DOCTOR 2020 | JU

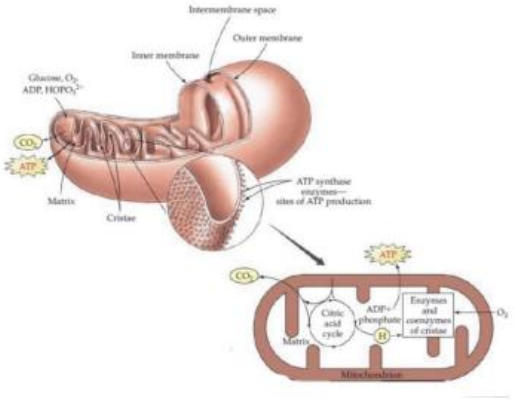
# METABOLISM


*WRITER :* ALI ALMAHROOK

*CORRECTOR :* MOHAMMAD ABU-LOUZ

*DOCTOR:* NAFETH ABU-TARBOUSH

# The mitochondria: -




- **OMM (Outer Mitochondrial Membrane): permeable to small molecules (MW<5000) & ions, porins (transmembrane channels).**
- **IMM (Inner Mitochondrial Membrane): impermeable even to H+; thus it needs a specific transporter.**
  - The oxidative phosphorylation process yield efficiency is not that much because a lot of energy will be lost for these transporters.
- **IMM bears the components of the respiratory chain and the ATP synthase.**
- **Matrix: contains pyruvate dehydrogenase complex & TCA cycle enzymes, fatty acid β-oxidation pathway, and the pathways of amino acid oxidation.**
- **In other words: matrix contains all pathways of fuel oxidation except glycolysis (cytosol).**

- Recall the 4 stages for energy production
  - 1-Digestion.
  - 2-Acytel Co A production.
  - 3-TCA (kerbs cycle): the main purpose is to extract electrons from molecules to supply them to OxPhos.
  - 4-OxPhos (oxidative phosphorylation).

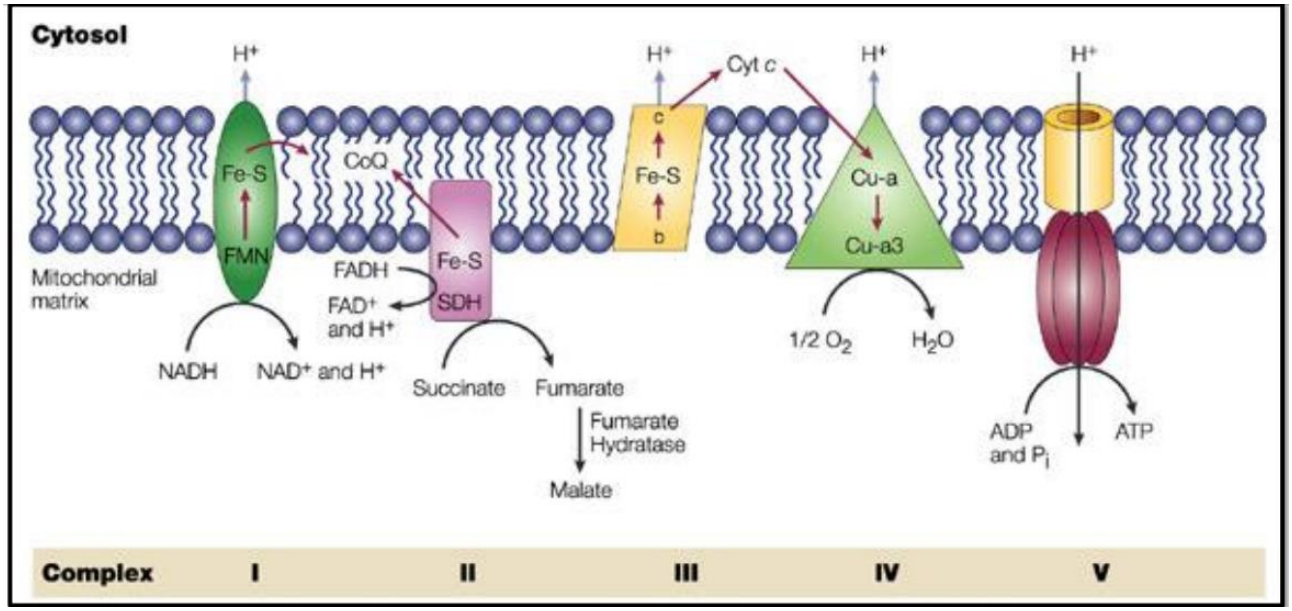
# Oxidative phosphorylation (OxPhos)

