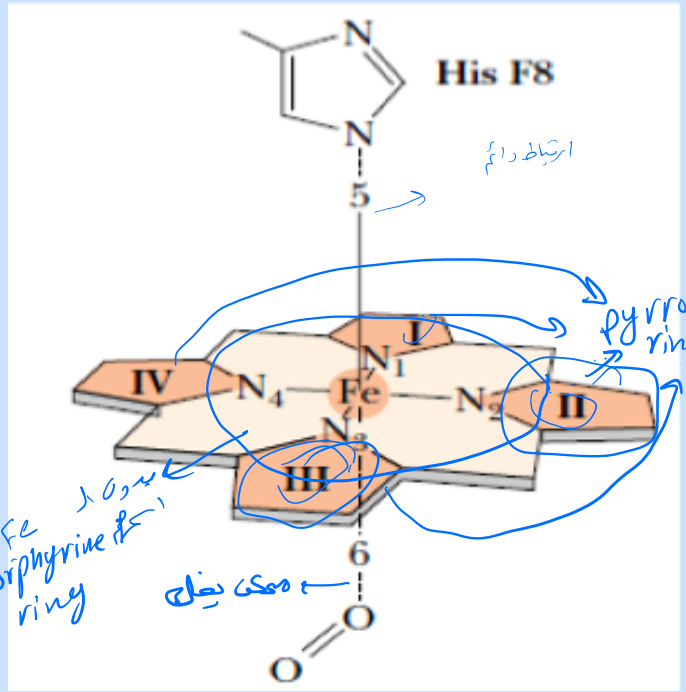
Heme structure

The iron is held in the center of the porphyrin ring.

Iron ions prefer to interact with six ligands.

Four of the ligands to this iron ion are provided by nitrogen atoms in the pyrrole ring system.



-The fifth ligand is provided by a nitrogen atom from the imidazole group of His 93 (proximal histidine) (also known as His F8 the eighth residue of the 'F helix' of myoglobin).

The sixth ligand to iron is provided by molecular oxygen, which binds to the heme group in a pocket formed by Mb.

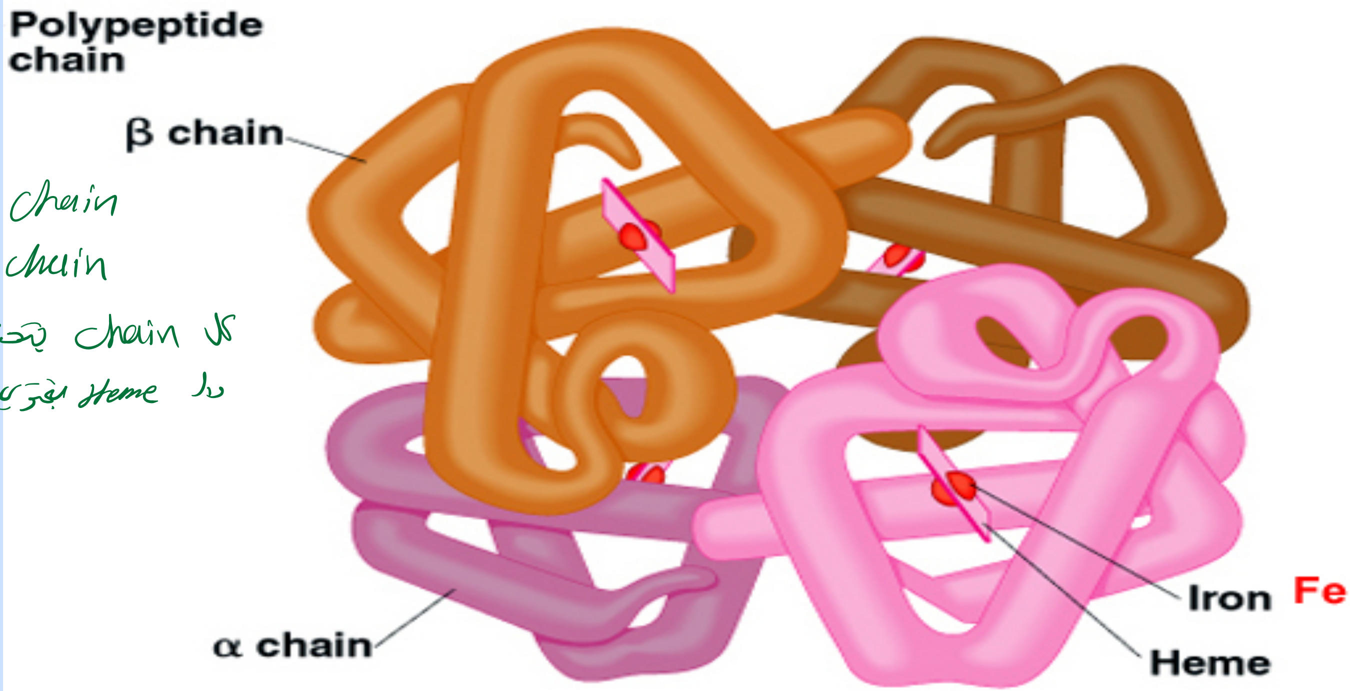
Mb can bind only one oxygen molecule.

