Hematology – Biochemistry

(Numbering is according to the 4th set of slides on the website)

ONLY EXTRA NOTES

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- We don't produce different heme chains with one more than the other; they're not produced in excess amounts in order not to form polymers and aggregates composed of the excessively-produced chain.

- Decreased synthesis of one of the chains causes the other to precipitate and form Heinz bodies (alpha chains have more tendency to precipitate), thus distorting the RBCs plasma membranes (hemolytic effects) and hypochromic anemia.

- In beta thalassemia, high levels of HbA_2 and HbF are found due to increased production of other chains of the beta family (delta and gamma) because of decreased expression of beta chain itself.

- Beta minor is a mild anemia with no crisis because the unaffected gene is sufficient for the required function. Beta major patients require intermittent blood transfusions, and that will cause more iron to accumulate, thus producing damage (Reactive oxygen species and other mechanisms). This iron needs to be scavenged, but the usual way for that (blood withdrawal) cannot be done because those patients are already anemic, so we give them iron chelators in order to overcome the accumulation resulting from transfusions.

- If the patients are born with beta thalassemia major, the manifestation will not appear in the first months because the HbF present in their blood will cover that anemia.

Slide 12

- Because we have two different genes for alpha chain in each homologous chromosome, alpha thalassemia has wilder spectrum of severity as a disease.

- In increased levels of HbH (four beta chains), the molecule is more soluble than cooley's Hb but shows hyperbolic kinetics rather than sigmoidal, thus low p50, high affinity and no oxygen delivery.

- In HbBart, we have no alpha chain synthesis, no beta, but more gamma production (4 gamma chains). Neonates with this gamma tetramer develop what is called hydrops fetalis, and they usually die before birth or short time after birth.

Slide 13

- HbE is a form of abnormal hemoglobin with altered exterior (discussed previously) and is popular in Asia (e.g. Malaysia). It can be due to a substitution in 26th Glu > Lys, or due to diminished production of beta chain (60% only is produced).

- HPFH is also discussed in a previous lecture; it's beneficial in sickle cell anemia patients.

Slide 14

- All porphyrinogens (reduced-form precursors) are colorless; they need oxidation (e.g. photo-induced) to become porphyrins (colored).

- This structure is ferroprotoporphyrin IV (the name of heme), which is the end product of isomer III (heme precursor which is found in humans). Both are asymmetric; the only symmetric one is isomer I (precursor) which is an intermediate (excreted later).

Back to slide 2

- Biosynthesis of the heme is critical in most of the tissues because it's important in many essential pathways, but major amounts are made in the BM (85% of all heme is synthesized in BM in erythroid tissue) then in the liver.

- Notice the first reaction, the enzyme is regulated (inhibited) by the hemin (a free type of heme (without globin chains) that contains oxidized iron (ferric) and is present in aqueous solutions). The enzyme catalyzing this step is the rate-limiting enzyme. This occurs in the mitochondria.

- This enzyme has two isoforms; ALAS 1 is present in many tissues and is regulated by the so-called hemin mechanism. On the other hand, ALAS 2, which is specific to erythroid tissue, is mainly regulated by iron.

- ALAS 1 enzyme inducers are used in the tissues that require large amounts of heme (like in cyt. P450 pathways).

- Mutations in ALAS 2 are X-linked; they reduce the efficiency of the enzyme and produce sideroblastic anemia (iron granules are found).

- The second product is an unstable intermediate which is therefore decarboxylated.

- After decarboxylation, the ALA moves to the cytosol. 2 ALA are needed to form one ring, thus we need 2 Succinyl CoA and 2 Glycine molecules for that, and because we need four rings to synthesize the heme, we need 8 Glycine molecules and 8 Succinyl CoA molecules.

- The reaction is catalyzed by ALAD; this enzyme requires zinc to function. Lead (as in lead poisoning) can replace the zinc and inhibit the enzyme.

- ALAD deficiency is very rare.

Slide 3

- The first reaction here gives a linear tetrapyrrole structure, and then it undergoes closure and isomerization.

- Uroporpyhrinogen I is a symmetrical intermediate (isomer I) that has A-P instead of P-A which is present in uroporphyrinogen III (in the lower left corner from down to up). That isomer I is a precursor which is colorless; if it undergoes oxidation (photo-induced), it will become colored (uroporphyrin I), but the further product of that precursor I is then excreted (coproporphyrinogen I).

- Uroporphyrinogen III then undergoes decarboxylation (all acetyls become methyls) to give coproporphyrinogen III. This product then - and again - returns back to the mitochondria and undergoes oxidative decarboxylation (2 proprionyls become vinyls), and gives protoporpyhrinogen IV (IX is written here because it's just a similar minor branch of the isomer III family), and this is also a colorless compound. It lastly undergoes oxidation and becomes colored.

- Ferrochelatase enzyme (last step) is also inhibited by lead.

Slide 6

- Patients who are photosensitive - after accumulation of tetrapyrrole - may undergo photo-oxidation and this converts the colorless precursors (porphyrinogens) into colored ones (porphyrins). These accumulated active porphyrins produce ROS and cause damage to lysosomal membranes causing their enzymes to leak out (skin lesions, redness and itching are manifestations of this photosensitivity).

Slide 9

- The most important porphyrias are the congenital erythropoietic and chronic hepatic ones (deficiencies in enzymes number 4 and 5, respectively).

- Lead poisoning is also important (affecting the 2nd step and the last one).