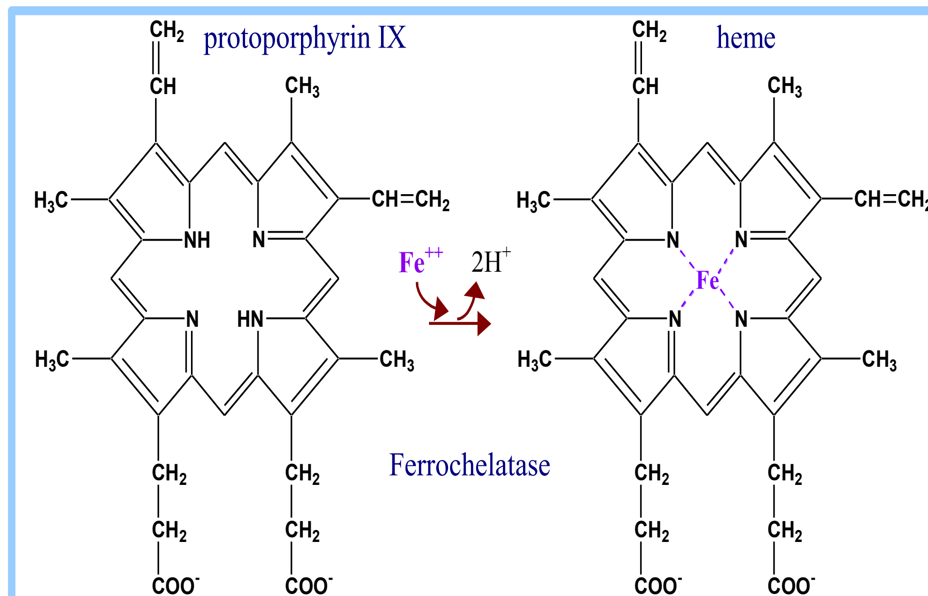


4 methyle
proponiat 3

propionat
4

- Conversion of uroporphyrinogen III to protoporphyrin IX occurs in several steps.
- All 4 acetyl side chains are decarboxylated to methyl groups (catalyzed by uroporphyrinogen decarboxylase)
- Oxidative decarboxylation converts 2 of 4 propionyl side chains to vinyl groups (catalyzed by Coproporphyrinogen oxidase) (1,2) [Methyle – methyle venil – venil
- Oxidation adds double bonds (Protoporphyrinogen oxidase). methyl propinal – propinal methyl
- Fe++ is added to protoporphyrin IX via Ferrocheletase, a homodimeric enzyme containing 2 iron-sulfur clusters. ↳ 4 links 4 links.
- A conserved active site His, along with a chain of anionic residues, may conduct released protons away, as Fe++ binds from the other side of the porphyrin ring, to yield heme.





Q: Ferrous in the heme molecule has 6 bonds , although its valincy are 4 not6 , why ??

A: although there are alot of defense mechanism to prevent oxidation of ferrous iron into ferric , but some times oxidation occur , so there are enzymeinside erythrocytes known as (methemoglobin reductase enzyme) which will convert hemoglobin to its active functional form after any change of any part of hemoglobin into methemoglobin .

More Defenes Mechanism

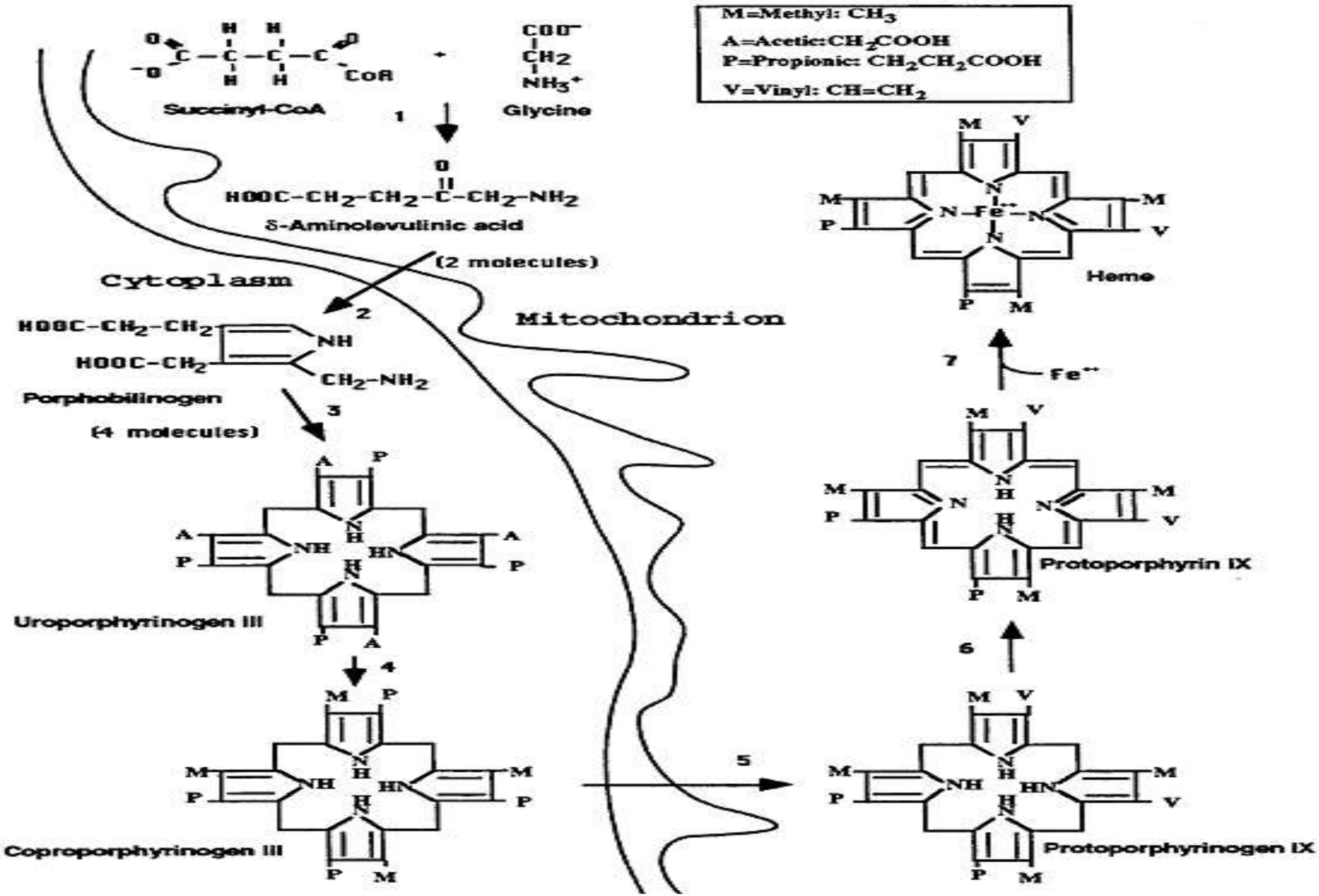
+ will Never oxedize .