The O2- binding site is a sterically hindered region this helps to stabilize the binding of oxygen to the ferrous iron through creating a special microenvironment for the heme.

Hemoglobin

يتكون من 4 chains (4 poly peptides) مرتبطين مع بعض ب non covalent bonding

2 α chain
2 β chain
كل chain بتحتوي على heme group
وال Heme بتحتوي على iron ion



(b) Hemoglobin

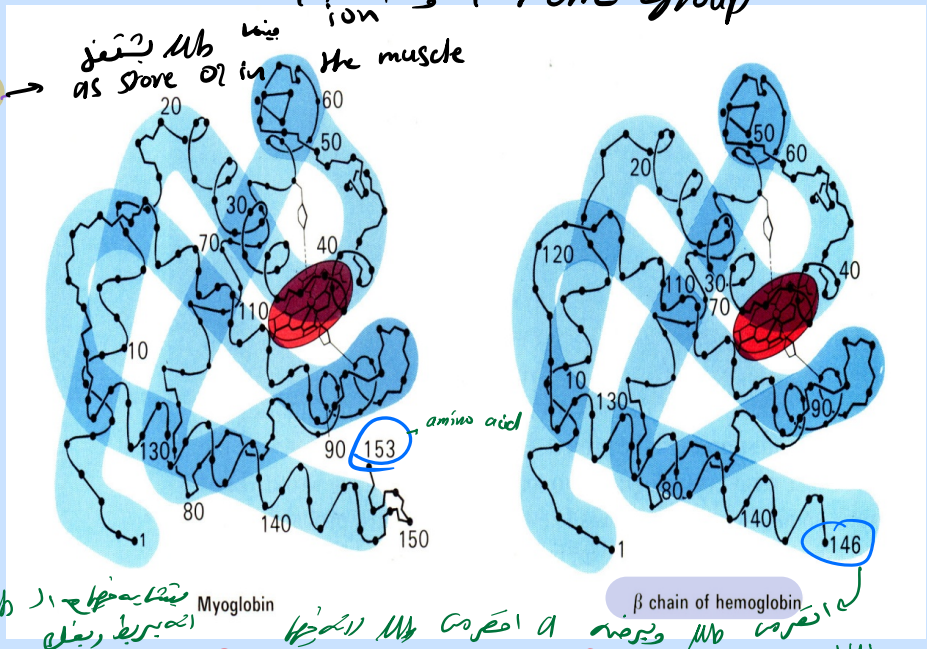
الاختلاف بين ال MB وال Hemoglobin انه ال MB بتكون من one chain و one heme group فيها chain heme group
بينما ال hemoglobin بتكون من 4 chains لذلك ال hemoglobin فيه 4 chains

Hemoglobin (Hb)

- O2 transporter in erythrocytes
  - 2 α subunits, (141 Amino acids each)
  - 2 β subunits, (146 Amino acids each)

Each subunit contains one heme group.

- Hb can bind O2 reversibly, just like Mb.
- Both α and β chains are strikingly similar to that of Mb.



Structural similarity of Mb and Hb

- β chain at 146 AAs residues is shorter than the myoglobin chain (153 AAs), because H helix segment is shorter.
- α -chain at 141 AAs also has a shortened H helix and lacks the D helix.

