



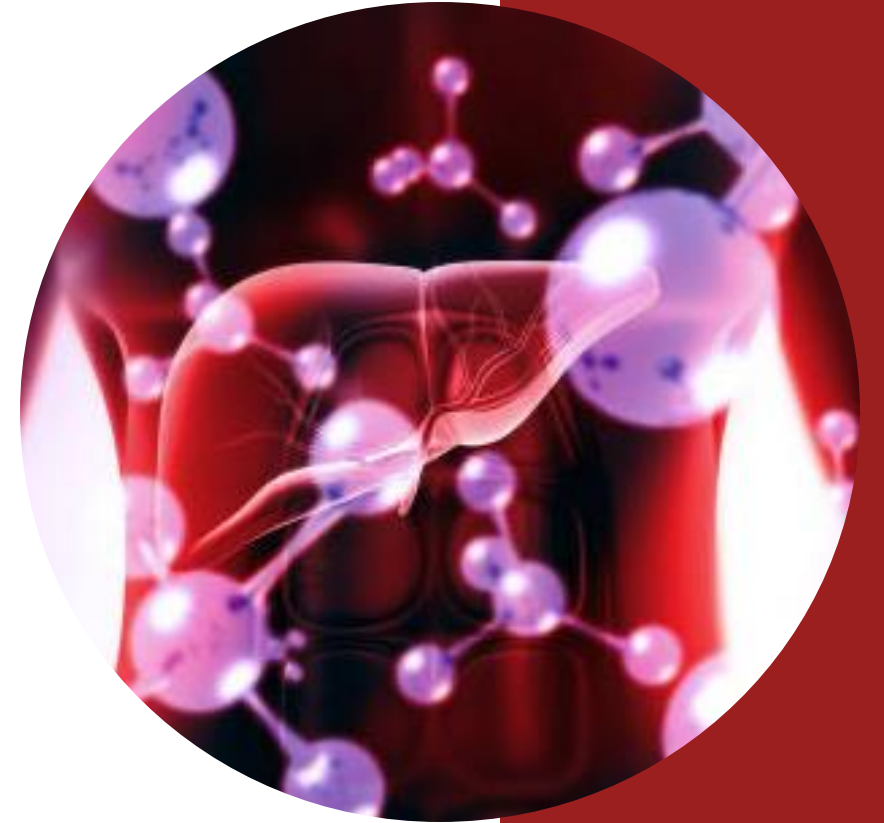
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METABOLISM

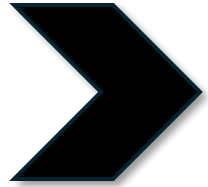
MID | Lecture #5

TCA Cycle Pt.1

Reviewed by: Abdullah Abu Omar



Color coding used in the modified:



Black: the original slides



Maroon: the doctor's explanation/words



*Gray: additional information and
explanation*



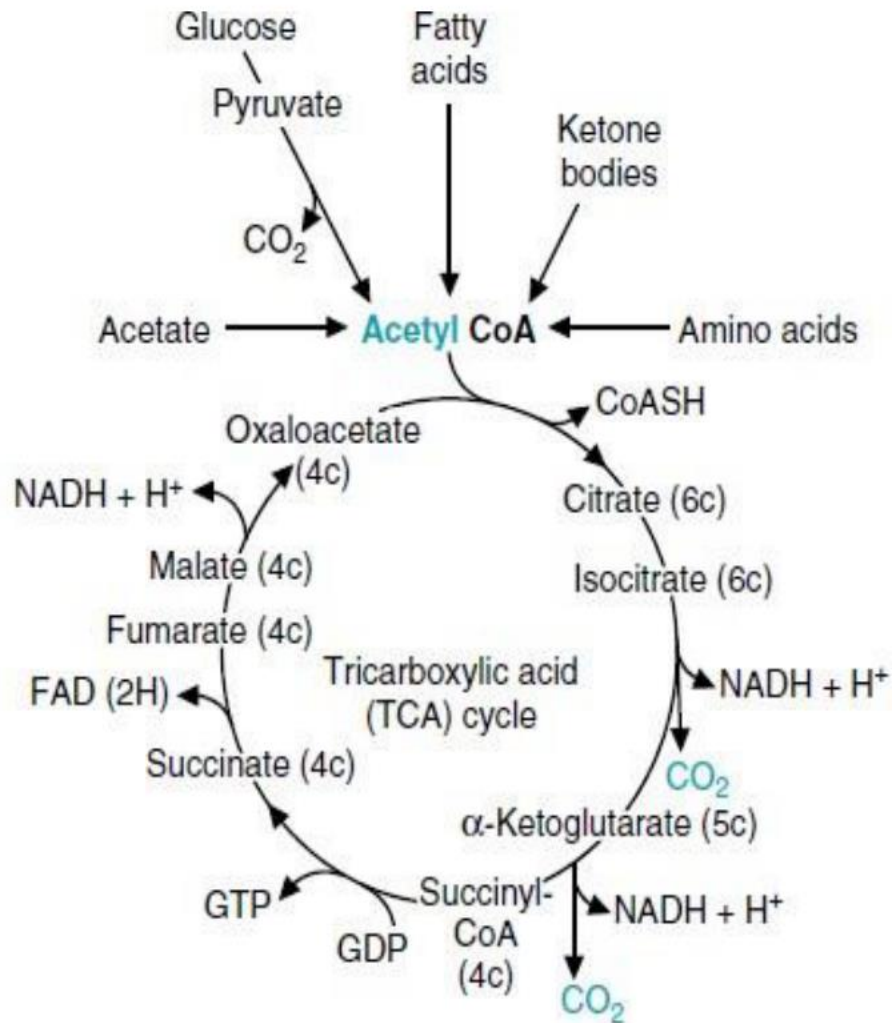
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**(KREBS, CITRIC
ACID, TCA) CYCLE**

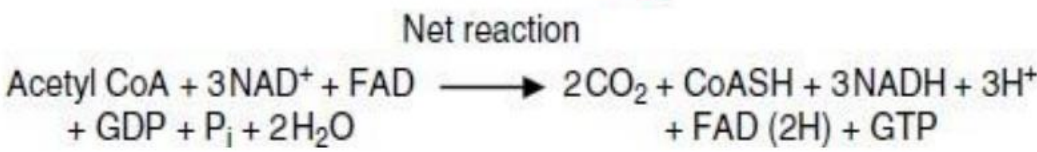
**The Central
Metabolic Hub**

Prof. Nafez Abu Tarboush

- The **Krebs Cycle** (refers to the scientist : Hans Krebs) , also known as the **Citric Acid Cycle** or the **TCA** (tricarboxylic acid) Cycle , all these names refer to the same metabolic pathway. It is a central metabolic hub inside the cells. It is considered the electron extraction machinery within cells, inside the mitochondria.
- Why is it called the Citric Acid Cycle?
Because one of its **intermediates** is **citric acid** , which is the first product of the cycle.
- And why is it called the TCA Cycle or Tricarboxylic Acid Cycle?
Because citric acid has **three carboxylic groups** in its structure. That's why it's referred to as tricarboxylic acid.
- Citric acid – or tricarboxylic acid – is also the acid found in lemon juice & lemon salt (ملح الليمون)



This cycle constitutes 8 steps, 8 intermediates, 8 enzymes all these intermediates are required by name & structure with their catalyzing enzymes .