Bonds of ferrous are :

4 bonds with the nitrogen of four pyrrole rings .

one with proximal histidine

one with O2



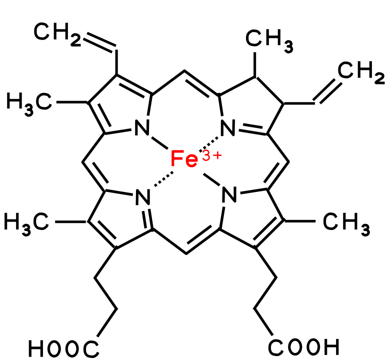
Pathway of Heme Biosynthesis

- In addition to the heme *b* found in hemoglobin, there are two different forms of heme found in cytochromes such as those involved in the process of oxidative phosphorylation.
- Cytochromes of the *c* type contain a modified iron protoporphyrin IX known as heme *c*.

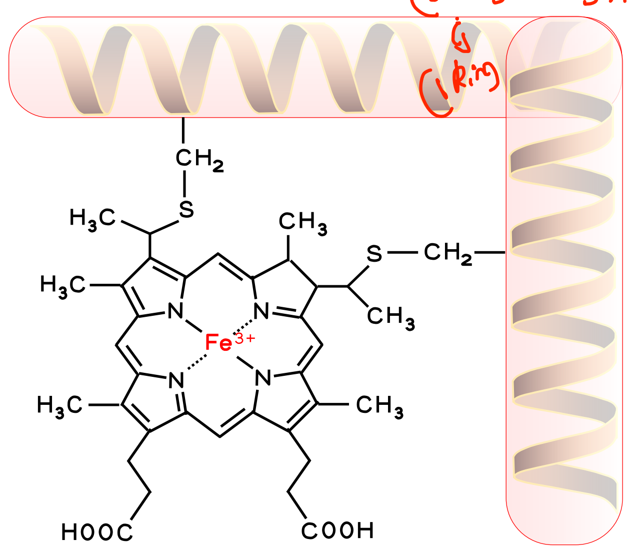
Ring 1 & Ring 2

- In heme *c* the 2 vinyl (C=C) side chains are covalently bonded to cysteine sulfhydryl residues of the apoprotein.
- Only cytochromes of the *c* type contain covalently bound heme.
- Heme *a* is also a modified iron protoporphyrin IX.
- Heme *a* is found in cytochromes of the *a* type and in the chlorophyll of green plants.

Heme *b*

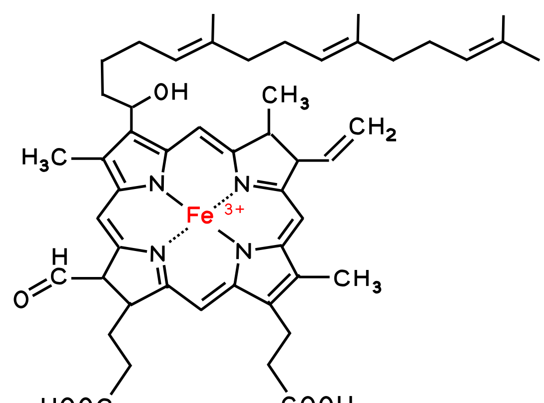


Heme *c* (2 venyle - cystine)



Polyunsaturated Ring 1

Heme *a*



- Regulation of transcription or post-translational processing of enzymes of the heme synthesis pathways differs between erythrocyte forming cells & other tissues.

- In erythrocyte-forming cells there is steady production of pathway enzymes, limited only by iron availability.

- In other tissues expression of pathway enzymes is more variable & subject to feedback inhibition by heme.

-The rate-limiting step in hepatic heme biosynthesis occurs at the ALA synthase catalyzed step, which is the committed step in heme synthesis.

-The Fe^{3+} oxidation product of heme is termed hemin which acts as a feed-back inhibitor on ALA synthase.

- Hemin also inhibits transport of ALA synthase from the cytosol into the mitochondria as well as represses synthesis of the enzyme.

- In erythroid cells all of the heme is synthesized for incorporation into hemoglobin and occurs only upon differentiation when synthesis of hemoglobin proceeds.