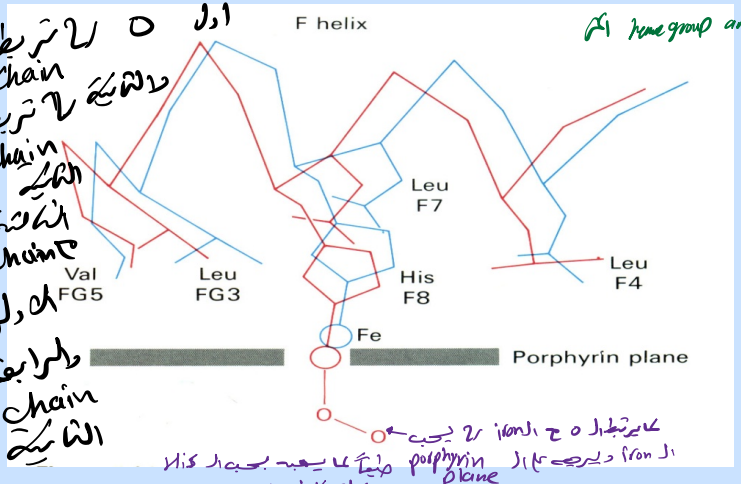
Binding behavior of Hb

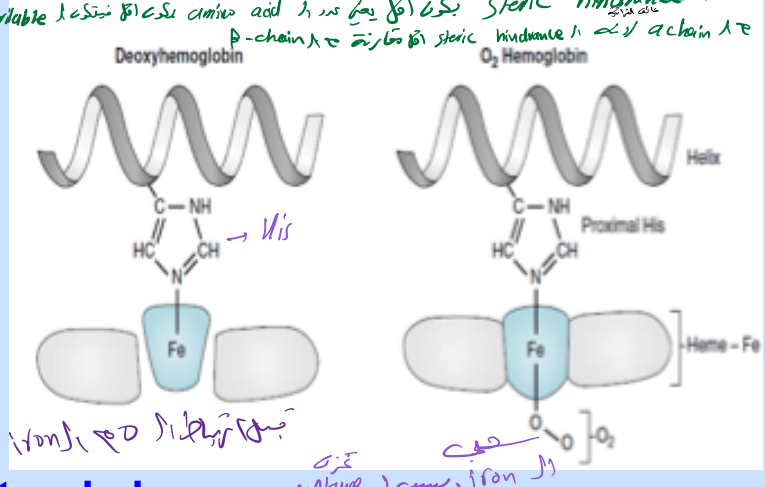
Hb has a lower affinity for O2 than Mb.

The O2–binding to the 1st subunit enhances the O2–binding to the 2nd and 3rd subunits. Such process further enhances the O2–binding to the 4th subunit significantly.

Hb binds O2 in a positive cooperative manner, which enhances the O2 transport.

Upon oxygenation, the Fe ion is moved into the porphyrin plane, leading to the formation of a strong bond with O2.





Local structural change

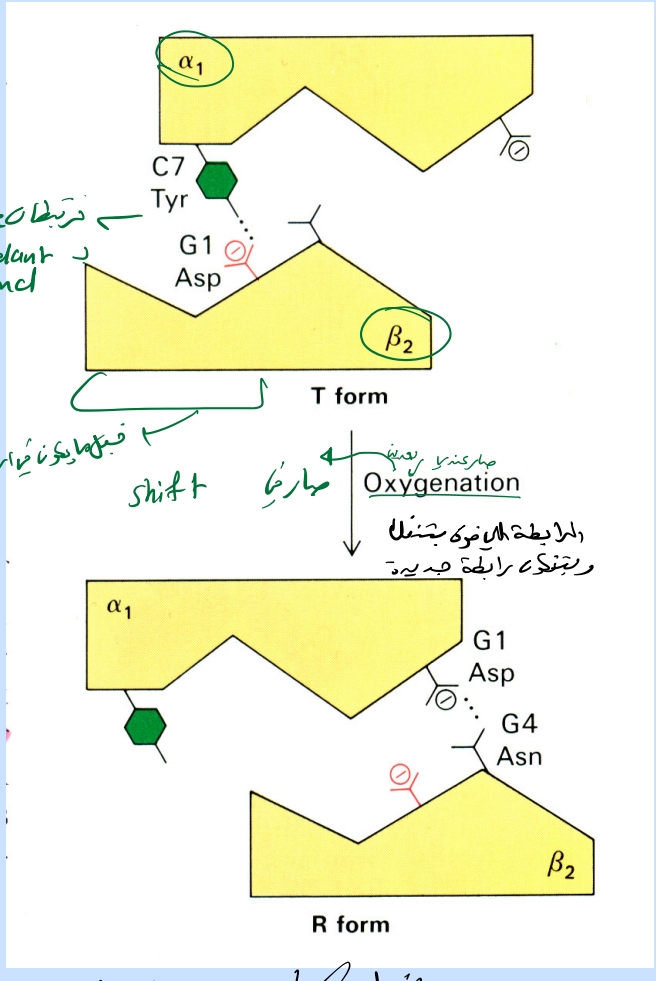
Global structural change

The quaternary structure of Hb changes markedly from the tense (T) form to the relaxed (R) form upon oxygenation.

Hemoglobin exists in two forms, T-state and R-state.

The T-state is also known as the "tense" state and it has a low-binding affinity to oxygen.

The R-state is known as the "relaxed" state and it has a high affinity state to oxygen.