- **Generation of ATP aided by the reduction of O2.**
- **Was discovered by Peter Mitchell (1961): the chemiosmotic theory.**
- **Oxidative phosphorylation has 3 major aspects:**
  - **(1) It involves flow of electrons (reduction potential driving force) through a chain of membrane-bound carriers (prosthetic groups)**

- **(2) The free energy available (exergonic) is coupled to transport protons across a proton-impermeable membrane (pumping the protons against their electrochemical gradient).**
- **(3) The transmembrane flow of protons down their concentration gradient provides the free energy for synthesis of ATP (ATP synthase).**

## General view of OxPhos

- ✓ The electron carriers which result from kerbs cycle (**NADH**,**$FADH_2$** ) get oxidized and give their electrons to the complexes this redox reaction (oxidation-reduction) will result in energy that can be used to **pump protons (H+)** against theirs concentration from inside the mitochondrial matrix to intermembrane space ,after that the protons will flow back down their concentration but because of the **impermeably** for the **IMM** they need a transporter which is ATP synthase that will couple the flowing back of the protons (H+) with synthesis of ATP.




**The route of NADH electrons :Complex I → CoQ → complex III → Cytochrome c → complex IV → $O_2$**

**The route of $FADH_2$ electrons :Complex II → CoQ → complex III → Cytochrome c → complex IV → $O_2$**

- **Complex I** (**NADH dehydrogenase** or **NADH CoQ Oxidoreductase**): electron acceptor from **NADH**, it can work as an Oxidoreductase due to the presence of **FMN** (Flavin mononucleotide) which can accept 2 electrons and passes them to (Fe-S) iron sulfur clusters (7 cluster in complex I), now the enzyme is reduced and it will get oxidized by passing the electrons to **CoQ**.

- **Complex II (Succinate dehydrogenase-SDH**): electrons acceptor from **$FADH_2$**, because $FADH_2$ cannot swim freely in the cell, it should be embedded into its enzyme, recall that $FADH_2$ is produced in Krebs cycle through **SDH** (Succinate dehydrogenase), and it's the only enzyme from Krebs cycle that is **linked** (embedded) into the **IMM**, it has (Fe-S) iron sulfur clusters that carry the electrons and passes them to **CoQ**.

- **Complex III** (**cytochrome bc1** or **CoQ cytochrome c oxidoreductase** ) :receives the electrons and get reduced from CoQ, it contains heme b and heme c and (Fe-S) iron sulfur clusters so it can work as Oxidoreductase : **CoQ→heme b→Fe-S→heme c**, heme c passes the electrons to **cytochrome C**.

- **Complex IV (cytochrome c-oxidize**): receives electrons and get reduced from **Cyt c**, **it contains 2 types of heme close to cupper**, cupper has the capacity to carry one electron as well as the heme and Cyt c can also carry one electron so when Cyt c gives its electron to the (cupper – heme a) the same electron will be shared between the (cupper and the heme a) then it passes to (cupper – heme a3) and the electron will be shared between the (heme a 3 and cupper) then it passes to **O2.**

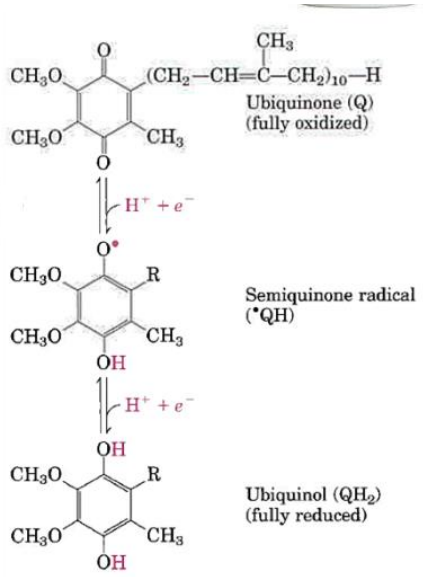
**الرجاء النظر إلى الصورة في الأعلى ↑بعد قراءة كل (complex) + مطلوب حفظ الأسماء المرادفة لكل (complex)**

