Biochemistry

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

ONLY ADDITIONAL NOTES – 1st lecture

Slide 1

- They are unique, well-studied proteins.

- Allosteric proteins: they behave like enzymes.

- Hbf (fetal hemoglobin) contains alpha & gamma chains.

Slide 2

- They belong to a class of globins; which is globular hemeproteins (contain heme).

- Apoprotein: responsible for determining the function of heme (different proteins containing heme have different functions, and that is determined by the apoprotein through working on the 3-dimensional microenvironment of the heme). Look at the examples.

Slide 3

- Prosthetic group (~coenzyme).

- Heme structure: 4 pyrrole rings, linked by methine bridges (methine: a carbon with 2 single bonds & 1 double bond)

- Many substitutes (isomers) depend upon the attached groups. For example, isomer III has: (clockwise: methyl, vinyl,methyl, vinyl, methyl, propionyl, propionyl, methyl).

- Isomer 1 is produced in cells then excreted.

Slide 4

-The chains of hemoglobin (Hb), although they come from different genes, share many similarities together.

- Beta chain:

- 8 helical segments (~75-80% of the structure is helical).
- (NA, AB, BC ....) are the names of segments between the helical ones or between a helical segment and an N or C terminal (Correct the last one, it's HC not HA)
- Histidine beta 63 (as an example): is another nomenclature form. According to the residues from the start, it's His beta 63. On the other hand, it's His e7 according to the beginning of a certain segment.

- Helical segments are terminated by:

- The presence of proline that interrupts the helical structure formation (around 4 helical segments are terminated by proline).

- Beta bends and loops: result in the formation of electrostatic interactions and salt bridges (interfere with the helical structure formation).

Slide 5

- Alpha chain.

- No d helical segment.

- His (present in all heme), same name with regard to helical segments, but different with regard to residues. Proximal or distal variation is set according to the distance from heme.

Slide 6

- The heme is located between e and f segments in the heme pocket (presumably called the catalytic site of the hemoglobin).

- Iron is located in the core of the heme between the 4 nitrogens of the tetra pyrrole structure.

- It can take 2 coordination positions: direct with proximal histidene and indirect with distal histidine (doesn't bind to the heme but indirectly stabilizes O2-Fe binding).

- Iron is not in the same plane with the tetra pyrrole ring (forms a pyramid head) without oxygen, but when it binds oxygen, it is in the same plane.

- Hydrophobicity (except histidine): stabilizes the heme in the molecule so that Hb does not precipitate in the absence of heme. Also, it doesn't allow electron transport from ferrous to oxygen (it prevents transformation of ferrrous into ferric because that will interrupt the binding with oxygen). So, the interaction with oxygen remains reversible.

- Mutations in this region (adding hydrophilic amino acids for example) will cause oxidation of ferrous into ferric (loss of electrons) and thus, no more binding with oxygen.

Slide 7

- Myoglobin (Mb): 153 a.a.

- Mb is definitely not an exception regarding the fact that the interior is hydrophobic and the exterior is hydrophilic (except for histidines).

Slide 8

- Notice the propionate groups (hydrophilic) which are exposed to the exterior surface.

Slide 9

- Many Mb molecules are sequenced and there are certain findings:

- 83 residues (a.a) are invariant in all Mb.
- 15 of those 83 are the same with Hb.

- Those invariants include the prox & dis histidines and some other residues from the hydrophobic region of the heme pocket.
- The variant residues usually have similar charges (no large effect on the function even with variant amino acids).

Slide 10

- Hb is an excellent buffer as well (binds protons).

Slide15

- The strong interaction between alpha and beta chains in each dimer is due to the presence of hydrophobic regions on certain areas on their surfaces (strong hydrophobic interaction). This is not present in Mb.

- The polar regions produce weaker interactions between the 2 identical dimers.

- 4 oxygens are added (cooperativity concept), then this induces the change into the R (relaxed) form.

- Each oxygen upon binding induces movements (conformational changes) that increase the affinity for the next oxygen to bind, and this is carried on toward the 4^{th} oxygen.

- Hb follows the concerted model of allosteric enzymes.

- The heme to bind the 4th oxygen has a 300x higher affinity than the 1st deoxy- form.

- More substrate (more oxygen) increases the proportion of the R form in the molecule (this is a characteristic of the concerted model not the sequential one of the allosteric enzymes. In the concerted, when a change occurs in the first subunit, it's conferred to the others dependently, but in the sequential, when a change occurs in the first subunit, it's not conferred to the others, but it offers the change independently by reducing the energy needed for the next subunit to meet that required change).

- Mb is one subunit: no allosteric inducers. Hb have other inducers like protons, CO2, BPG … etc.

Slides 11+13

- p50 is the oxygen partial pressure in the blood at which 50% of the hemoglobin (or myoglobin) is saturated.

- Mb takes a hyperbolic shape, thus and at even low oxygen partial pressures, it's highly saturated > higher affinity> lower delivery of oxygen toward tissues (p50=1 mmhg). So, myoglobin does not release oxygen in the muscles unless there is an excessive demand.

- But for Hb, it takes a sigmoidal shape, p50 is around 26 mmhg, thus, at the partial pressure in tissues (pO2) which is about 30-40 mmhg, it's partially saturated (above 50%) and at this very area, the curve is steep, so any little fluctuation of pO2 in the tissues will be overcome by Hb through adjustment of its delivery (as cooperativity rules, higher pO2 means more oxygen bound to the Hb, more oxygen bound means higher affinity, higher affinity means more saturation and less delivery. So, if pO2 slightly falls down, it means that less oxygen is bound > less affinity and saturation > more delivery of oxygen from Hb toward the tissues).