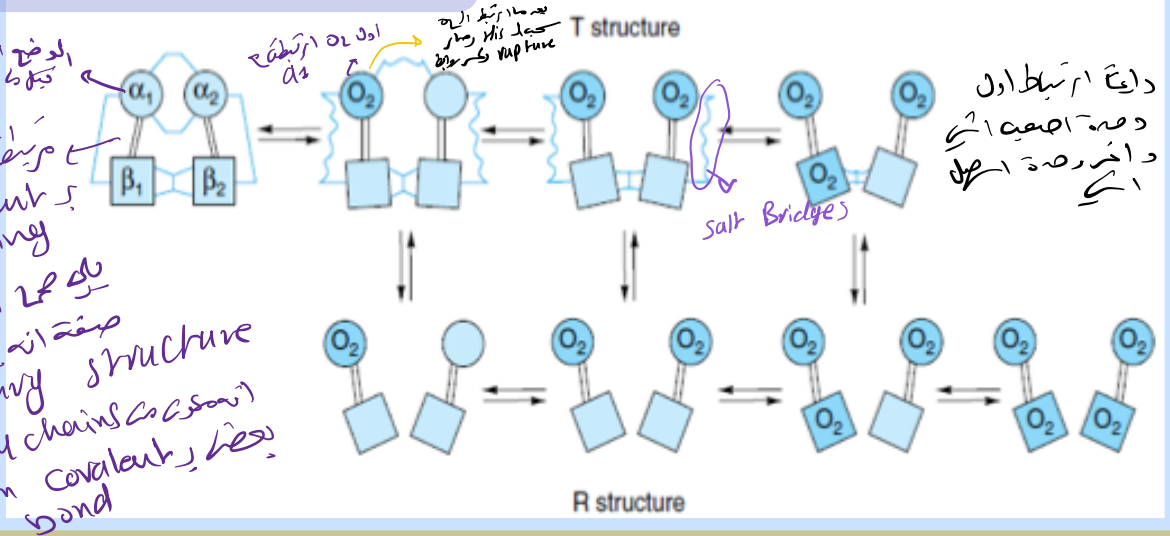


The allosteric behavior of hemoglobin

The ability of hemoglobin to bind oxygen is affected by:

1- pressure of O2 2- pH of the environment 3- CO2 pressure

Oxygen binding to Hb is a cooperate binding (allosteric behaviour). Cooperative binding of oxygen by the four subunits of hemoglobin means that the binding of an oxygen molecule at one heme group increases the oxygen affinity of the remaining heme groups in the same hemoglobin molecule.

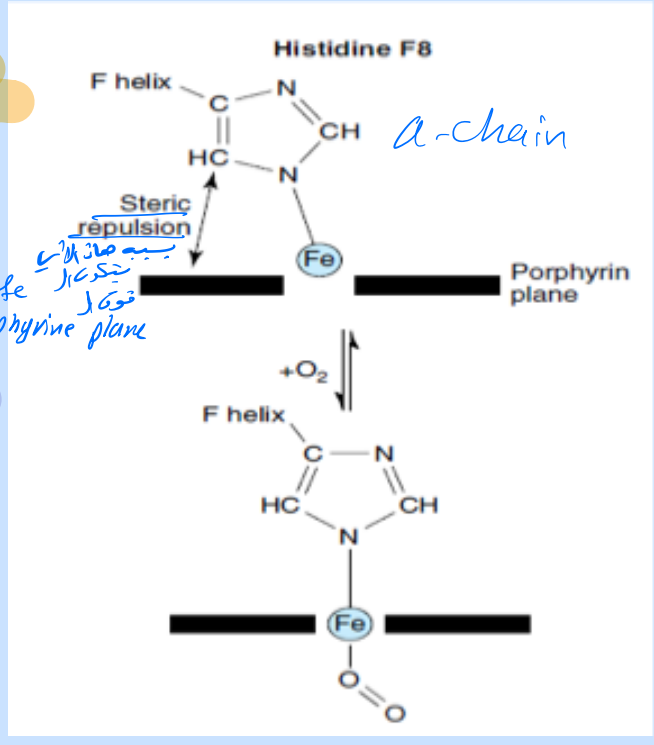


Transition from the T structure to the R structure. Salt bridges (thin lines) linking the subunits in the T structure break progressively as oxygen is added.

O2-Hemoglobin binding

Oxygen is accessible only to the heme groups of the α-chains when hemoglobin is in T conformational state.

The heme of β-chains in the T state is virtually inaccessible because of steric hindrance by amino acid residues.
The proximal histidine of hemoglobin is sterically repelled by the heme porphyrin ring.



Thus, when the histidine binds to the Fe2+ in the middle of the ring, it pulls the Fe2+ above the plane of the ring.
When oxygen binds with Fe2+ it pulls the Fe2+ back into the plane of the ring.

The pull of O2 binding moves the proximal histidine toward the porphyrin ring, which moves the helix containing the proximal histidine.

This slight movement is transmitted to adjacent subunits causes the rupture of salt bridges and causes a conformational shift from T to R in all other subunits.

Oxygen release hemoglobin

The release of oxygen from hemoglobin is enhanced by:

1- low pH 2- increased pressure of CO2 3- low O2 pressure.

Carbon dioxide reacts with water to give carbonic acid, which decomposes into bicarbonate and protons:

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$

Therefore, blood with high carbon dioxide levels is also lower in pH (more acidic) which leads to a decrease in affinity for oxygen by hemoglobin.

Hemoglobin can bind protons and carbon dioxide which causes a conformational change in the protein and facilitates the release of oxygen.

This decrease in hemoglobin's affinity for oxygen by the binding of carbon dioxide and acid is known as the Bohr effect.