**Each O need a 2 electrons to get reduced so $O_2$ need 4 electrons to get reduced to $H_2O$.**

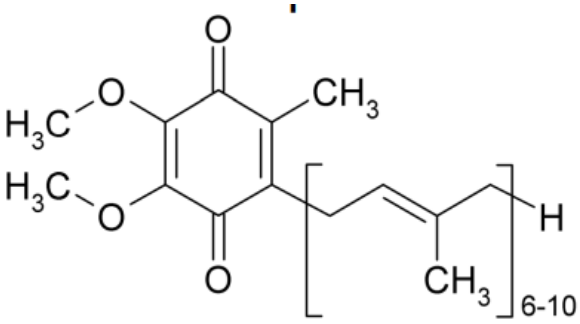
- Why we should reduce the heme in complex IV??
- Because heme contain iron and iron cannot bind to $O_2$ unless it was in a ferrous state ($Fe^{+2}$) -reduced state-, so we reduce the heme to allow it to attach to the $O_2$ and transfer the electrons to $O_2$.
- What makes the complex(enzyme) work as Oxidoreductase??
- If it contains at least one of these molecules (Fe-S), $NAD^+$, FAD, FMN or heme.

# Co Q (Ubiquinone): -

- **Electron acceptor from Complex I or Complex II and passes them to Complex III.**
- It is a cyclic diene structure.
- **It can bind 2 electrons, first electron (comes as a hydrogen) will bind to double bond and convert it to hydroxyl and become semiQuinone , the second electron (comes as a hydrogen) will bind to the second double bond and convert it to a hydroxyl and become Ubiquinol (alcohol).**




- **Also called coenzyme Q, or Q**
- **Lipid-soluble benzoquinone with a long isoprenoid side chain**
- **Small & hydrophobic (freely diffusible)**
  - Its small and cannot allow the Coq to be lipid soluble but because it is repeated 6-10 time its make CoQ lipid soluble.

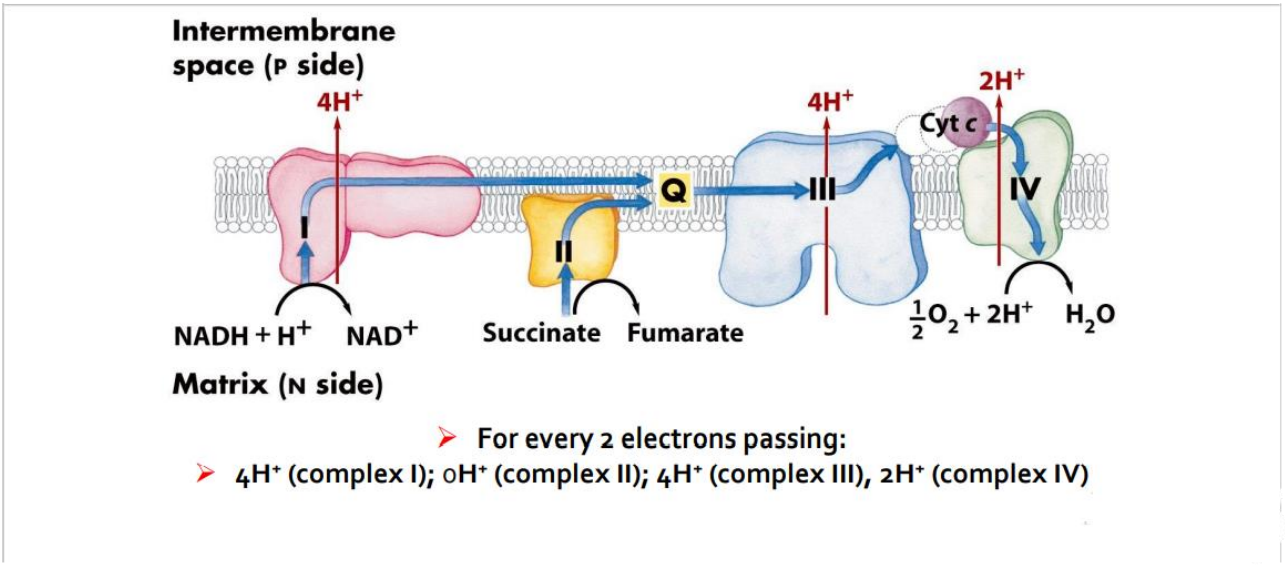



- **Carries electrons through the IMM**
- **Can accept either 1 e- or 2 e-**
- **Act at the junction between a 2-electron donor and a 1-electron acceptor**
- **Sometimes prescribed for recovering MI patients**
  - MI (myocardial infarction) patients have less energy production so they take CoQ to pass more electrons through the ETC (electron transport chain) which will result in more the ATP production.

