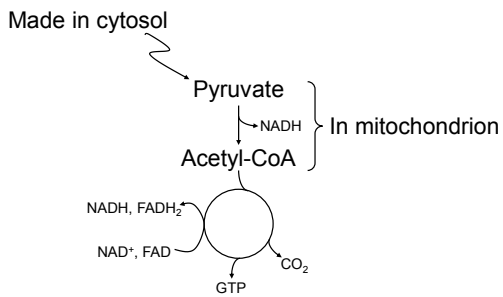
Topic 13

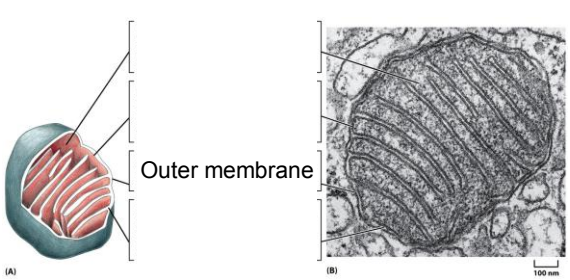
Acetyl CoA I: The citric acid cycle



Topic 10 learning objectives

- Mitochondrial structure
- Metabolic fates of pyruvate
- Pyruvate ⟶ acetyl-CoA and CO_2, citric acid cycle
- Regulation of pyruvate oxidation

The mitochondrion



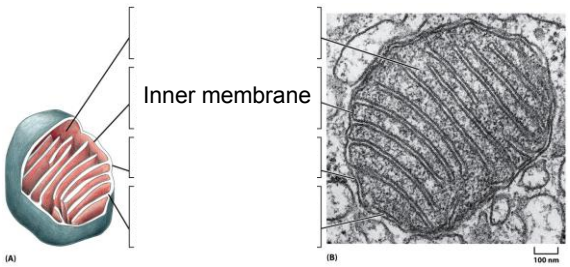
- Small molecules can cross through pores

Figure 14-8

mitochondrion has its own genome in the prokaryotic cell

outer membrane is lipid bilayer and it has big pores, small molecules 5000 daltons but proteins are larger than the pore
small polar can also pass through

The mitochondrion



- Impermeable to small molecules

Figure 14-8

increase the surface area of the mitochondrion and increase the actions

it needs channels or transporter to do transport

The mitochondrion

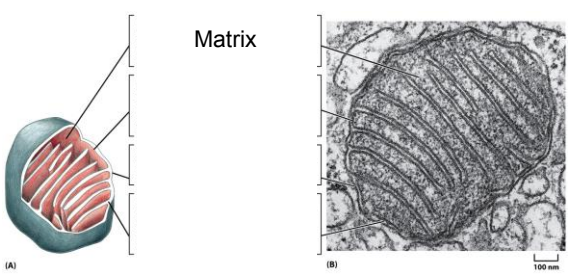
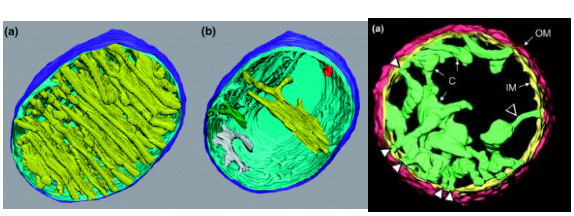


Figure 14-8

the space enclose the innner membrane

The mitochondrion – better images



Frey and Mannella (2000) *Trends Biochem Sci* 25:319-24

inter-membrane space -the space between the membranes

Cellular respiration

Pyruvate + O_2 ⟶⟶⟶⟶⟶ CO_2 + H_2O

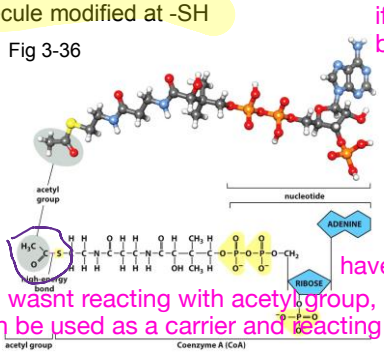
- Two stages to pyruvate oxidation
  - I. Decarboxylation of pyruvate
  - II. Citric acid cycle

oxidizing reaction

Coenzyme A

- A carrier molecule modified at -SH

Fig 3-36



can have an acetyl group = acetyl coenzyme A

if its given NADH, ATP and coenzyme A you should know which is which by the structure

have to recognize this from the structure not ATP or NA

if it wasnt reacting with acetyl group, it will be SH

can be used as a carrier and reacting with things like fatty acid

I. Decarboxylation of pyruvate

Pyruvate + NAD^+ + CoA

fascinated enzyme ,quite large

pyruvate dehydrogenase

irreversible reaction

Acetyl-CoA + CO_2 + NADH

- Pyruvate dehydrogenase complex:
  60 polypeptide chains, 3 different enzymes
- Acetyl-CoA and NADH are competitive inhibitors