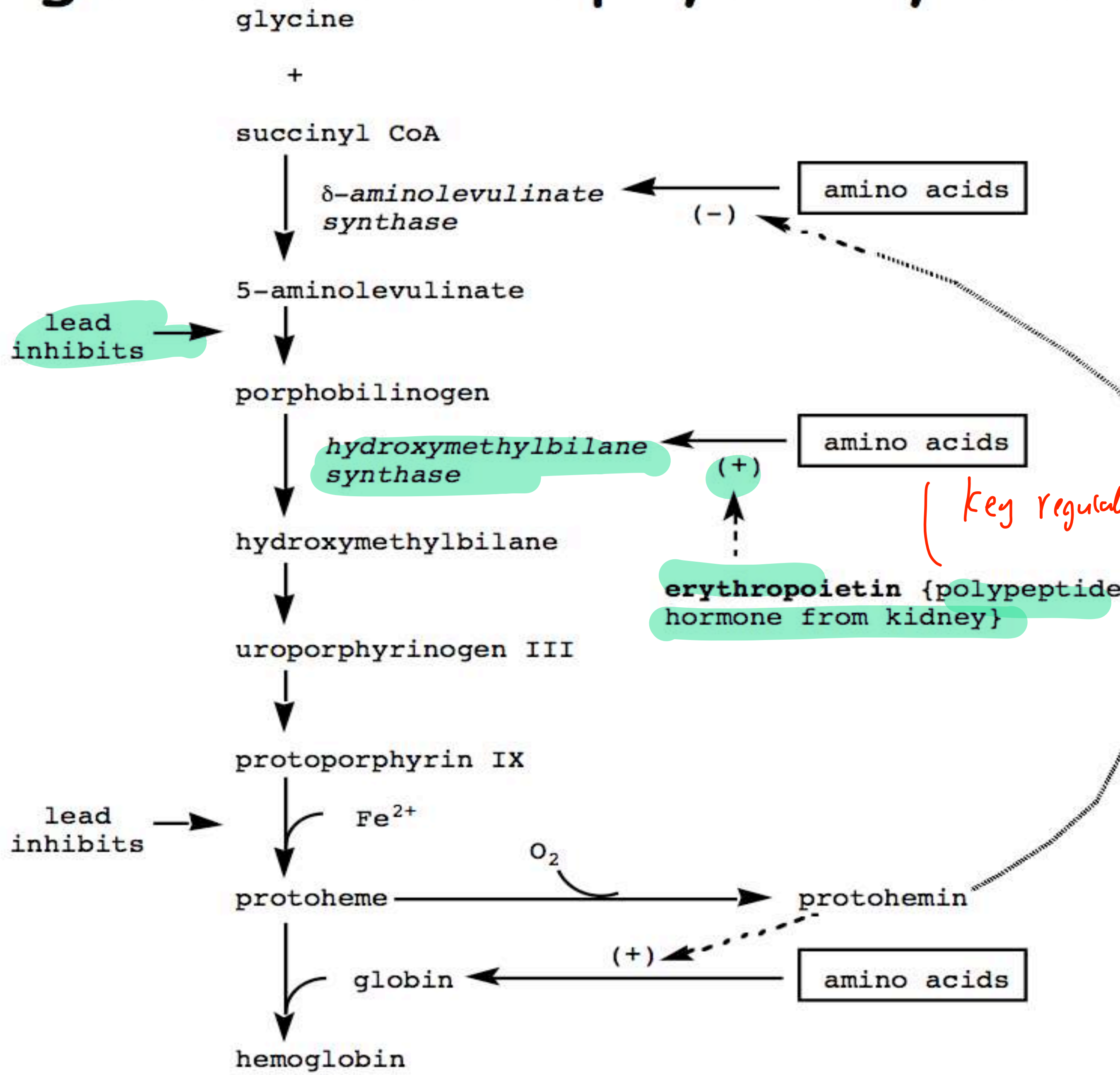
-When red cells mature both heme and hemoglobin synthesis ceases.
-The hemoglobin must, therefore, survive for the life of the erythrocyte.

- In reticulocytes (immature erythrocytes) heme stimulates protein synthesis.

- Additionally, control of heme biosynthesis in erythrocytes occurs at numerous sites other than at the level of ALA synthase.

- Control has been shown to be exerted on ferrochelatase, the enzyme responsible for iron insertion into protoporphyrin IX, and on porphobilinogen deaminase.