Until now we finish the ETC which results in reduction of $O_2$ to water and pumping protons (H+) against their concentration gradient, now these protons will flow back down their concentration gradient through ATP synthase (Complex V) which will couple this exergonic process with ATP production.

## Pumping of protons: -

- What make the electrons move through these different complexes??
- Due to the difference in their reduction potential, they move from more negative complexes to the more positive complexes.




- When electrons pass from **complex I to CoQ** it will result in a difference of energy that is capable for pumping 4 protons against their gradient.
  - **Complex I→ CoQ results in energy capable for pumping 4 (H+).**
  - **Complex III→Cyt c results in energy capable for pumping 4 (H+).**
  - **Complex IV→ $O_2$ results in energy capable for pumping 2 (H+).**

- **From Complex 2 II → CoQ ::zero (H+) :the difference in the energy is almost zero so it isn't capable for any protons (H+) pumping and that's why complex II spans the IMM only (not integral like others).**

✓ **In conclusion:**

- **one pair of electrons from NADH result in pumping 10 (H+)**
- **one pair of electrons from $FADH_2$ result in pumping 6 (H+)**

**For every 4 (H+) crossing the IMM through ATP synthase (Complex V), one ATP is generated.**

- **Thus NADH gives 2.5 ATP, $FADH_2$ gives 1.5 ATP.**
- Scientifically there is no half ATP, so for simplifying we say NADH gives 3 ATP, $FADH_2$ gives 2 ATP.
- **But exactly we can say 2 NADH give 5 ATP, 2 $FADH_2$ give 3 ATP.**

OxPhos is coupled process **redox part (ETC)** and **phosphorylation part** and what links the two parts is the (H+) gradient.

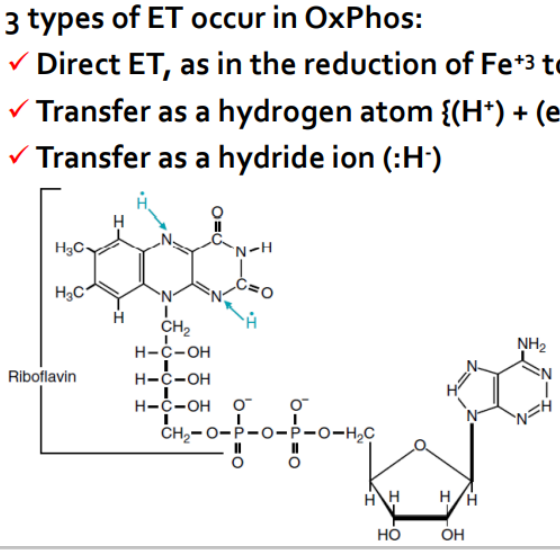
- Can this process be uncoupled (one part occurs without the another)??
- Yes, it can there are a channels (**uncoupling proteins UCPs**) in the IMM that bring back the (H+) to the matrix without passing through the ATP synthase (without generating ATP), but instead of that it generates heat.
- What's the difference between the brown fat tissue and white fat tissue??
- The brown fat generate much high heat compared to the white fat, that's because we have more **UCPs** in brown fat than white fat.
- New-borns have much brown fat compered to white fat because they cannot cover themselves.
- Generating heat by this process is called **adaptive thermogenesis**.