Comparison between Hb and Mb

Myoglobin	Hemoglobin
In muscle	In RBCs
Reservoir of O2	Carrier of O2
No quaternary structure	Has a quaternary structure
Can't carry CO2	Carries CO2
No cooperativity of O2 binding	Shows cooperativity
O2 affinity is higher	O2 affinity is lower

Fibrous vs. Globular Proteins

Globular	Fibrous
1. Compact protein structure	Extended protein structure
2. Soluble in water	Insoluble in water
3. Secondary structure is complex with a mixture of a-helix, b-sheet and loop structures	Secondary structure is simple based on one type only
4. Functions in all aspects of metabolism (enzymes, transport, immune protection, hormones, etc).	Functions in structure of the body or cell (tendons, bones, muscle, ligaments, hair, skin)

Membrane proteins

A membrane protein is a protein molecule that is attached to, or associated with the membrane of a cell or an organelle.

Membrane proteins categories:

1-Integral membrane proteins which are permanently bound to the lipid bilayer

2-Peripheral membrane proteins that are temporarily associated with lipid bilayer or with integral membrane proteins

3-Lipid-anchored proteins bound to lipid bilayer bound through lipidated amino acid residues

Two common structural classes of transmembrane proteins are alpha-helices and beta-sheets.

The portion of the protein that is not touching the lipid bilayer and is protruding out of the cell membrane are usually hydrophilic amino acids.

Six major functions of membrane proteins:

a-Transport as a channel

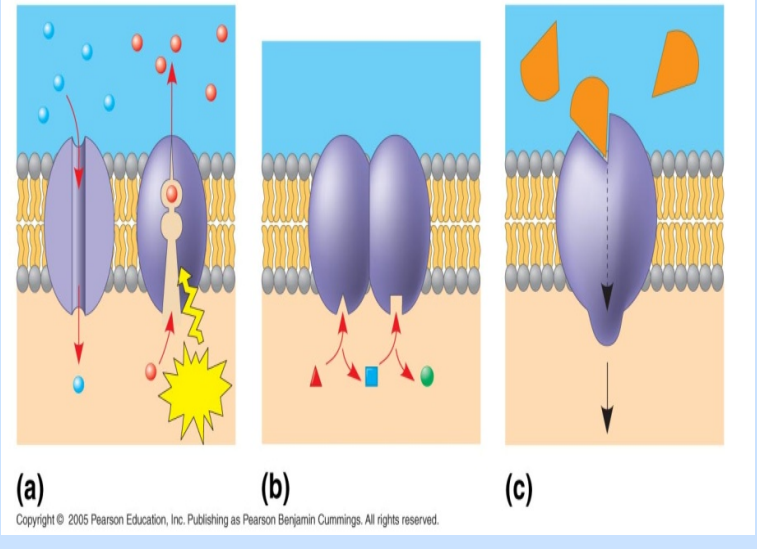
b-Enzymatic activity

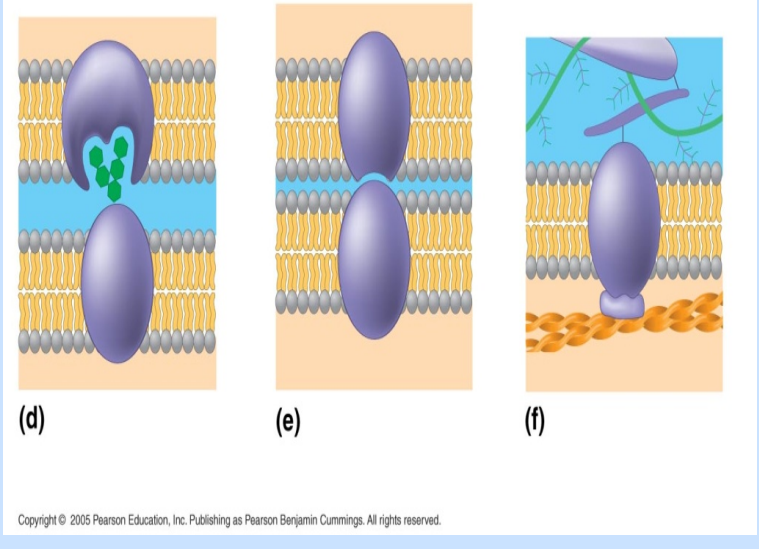
c-Signal transduction ligand with receptor

d-Cell-cell recognition

e-Intercellular joining

f-Attachment to the cytoskeleton and extracellular matrix (ECM)