Regulation of Porphyrin Synthesis



Regulate

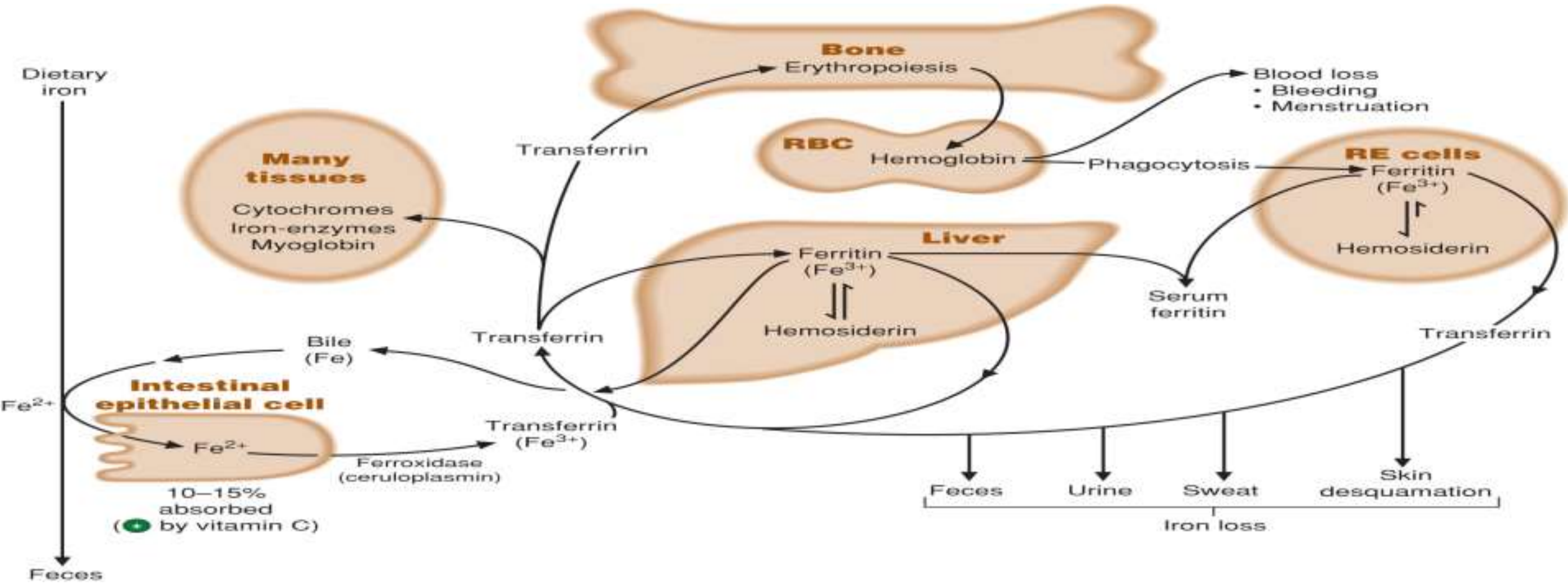
key regulator → oxidized hem

hemin

cyto - mitochond

Regulation of iron absorption and transport

- Iron for synthesis of heme, Fe-S centers and other non-heme
- Iron is obtained from:
  1- The diet
  2- Release of recycled in liver iron from macrophages of the reticuloendothelial system that ingest old & damaged erythrocytes.
- There is no known mechanism for iron excretion.
- Iron is significantly lost only by bleeding, including menstruation in females.



The treatment & dignosis of iron metabolism & deficincy are very complicated because it has diffrent types of proteins playing very important roles in the metabolism of iron , it is subdivided into 3 groups :

1- Key determininats of iron regulation at different physiological levels >

This proteins determine what are the requirments of iron under physiological conditions ?? , is it absorbed ?? and determining their level in blood either increasing or decreasing ?? etc

Examples : ferritin & transferrin

** ferritin : when we investigate iron deficincy anemia , not Hb & iron are the only mesurments .. we have to complete full investigation to treat IDA in a full term . (storage form)

** transferrin : carrier protein which carry ferrin from side to side . [side of storage's → side of utilization]

** hepcidin : secreted from liver as hormone . (IRON Regulating)

2- Transportation of iron across cellular membrane .

Examples : slide

- Iron utilized in synthesis requierments you need absorption it will increased , you don't need absorption it will decrase .

But under normal physiological conditions , the iron absorption are not exceede 5% although the cause of increasing demand of it .

** so absorption of more iron = formation of more heme = formation of more RBCs = polycythemia

+

Iron in circulation if doesn't carreid it is toxic

** The iron which we take have to be bounded = salt . → iron chloride

** Salt is not allowed to be absorbed , so the ionization occur , this ionization occurs by gastric acid (HCl) + Glutathion so you have to be carful , don't drink coffee at the early morning because it will lead to acute gastritis , which will lead to chromic gastritis , so parital cells function will decrease and HCl production decrease .

Duodenum Cytoplasm Transfere from Ferric To Ferrous → hemoxygenas → Ferric form

** so before treatment of IDA , I have to make sure what is the situation of the gastric mucosa because in the state of gastritis you will not use tablet or capsules , you will use I.V injections because of problems on absorbtion

** ionization may also occur by glutathion indirectly .

** most of doctors during treatment of IDA by tablets or capsules add vit. C to increase state of ionization .

* Ferric form To join Apoferritin *

** iron to croos any membrane must to be ferrous form (Fe^{+2})

** iron to bind to any type of protein must to be in ferric form (Fe^{+3})

Release iRON From ferric form To join Apoferritin → ferritin

** If iron take in diet as heme (not free iron) there are no ionization in this state , there are special receptor
for heme , which increase ability of heme to cross inside , then inside the heme oxygenase → Release iron in ferric form enzyme system(which are more than one enzyme , it is group of enzymes not one enzyme) ....
either iron cross by DMT1 or by heme oxygenase enzyme system , inside cell it will bind to apoferritin and convert into ferritin which are known stored iron ....

When the body need this iron for utilization , iron exit from the cell by protein known as ferroportin (in ferrous form)..when it bind to any protein (as ferroportin) it have to be converted into ferric form , how it will be converted from ferrous into ferric in this state ??
By effect of protein known as (cupper dependant ferroxidase)
transferrin

** This process regulated by hepcidin protien / hormone . [under Control] by hepcidin

** Outside the intestinal cell , iron have to be converted into ferrous form by effect of ferroxidase (Cu^{+2}) =copper dependent ....

Iron metabolism and proteins

(iRON Regulating

- Many proteins have been identified playing roles in iron metabolism such as ferritin or transferrin are the main cargos of blood iron, whereas peptides such as iron regulatory proteins, hepcidin, and matriptase2 are **key determinants of iron regulation at different physiological levels**.

stored form · carrier

② * Transportation iRON Cross Cell Membrane.