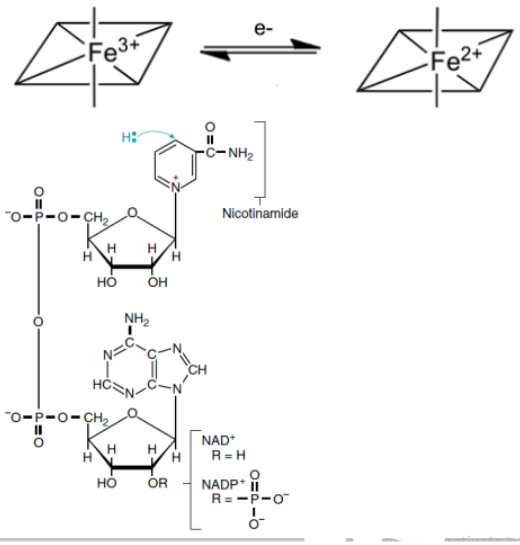
- Why we need ATP??
- To build up molecules (anabolism),↑ATP↑anabolism↑fat↑obesity.
  - ↑UCPs ↓ATP↓fat↓obesity.

صلّ على النبي

## Three ways to electron transfer (EC): -

- 3 types of ET occur in OxPhos:
  - ✓ Direct ET, as in the reduction of $Fe^{+3}$ to $Fe^{+2}$
  - ✓ Transfer as a hydrogen atom {($H^+$) + ($e^-$)}
  - ✓ Transfer as a hydride ion ($:H^-$)



