***TCA cycle intermediates :***

These intermediates are precursors for biosynthetic pathways ,for example :

-citrate  ---- fatty acid synthesis .

-α-ketoglutarate ----amino acid synthesis & neurotransmitter “GABA” .

-succinyl CoA----heme synthesis.

-malate----gluconeogenesis pathway.

-oxaloacetate ---- amino acid synthesis.

***Anaplerotic reactions :***

they are reactions that replenish the intermediates of the TCA cycle. (reactions that compensate the intermediates that are taken away ).

-***pyruvate carboxylase*** is a major anaplerotic enzyme .(its an enzyme that adds carboxyl group to pyruvate ):

• it requires biotin ( vitamin B7)as a cofactor .

•it is activated by acetyl CoA. (Why?) to complete the citric acid cycle , so if the acetyl CoA conc. increases ,then oxaloacetate conc. increases , together  they form citrate .

•very high conc. in liver and  kidney. (gluconeogenesis)

***Oxidative phosphorylation :***

-mitochondria has two membranes , outer and inner with intermembrane space between them .

- all energy metabolic procedures occur in the matrix of mitochondria except for glycolysis ( occurs in the cytosol)

-oxidative phosphorylation is the 4th step & the last stage where we generate ATP through it .

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| ***Oxidative phosphorylation :***Generation of ATP aided by O2 . |

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| **Substrate level phosphorylation:**Generation of ATP without O2.e.g: formation of succinate from succinyl  CoA ,which gives energy used to transfer GDP toGTP. |

**Chemiosmotic theory:**

-electron carrying molecules from krebs cycle are :

•NADH

•FADH2

-both of these carries donate their electrons to complexes of protein “ enzymes “, these complexes need to have a structure that undergoes reduction and oxidation ( accept and donate electrons)

- they are oxidoreductase enzymes , conjugated enzymes .

**Note that :**

**-**not all proteins can serve ( function ) that way ,e.g: amino acids .

- heme can donate and accept electrons .

- metals as well, such as zinc,copper and lead.

\*                                           \*                                       \*

-NADH from krebs cycles has the highest ability to donate electrons , in terms of reduction potential its charge is –ve and its high .

-other carries should be more +ve

-O2 has the highest reduction potential & more +ve than the others .

- electrons are moving according to gradient potential in terms of ΔG .

- difference in energy between complexes will be used to pump protons (H+)outside the inner mitochondrial membrane , these protons form a force ,”concentration force “ : atoms  outside the membrane more than in ,& “ electrical gradient  “: more +ve charge outside than in ,so there will be an electrochemical gradient across the inner mitochondrial membrane .

- this membrane is impermeable to protons (H+),so it needs a carrier or transporter allowing it to pass through the membrane , which is ATP synthase .

-these protons move according to:

•Their chemical gradient .

•Difference in energy.

**Steps :**

**-**there are 5 complexes (1,2 ,3,4.

-NADH donates its electrons to complex 1 .

-Complex 1 donates its electrons to complex 3.

-then complex 3  donates to complex 4 then to O2 ,converting O2 to H2O.

**Note :**

There are two entry points for electron transport chain :

•complex 1

•complex 2

-both of these complexes donate their electrons to complex 3.

- complex 1 has no relation to complex 2 .

\*                                                   \*                                                 \*

-the complexes are enzymes “ proteins”, oxidoreductases .( when they accept electrons they become reduced ,and  when they donate electrons they become oxidized) .

-also ,these complexes are integral proteins – transmembrane proteins ;spanning the membrane , all except complex 2 .

-these proteins are cant move ,so there should be carries which have the ability to transport electrons from complex to another , a carrier is called” Co Q” ,Co enzyme Q , Ubiquinone .

- this CoQ  carry electrons from complex 1 & 2  to complex 3 .

-what transport the electrons from complex 3 to complex 4 is “cytochrome C”  ;  a protein that has heme C , used in electron transport.

-difference in energy used in transferring electrons from complex 1 to CoQ

-NADH donates 2 electrons to complex 1 becoming NAD+ .

-complex 2 donates its electrons to CoQ but no protons pumped out . (why?)

Because difference in energy resulted from transferring electrons from complex 1 to CoQ is 4 protons , while the resulted energy from transferring electrons from complex 2 to CoQ is almost zero, so complex 2 is  designed not to span the membrane .

-when complex 3 donates its electrons to cytochrome C , there will be enough difference in energy to pump  4 protons out .

-when complex 4 donates its electrons to O2 , there will be enough difference in energy to pump 2 protons out .

- entry point of NADH is complex 1 , now the number of protons pumped out through complexes :

• 4 protons from complex 1 .    •4 protons from complex 3 . •2 protons from complex 4.

So total number of protons pumped out is 10 protons .

-now for these protons to move back inside through ATP synthase , the equation is ( per 4 protons passing through ATP synthase there will be 1 ATP generated .)-----so, the amout of ATP generated is  10/4=2.5   ̴3 ATP.

-for FADH2 , its always bound to complex 2 , which is succinyl dehydrogenase (from krebs cycle, step 6),this is the only direct link between krebs cylcle and oxidative phosphorylation.

- entry point of FADH2 is complex 2 , now the number of protons pumped out through complexes:

•no protons from complex 2    •4 protons from complex 3      •2 protons from complex 4.

So total number of protons pumped out is  6.

- the amount of ATP generated is 6/4=1.5   ̴2 ATP.

**Note:**

-For 2 electrons moving from NADH there will be a generation of 2.5 ATP.

-For 2 electrons moving from FADH2  there will be a generation of 1.5 ATP.

  SO, the amount of energy ATP  generated from NADH is more than FADH2.

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Note : this sheet is not complete i’ll complete it as soon as the dr. send the slides .

Done by : Farah Al-Nazer .