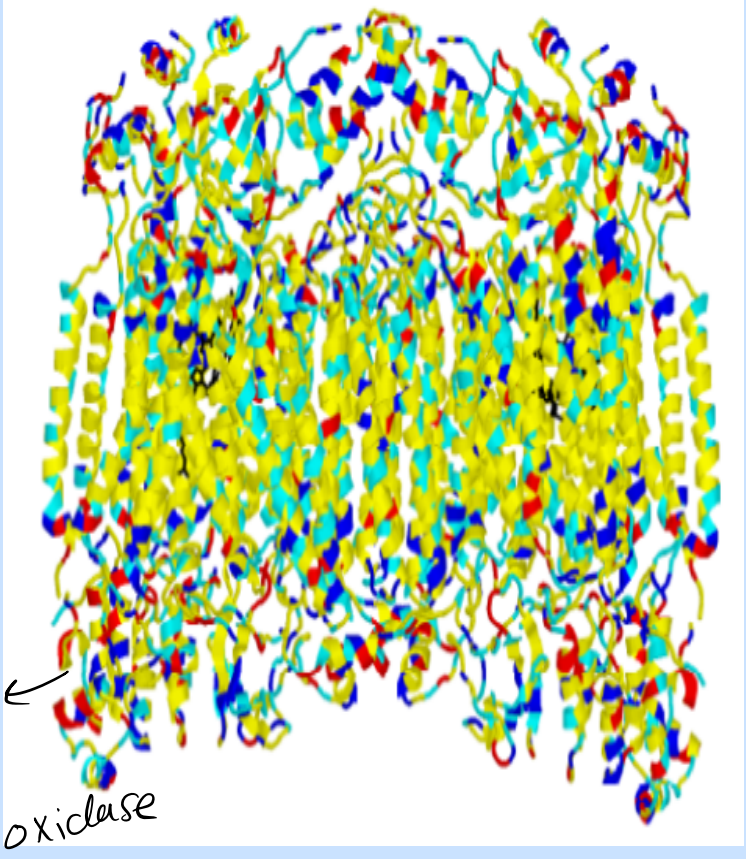




Cytochrome c oxidase.

Cytochrome c oxidase is the primary oxygen-utilization enzyme in aerobic organisms, it is the protein that donates electrons to oxygen in the electron transport chain.

The region of the cytochrome c oxidase protein that interacts with the membrane is readily visible, yellow residues are non-polar, light blue residues are polar, blue residues have basic side chains, and red residues have acidic side-chains.



Cytochrome c oxidase

Clinical examples on protein abnormalities

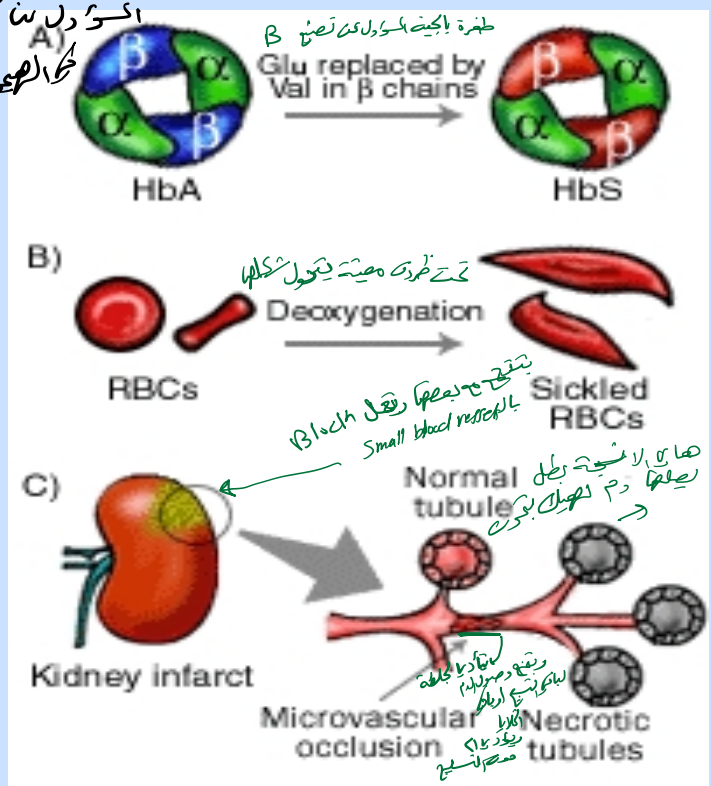
اذا البروتين كان misfolded بطل لاي سبب من الاسباب اشعة او عوامل كيميائية --- mutations
او حتى انه البروتين خسر ال 3D فبيتشوه ويمرض .

Anemia, sickle cells

SCA is an autosomal recessive disease caused by a point mutation in the hemoglobin beta gene (HBB) found on chromosome 11p15.5.

A mutation in HBB results in the production of a structurally abnormal hemoglobin (Hb), called HbS.

Under certain conditions, like low oxygen levels or high hemoglobin concentrations, in individuals who have Anemia (HbS), the abnormal HbS clusters together, distorting the RBCs into sickled shapes. These deformed and rigid RBCs become trapped within small blood vessels and block them, producing pain and eventually damaging organs.



A) Hemoglobin is made up of 4 chains: 2 α and 2 β. In SCA, a point mutation causes the amino acid glutamic acid (Glu) to be replaced by valine (Val) in the β chains of HbA, resulting in the abnormal HbS. **B)** Under certain conditions, such as low oxygen levels, RBCs with HbS distort into sickled shapes. **C)** These sickled cells can block small vessels producing microvascular occlusions which may cause necrosis (death) of the tissue.

Sickle-cell of anemia

Sequence analysis showed the difference in Amino Acids sequences.