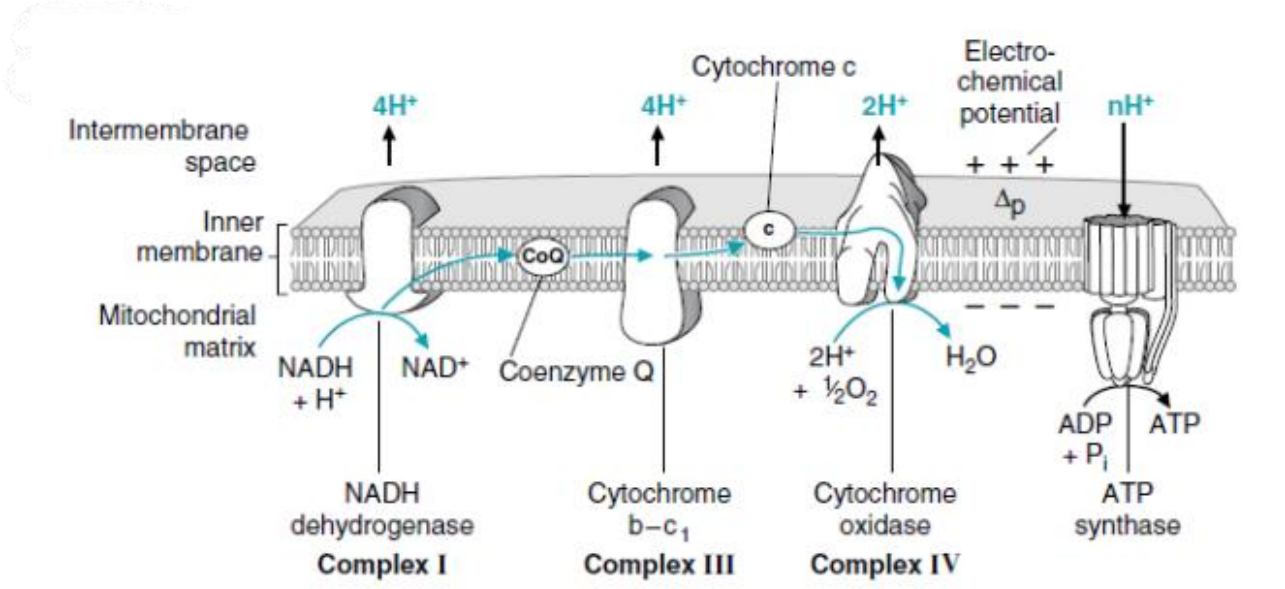



**Electrons are funnelled to a universal electron acceptor: -**

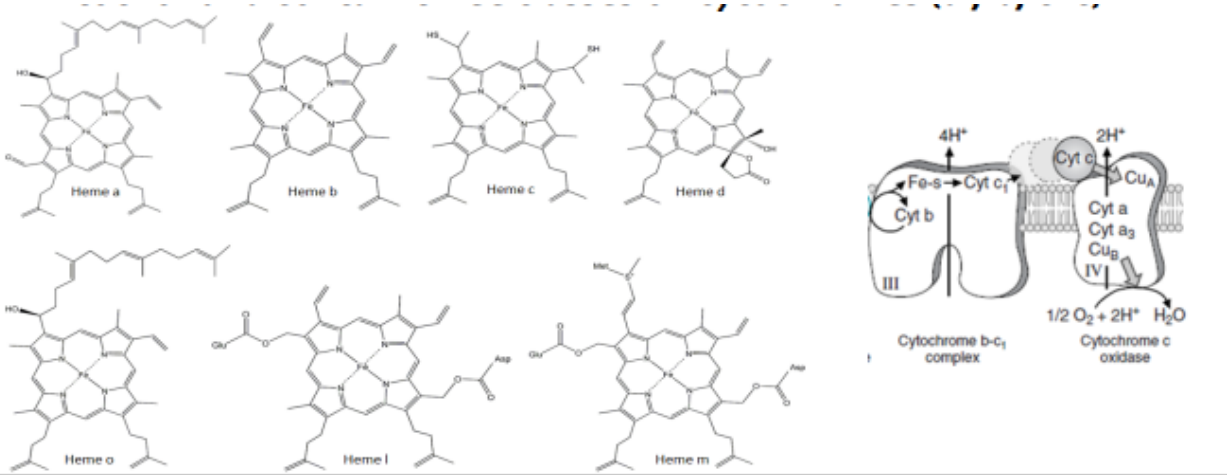
| COENZYME | AS OXIDIZING AGENT | AS REDUCING AGENT |
|---|---|---|
| Nicotinamide adenine dinucleotide | $NAD^+$ | $NADH/H^+$ |
| Nicotinamide adenine dinucleotide phosphate | $NADP^+$ | $NADPH/H^+$ |
| Flavin adenine dinucleotide | FAD | $FADH_2$ |
| Flavin mononucleotide | FMN | $FMNH_2$ |

## Requirements of OxPhos

- Redox reaction: electron donor (NADH or FADH2) & electron acceptor (O2).
- An intact IMM
- ETC of proteins
- ATP synthase

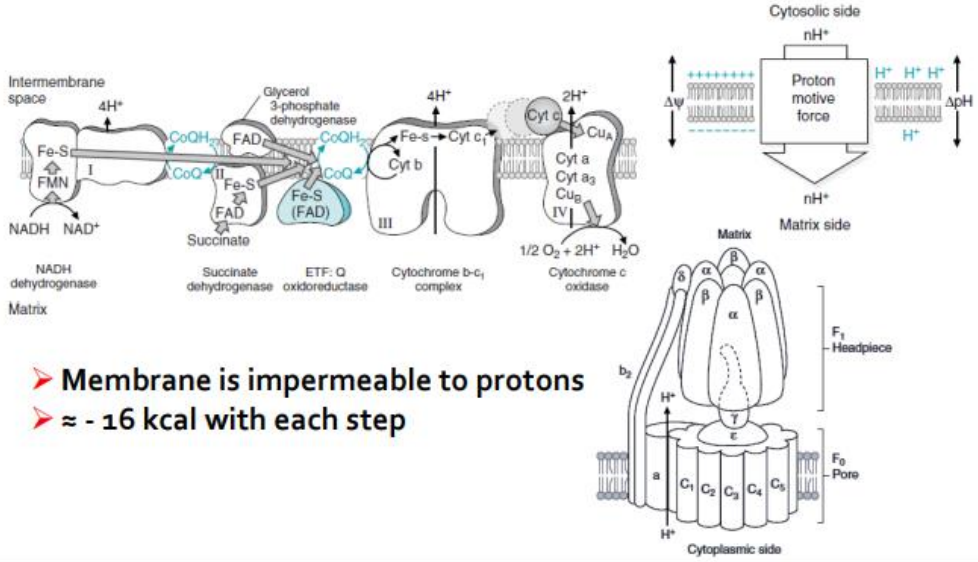


# Cytochromes: -




- **Electron carrier molecules**
- **Proteins with characteristic strong absorption of visible light (Fe-containing heme prosthetic groups)**
- **Classification based on light absorption**
- **Mode of binding (a, b, c)**
- **Mitochondria contain three classes of cytochromes (a , b, & c).**
  - **We call the cytochromes according to the heme that contains.**
  - **All heme structures have similar rings but they differ in the group attached to the ring.**

## ET to $O_2$, how does the process occurs? "The chemi-osmotic theory"




- Membrane is impermeable to protons
- ≈ - 16 kcal with each step

تم بحمد الله