Genetic incoding matriptase 2 → iRON Deficiency Anemia

- A set of different proteins, notably divalent metal transporter-1, ferroportin, and transferrin receptors in association with ferroxidases such as duodenal cytochrome B, ceruloplamin and heme carrier protein, are involved in **the cellular membrane transportation of iron**.

copper

→ Transport iRon site of storage → utilization

- Others proteins such as myoglobin, Hb, and many different enzymes are the 'end' products of iron metabolism, because **they require iron for their functions.**

→ Cytochrom A: B: C:

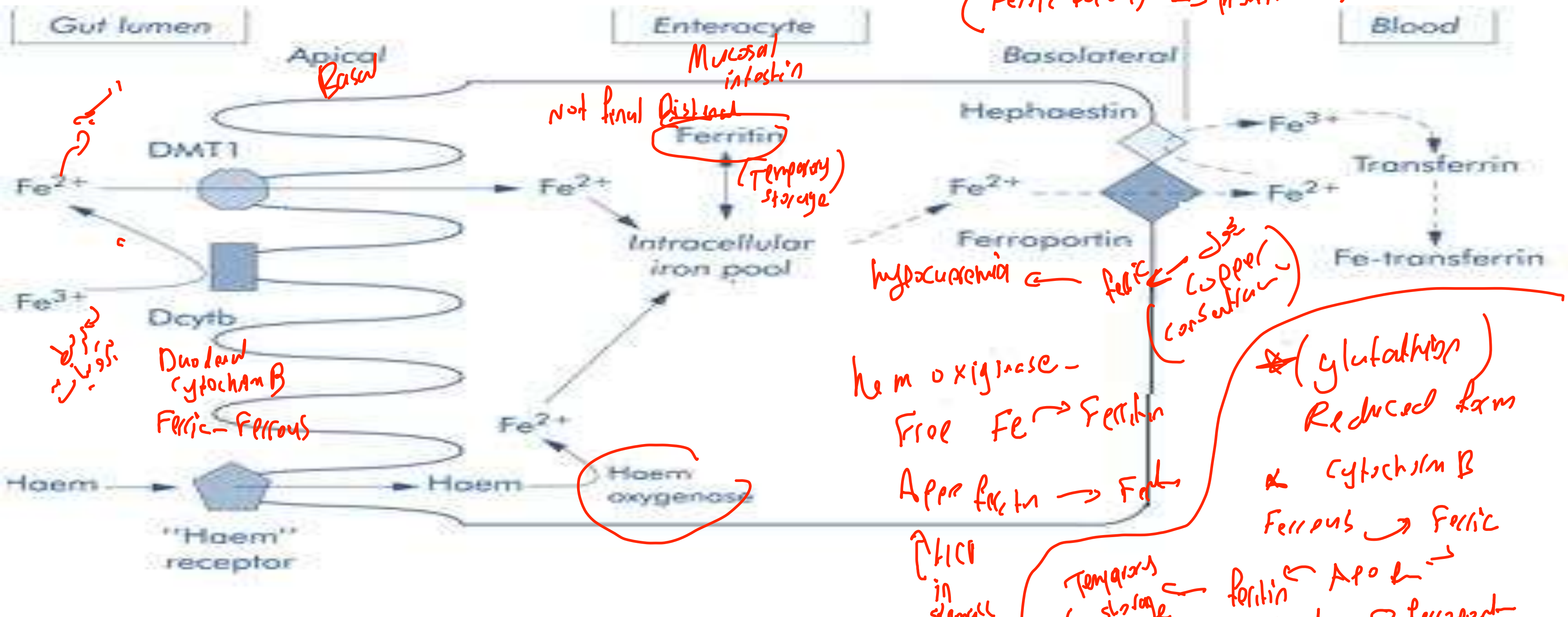
* Cyanin poisoning AFFEC cytochrom oxidaze

* Used in Diagnostic test of IDA, when patient hypoceruloplasmia Affect Ceruloplasmin → Ferrin → AFFected iRON transport Form to cells From site stage TO utilization

Absorption of Iron

ferric → Apo ferritin

(Ferrous form) (Ferric form) → protein



1- Iron stores within cells as a complex with apoferritin (ferritin), the main storage site is liver

Disociation by HCl in stomach

2- Pass across basolateral membrane to be carried to transferrin through a protein ferroportin and hephaestin

From Ferrous to ferric

3- Fe+2 is converted to Fe+3 by ferroxidase (Cu+2)

4- Hepcidin act as down regulator peptide secreted by liver.

Regulation of iron absorption and exportation by enterocytes

- Transcription of the gene for the iron transporter ferroportin is responsive to iron.

Antimicrobial agent

- When iron levels are high or in response to cytokines produced at sites of inflammation, hepcidin is secreted to induce ferroportin internalization and degradation, thus, leads to decreased absorption of dietary iron and decreased serum iron.
- Inversely, in the absence of hepcidin, ferroportin is maintained on the cell membrane, and iron transportation is facilitated.
- The plasma membrane protein ferroportin mediates:

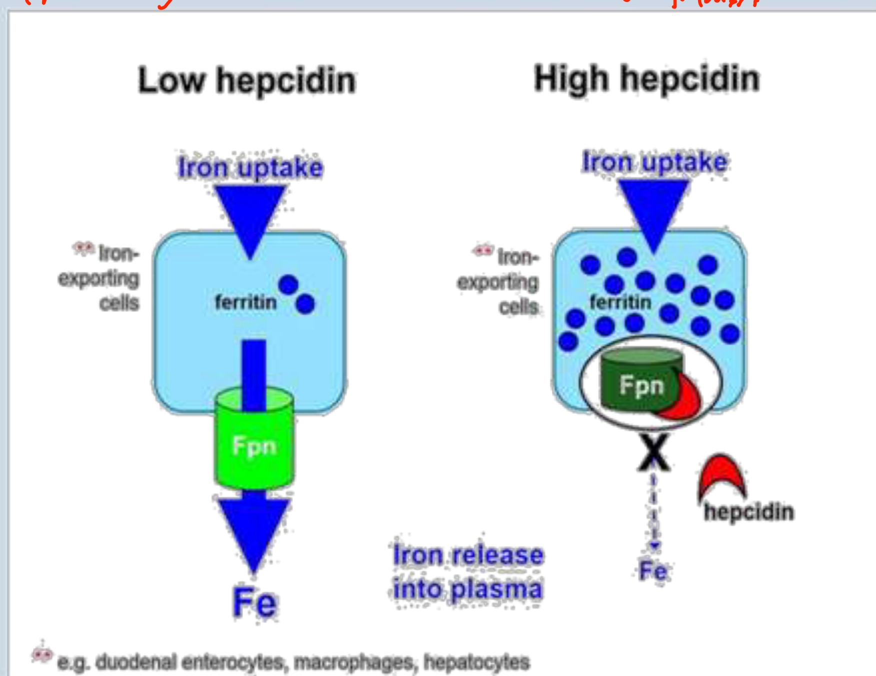
1- Release of absorbed iron from intestinal cells to blood.