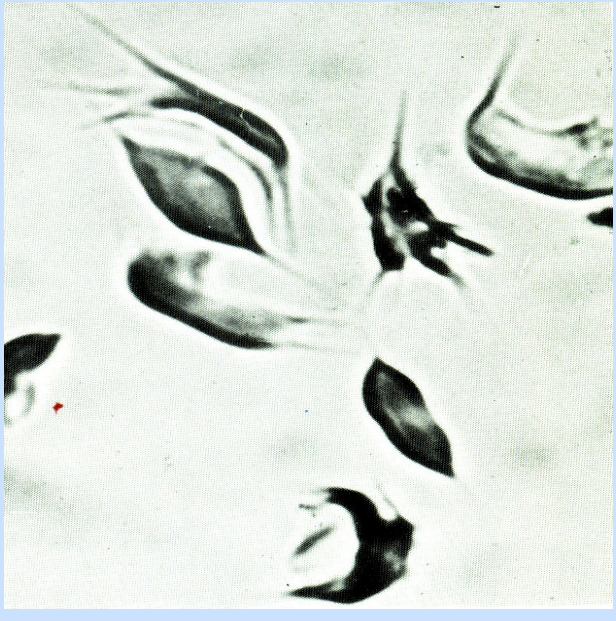
Hb A β: Val-His-Leu-Thr-Pro-Glu-Glu-Lys-
Hb S β: Val-His-Leu-Thr-Pro-Val -Glu-Lys-

Patient's symptoms:

Cough, fever and headache, a tinge of yellow in whites of eyes, visible pale mucous membrane, enlarged heart, well developed physically

Clinical test:

The shape of the red cells are very irregular, large number of thin, elongated, sickle-shaped and crescent-shaped forms.



Alzheimer Disease (AD)

Alzheimer disease (AD) is the fourth leading cause of death in adults. AD is twice as common in women than in men.

Some of the most frequently observed symptoms of the disease include a progressive inability to remember facts and events and, later, to recognize friends and family.

AD tends to run in families; currently, mutations in four genes, situated on chromosomes 1, 14, 19, and 21, are believed to play a role in the disease.

Research indicates that the disease is associated with plaques (extracellular deposits of amyloids (insoluble fibrous protein)) in the gray matter of the brain and tangles (aggregates تجمعات of hyperphosphorylated tau protein (proteins that stabilize microtubules)) in the brain.

deposition of amylode protein

member of the brain

Several competing hypotheses exist trying to explain the cause of the disease:

1-The oldest one is the *cholinergic hypothesis*, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.

يفترضها

2-The amyloid hypothesis postulated that beta-amyloid deposits are the fundamental cause of the disease.

Recently, use of a mouse model of the disease identified an enzyme that may be responsible for the increase in amyloid production characteristic of AD.

If a way to regulate this enzyme could be found, then AD may be slowed or halted in some people.

يعني لما يعطوهم العلاجات الهدف منها هو انهم يثبطوا الانزيم لانه ما بيصير الهم انهم يبطئوا من اعراض المرض
لانه خلايا الدماغ خلايا عصبية ما بتتجدد والخلية اللي بتموت خلص ما بتتجدد

Protein Misfolding in AD

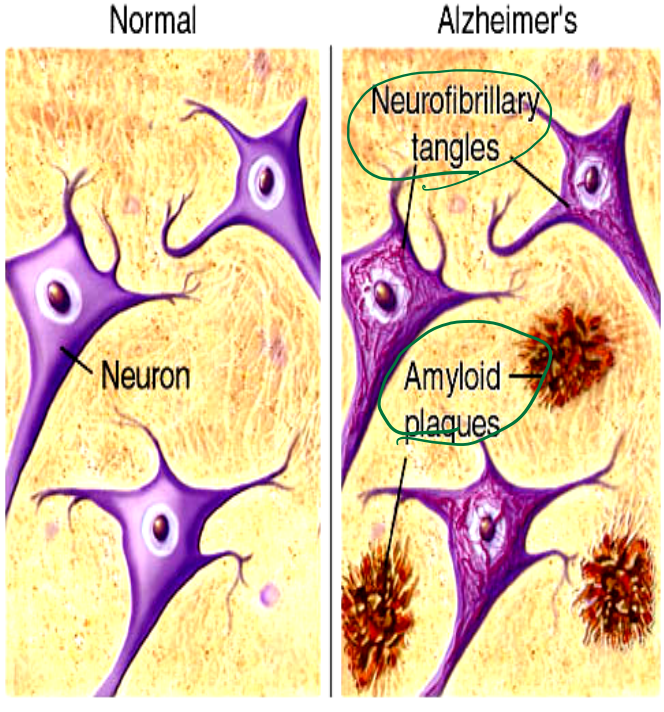
In AD, the misfolded proteins are beta-amyloid and a cleaved product of tau. Misfolded proteins then begin to stick together with other misfolded proteins to form insoluble aggregates, leading to disruption of cellular communication, and metabolism, and even to cell death.