good for making ATP

the same enzyme is not catalyzing the backward reaction

this enzyme is regulated carefully

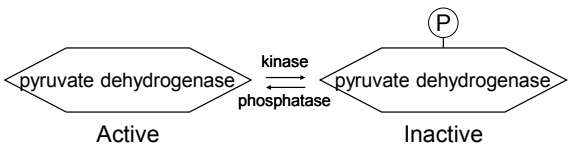
take the 3 carbons in pyruvate, and take one of them and oxidized to CO2, putting electrons to NAD+ to NADH, the other two electrons are attached to coenzyme A to make acetyl coenzyme A

single arrow here : irreversible reaction, the same enzyme cannot do the reverse reaction

but in this case : there is no enzyme that can proceed the backward process

you can go from carbohydrate to fatty acid but can't fatty acid to carbohydrate

Regulation of pyruvate dehydrogenase



Active | Inactive

Promoted by
- Pyruvate
- Insulin

Promoted by
- Acetyl-CoA
- NADH

substrates is high, pyruvate builds up
insulin promotes phosphorylation
insulin does not directly activate the process

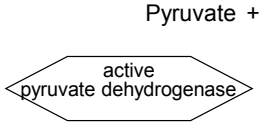
adding phosphates : kinase
remove phosphate : phosphatase
they are competitive inhibitors
indirect effect to inactivate kinase, you phosphorlate the enzyme and inactivates it

conversely, dephosphorlyation when substrate is high, pyruvate is building up and we will use the pyruvate
insulin promote glycolysis and that will make pyruvate

Regulation of pyruvate dehydrogenase

- When pyruvate and insulin are high:

Pyruvate + NAD^+ + CoA

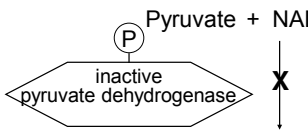


Acetyl-CoA + CO_2 + NADH

Regulation of pyruvate dehydrogenase

- When acetyl-CoA and NADH are high:

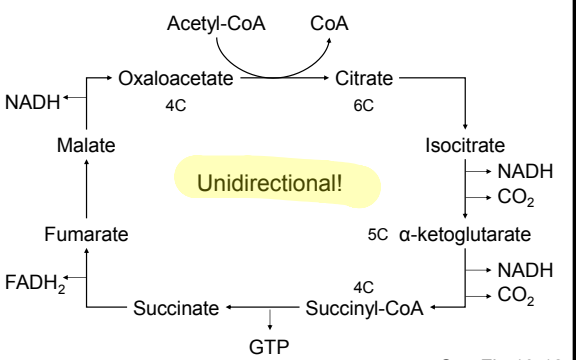
Pyruvate + NAD^+ + CoA



Acetyl-CoA + CO_2 + NADH

lots of ATP and shut down this process
dont have to memorize the specific inhibitor that reach the enzyme but you have to understand the process

II. Citric acid cycle (TCA cycle, Krebs cycle)



See Fig 13-12

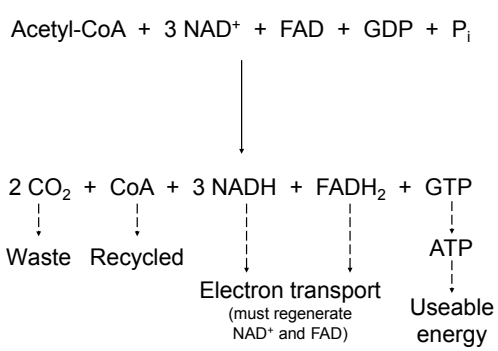
3 carboxylic acid group

unidirectional (always gonna go clockwise)
oxidize one of the carbon and put two others into acetyl CoA and put into the citric cycle/ TCA cycle
do not need to memorize the intermediate, understand what comes in and what comes out and how does the cycle work

1. the acetyl CoA comes form pyruvate, the two C makes oxalocacetate to citrate(6C) (isomerization)
2. citrate lose a carbon into CO2 and the electron goes on NAD+ and end with a 5 carbon ketoglytarate (oxidative)
3. (oxidative) ketoglutarate lose a carbon into CO2and CoA comes back into the process and form succinyl CoA and this is a high energy bond so GTP is released
4. squeese more electron out and give it to FAD2+ (2electrons)
5. one more electron to NADH

there are some irreversible process in the citric acid cycle and these are the regulation steps
the citric cycle do not go completely in the reverse direction because not all reaction has counter enzyme to perform the reverse process (always go clockwise)

Net reaction of the citric acid cycle



O2 is not directly involved in the citric acid cycle, but the citric acid cycle is dependent on O2 because O2 is needed to accept the electrons from NADH and FADH2, if there is no O2, then the citric acid cycle can't proceed

2 carbon in and 2 carbon out, oxidizing process, the NADH and FADH2 goes into the electron transport chain

Regulation of the citric acid cycle

1. Availability of substrates
2. Competitive inhibition by products
3. Allosteric regulation

Topic 10 summary

- Pyruvate is converted in mitochondria to CO_2 and acetyl-CoA; the latter enters the citric acid cycle
- In the citric acid cycle, the acetyl group from acetyl-CoA is oxidized to 2 CO_2
- Oxidation of pyruvate yields 4 NADH, 1 $FADH_2$, and 1 GTP (equivalent to 1 ATP)
- Oxidation of pyruvate is regulated by the energy state of the cell