iron low – no hepcidin – Allow transport iron

iron sensing protein → hemojuvelin

iron high → Ferroportin (internalized) & degradation

X Transport across cell membrane



Regulation of iron absorption and exportation by enterocytes

How hepcidin regulate the absorption of iron ??

With another protein inside cells known as (Hemojuvelin protein) , which also known as iron sensing protein , which sense the level if iron high or low .....

If iron level high and we are in no need of iron , iron will not go from stored site to blood , but the Hemojuvelin protein will increase the transcription of the gene encoded for the hepcidin to prevent exit of iron outside of cells by degredarion of ferroportin so iron can not go outside .

If are level low , there are no need for increase trancription of gene which encoded for hepcidin , so ferroportin activity don't stopped , and iron can cross outside to blood to the site of utilization .

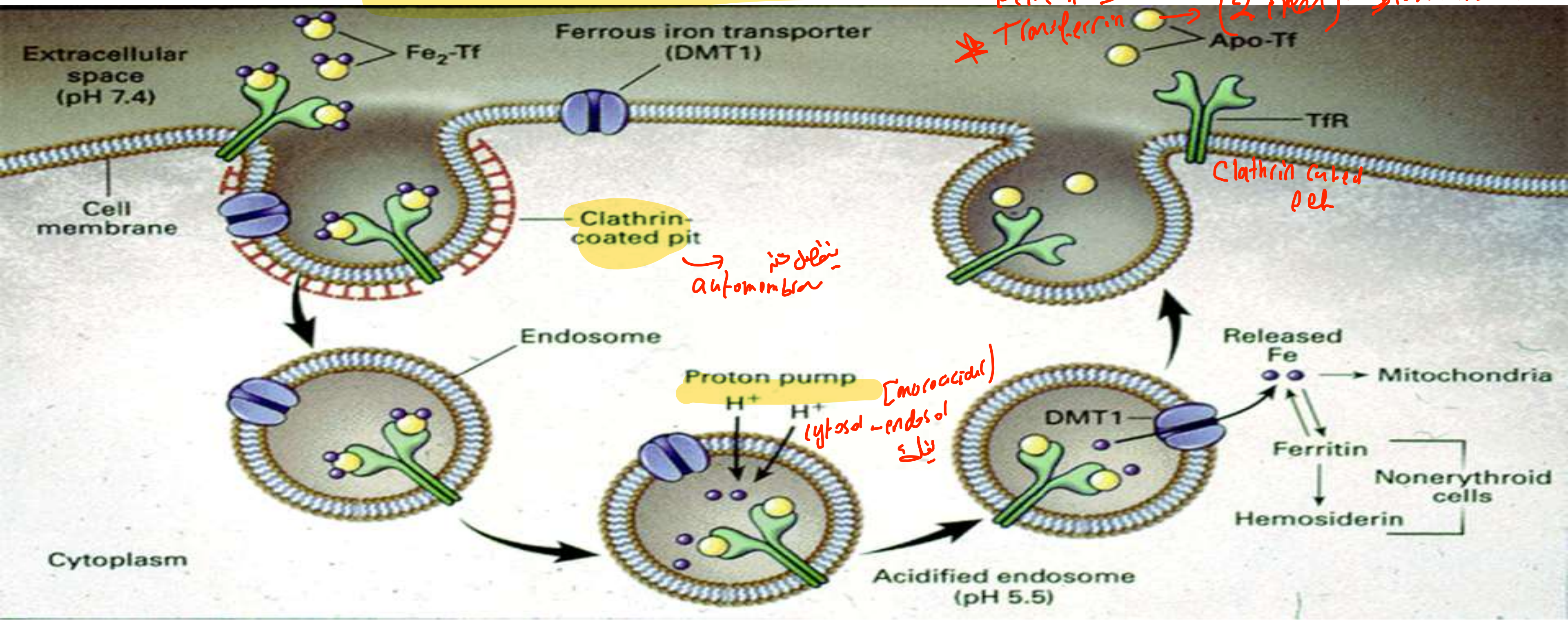
→ Negative Regulator of iron transcription

** so hepcidin has antimicrobial effect , because alot of microbes require iron , so because it regulate the iron absorption it also has antimicrobial effect .

* Bacteria Depriving under Hepcidin effect from iron

2- Release of iron from hepatocytes (liver cells) and macrophages.

- Control of dietary iron absorption and serum iron levels involves regulation of ferroportin expression.
- Hepcidin is considered an antimicrobial peptide because by lowering serum iron it would limit bacterial growth.



- The plasma membrane transferrin receptor mediates uptake of the complex of iron with transferrin by cells via receptor mediated endocytosis.

When iron bounded to transferrin and wnat to go inside the cells , how itwill enter inside the cells ??

