Lec 5 / dr. Diala

Slide2:

Heme : is a prosthetic group attached to hemoglobin,{ prosthetic group is a non-protein group forming part of or combined with protein }.

Tetrapyrrole ring : is a 4-repeated rings(A,B,C and D) called pyrrole rings , each has a N-atom and 2-attachments.

Slide 3:

The nature , orientation and the order of theses attachments specify different types of porphyrins.

Notice the order of these extensions on ring D in the left picture which represents the inactive form that need to be switched to the active form. .{A:acetate , P: propionate}

The order on ring D in the right picture represents the active form(Uroporphyrin 3)

Slide 4:

Distribution of side chains is either depending on the order (A and P) or on the numbers of these groups (two or three- as in the heme)

Porphyrinogen means that there is an inactive form needs activation .

Slide 5 :

The liver is a major site of heme biosynthesis as it plays a role in the production of clotting factors as well as red blood cell production and recycling that contain huge amounts of hemoglobin proteins.

Slide 6 :

ALAS is a mitochondrial enzyme .

Formation of ALA is catalyzed by ALAS1 or ALAS2 depending on the site of the rxn . During this step we are removing CoA and CO_2 by decarboxylation .

Slide 8:

We are reducing cyclic hydroxymethyl bilane (uroporphyrinogen 3) to coproporphyrinogen 3

Slide 9 :

Further reduction of coproporphyrinogen generates protoporphyrinogen 9 which need to be oxidized to facilitate the binding of Fe^{+2}

Slide 11: (regulation is mentioned at the end)

ALAS1 : mostly in the liver but it’s ubiquitously expressed

ALAS2: in erythroid tissue (bone marrow)

Cytochrome P450 need to be resynthesized and recycled as we're consuming it during metabolizing many drugs.

More degradation of RBCs means more degradation of hemoglobin and heme , and so less conc. of heme leads to increase ALAS1 activity.

Slide 13:

β-carotene is a precursor (inactive form) to vitamin A

Slide 15 :

NOT included: The mononuclear phagocyte **system** (MPS) (also called **Reticuloendothelial System** or Macrophage **System**) is a part of the immune **system** that consists of the phagocytic cells located in reticular connective tissue. The cells are primarily monocytes and macrophages, and they accumulate in lymph nodes and the spleen.
-Destruction of RBCs mostly occurs in the spleen .
-The cyclic structure is opened to form biliverdin by heme oxygenase which adds O2 during two oxidation steps.
Bilirubin is synthesized in the macrophage.

Slide 16:
Bilirubin is carried with albumin by non-covalent binding from spleen to the liver and it(bilirubin) enters the liver by facilitated diffusion due to the high conc. gradient.

Slide 17:
Conjugated bilirubin is actively transported into the bile canaliculi and then into the bile in the gallbladder to facilitate the function of bile acids that secreted in the small intestine.{ Don't memorize : **Bile acids** are steroid acids to facilitate the formation of micelles, which promotes digestion and absorption of dietary fat}.

Slide 11 : DON'T MEMORIZE , JUST TO UNDERSTAND
In developing red cells, levels of ALAS are regulated by increased gene transcription and by a post-transcriptional mechanism, in which iron most probably controls translation of erythroid ALAS mRNA through an iron-responsive element identified in the 5' untranslated region of the mRNA

-The **5' untranslated region of the erythroid-specific ALAS2 messenger RNA** (**mRNA**) **contains** an iron-responsive element (IRE) , which **acts** as a **binding site** for the **IRE binding protein 1** (IRP1) .**This protein-mRNA complex blocks translation in iron-deficient erythroid cells** , whereas the release of the **complex** from the ALAS2 IRE in iron-replete cells allows **translation** to proceed.

So : low levels of iron blocks the translation of ALAS2 .

Done by : Abdullah Sulaiman
Best wishes ☺