There are three major hallmarks in the brain that are associated with AD:

1- Amyloid plaques

2- Neurofibrillary tangles —that are made of misfolded proteins. This is especially true in certain regions of the brain that are important in memory.

3- Loss of connections between cells this leads to diminished cell function and cell death



Mad cow disease

Bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, is a fatal neurodegenerative disease in cattle that causes a spongy degeneration in the brain and spinal cord

The disease may be most easily transmitted to human beings by eating food contaminated with the brain, spinal cord or digestive tract of infected carcasses

The infectious agent in BSE is believed to be a specific type of misfolded protein called a prion

A prion is an infectious protein that is similar to a virus, but not a typical virus.

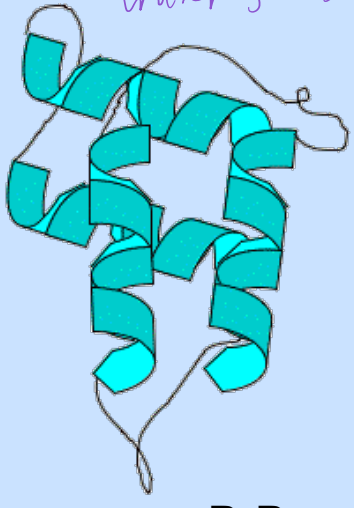
Unlike viruses, prions aren't alive, so they can't be killed with the usual disinfectants. Prion proteins can be denatured, but only at extremely high temperatures or with very strong chemicals, either way, not consistent with animal life so these are not treatment options.

Mammals have a prion gene which makes normally folded prion proteins; its mutations in this gene that result in abnormally-folded proteins, which are the disease-causing ones (it causes alpha-helices to be converted into beta-sheets).

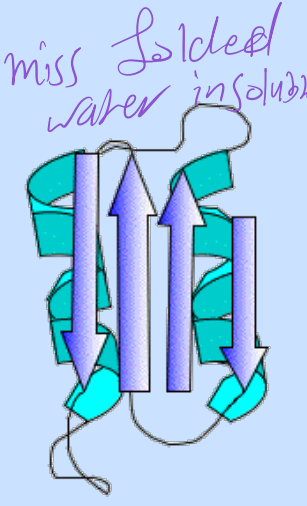
The conformational changes of prion protein (PrP)

PrPc: α-helix, water soluble

PrPsc: β-sheet, water insoluble



PrPc



PrPsc

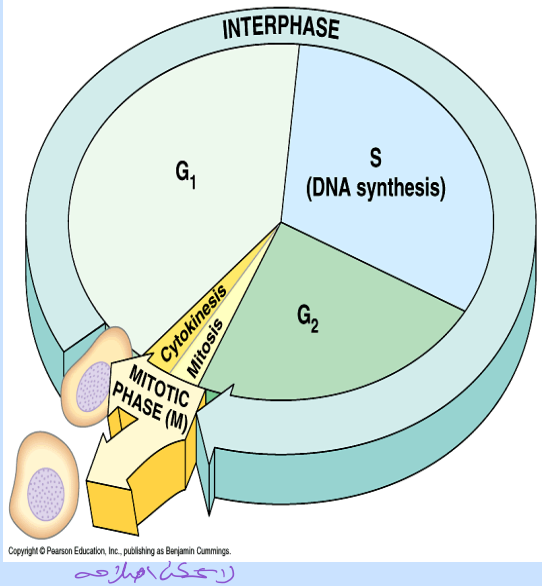
Tumour suppressor protein 53 (P53)

is a tumour suppressor protein that in humans is encoded by the *TP53* gene. p53 is crucial in multicellular organisms, where it regulates the cell cycle and, thus, functions as a tumour suppress or that is involved in preventing cancer.

p53 has many mechanisms of anticancer function, and plays a role in apoptosis, genomic stability, and inhibition of angiogenesis:

1- It can activate DNA repair proteins when DNA has sustained damage.

2- It can induce growth arrest by holding the cell cycle at the G1/S regulation point on DNA damage recognition (if it holds the cell here for long enough, the DNA repair proteins will have time to fix the damage and the cell will be allowed to continue the cell cycle).



3- It can initiate apoptosis, the programmed cell death, if DNA damage proves to be irreparable

If the *TP53* gene is damaged, tumour suppression is severely reduced. People who inherit only one functional copy of the *TP53* gene will most likely develop tumours in early adulthood, a disease known as Li-Fraumeni syndrome.

More than 50 percent of human tumours contain a mutation or deletion of the *TP53* gene.

The *TP53* gene can also be damaged in cells by mutagens (chemicals, radiation, or viruses), increasing the likelihood that the cell will begin decontrolled division.

The mechanism by which p53 chooses between growth arrest and apoptosis is not known. Several factors may influence the choice:

(1) Cell type
(2) Oncogenic composition of the cell
(3) The intensity of the stress conditions.
(4) The level of p53 expression and its interaction with specific proteins.