Ferritin is Responsible for 4300
Transferrin just 2 iRon

Transferrin with iron will bind to receptor of the transferrin on the cell membrane , the transferrin - iron complex bind , then the coated pit convert to endosome (which are seperated from cell membrane) ....
Endosome contains (transferrin - iron complex & transferrin receptors)

transferrin can't carry > 2 iRon Atom because can go to blood → cause Toxicity

Then , how iron will be seperated from tranferrin ??
There are proton pump , which pumping H+ inside the endosome , which lead to decrase Ph to be acidic inside the endosome , this leads to sepeartion of iron from transferrin , but transferrin still bounded withtransferrin receptors (iron will leave transferrin , transferrin will not leave its receptor)
(iron يعني الوحيد اللي بينفصل عن المجموعة هو)

Ferritin storage form of cell Never be Toxic 4300 iRON

Then iron will go outside by DMT1 (dimetal transporter 1) for utilization , while the endosome will go to bind to cell membrane , andthen transferrin will seperate from its receptor to take up more iron again .

* Transferrin iRON capacity just 2 atom

(siderosis

- Hereditary hemochromatosis is a family of genetic diseases characterized by excessive iron absorption, transport & storage.

- Genes mutated in these disorders include those:
  1- Transferrin receptor
  2- A protein HFE (Human hemochromatosis protein) that interacts with transferrin receptor to regulate iron absorption by inhibiting transferrin-receptor interaction
  3- Hemojuvelin, an iron-sensing protein required for transcription of the gene for hepcidin.
  4- Impaired synthesis or activity of hepcidin leads to unrestrained ferroportin activity, with high dietary intake and high % saturation of serum transferrin with iron. [liver, cardiac muscle)

- Organs particularly affected by accumulation of excess iron include liver and heart.

** Hemochromotaosis = more absorption & storage of iron .

** hemochromatosis may also occur with persons with hemolysis of erythrocytes , then blood transfusion is required , and we will add iron chelator to reduce iron storage by increasing iron excretion .

+ genetic Disorder

** The hemocromatosis that is related to gene mutation can not be treated .

** the liver (site of iron storage) are not the only organ which will be affected , other organs may be affected as heart , brain , and some irons go to Beta cells inside islets of langerhans and make destruction inside it which affect production of insulin .
So the cases of human hemochromatosis due to genatic factor mostly will be diabetic , which known as (brods diabetis) because of destruction of beta cells by accummulated iron in the islets of langerhans .

Genetic polymorphism of proteins involved in iron metabolism

- In humans, genome-wide association studies found linkage of various gene polymorphism (single nucleotide polymorphism; SNP) and iron status, notably polymorphism of the gene coding for matriptase2.

hemchromato

-There is an evidence that genetic polymorphism of the matriptase2 gene is associated with the risk to develop iron deficiency anemia.

- Also, the investigators found a significant association of SNPs at the transferrin gene as well as at the HFE gene with iron deficiency.

Globin synthesis

- Humans normally carry 8 functional globin genes, arranged in two duplicate gene clusters:
  A- The β-like cluster on the short arm of chromosome 11.
  B- The α-like cluster on the short arm of chromosome 16.
- These genes encode for 6 different globin chains: α,β,γ,δ,ε and ζ.

Embryonic, fetal, Adult

Type of Hb	Type of Globin Gene	Region	Time
Hb Gawer1 $(\zeta\varepsilon)_2$	ζ & ε	Yolk Sac	3 weeks of Gestation
Hb Portland$(\zeta\gamma)_2$	ζ &γ	Yolk Sac	5 weeks of Gestation
Hb Gawer II $(\alpha\varepsilon)_2$	α & ε		
Hb F $(\alpha\gamma)_2$	α & γ	Liver & spleen	6-30 weeks of Gestation
Hb A_2 $(\alpha\delta)_2$	α & δ	Liver	30 weeks of Gestation
HbA$(\alpha\beta)_2$	α & β	Bone marrow	At Birth

zeta epsilon

fetal hemoglobin

2 gene

Hemoglobin in adults

u switch on

	Hb A	Hb A_2	Hb F
Structure	$a_2\beta_2$	$a_2\delta_2$	$a_2\gamma_2$
Normal %	96-98 %	1.5-3.2 %	0.5-0.8 %

** At the embryonic life time for the first 5 weeks of gestation , there are4 types of globin genes which make Hb chains (alpha , gamma , zeta , epsilon)

(4) α Gama zeta epsilon

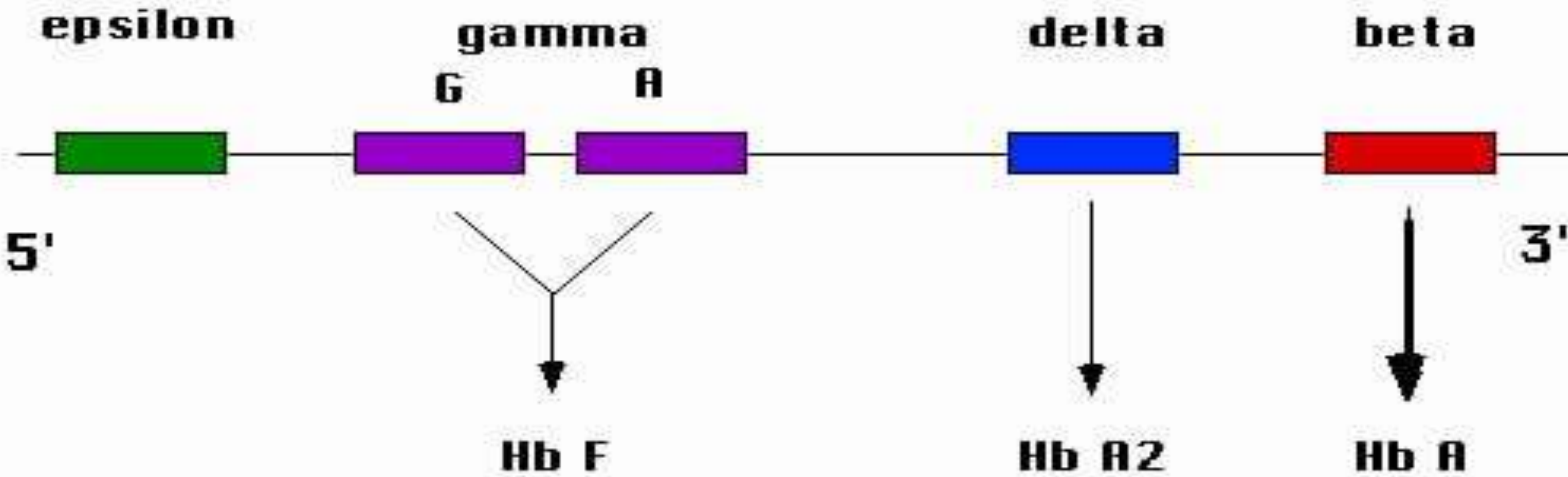
Gomer 1

** after first 5 weeks, when fetal Hb forms. Zeta & epsilon genes switches off , and the activated genes are for the globin chains (alpha & gamma chains) .

** after first 30 weeks = 6 months , when HB A2 is formed , gamma gene switches off and the delta gene switches on

** at birth , when HB A forms , delta gene switches off and Beta gene switches on ... the globin chains then will be (alpha & beta)

Beta Globin Gene Cluster
Chromosome 11



Alpha Globin Gene Cluster
Chromosome 16

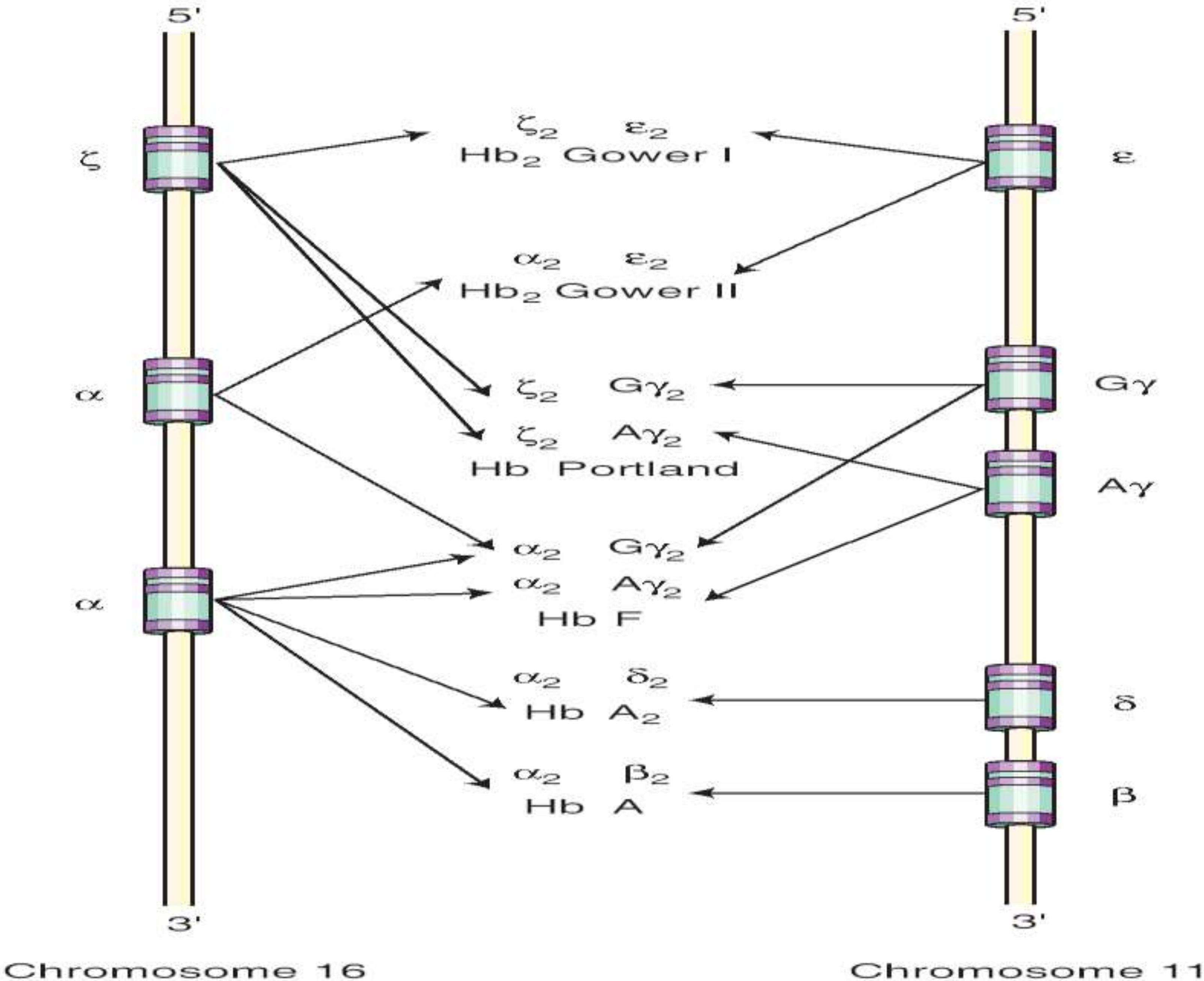


Figure 4.2 Specific chromosomes relative to human hemoglobin formation.