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COMPONENTS & STEPWISE REACTIONS

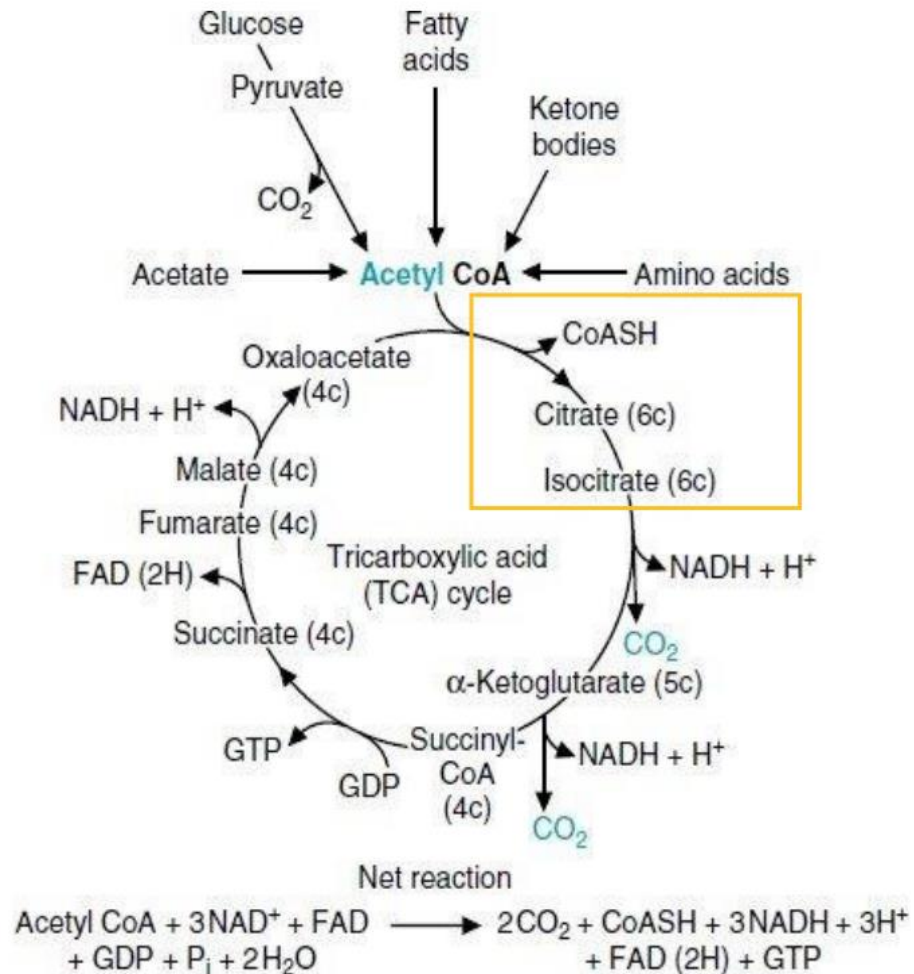
- CIA Sent Soldiers For My Office

The molecules involved in this pathway are not physically arranged in a circle inside the mitochondrial matrix. Hans Krebs worked out the order of the reactions, enzymes and their order. The cycle is a diagram showing this order, not a physical ring of connected molecules.



After the second stage of energy metabolism, various molecules – including fatty acids, ketone bodies, carbohydrates, acetate, and certain carbon backbones of amino acids – produce a compound known as **acetyl-CoA**. This molecule consists of a **two-carbon unit** attached to **coenzyme A** and is considered a **high-energy compound**, because breaking the bond between acetyl and coenzyme A releases energy that can be used in subsequent metabolic reactions.

Why is it called “a cycle” ?
 A cycle regenerates the molecule it starts with. Two carbon atoms enter the cycle, and two carbon atoms leave as CO₂, allowing oxaloacetate to be regenerated.



1. Formation of Citrate

The acetate molecule, which contains two carbon atoms, combines with a four-carbon molecule called **oxaloacetate**.

When these two molecules are joined together, they form a six-carbon compound known as citrate (**tricarboxylic acid**) – the first product of the Krebs cycle.

This reaction is catalyzed by the enzyme citrate synthase.

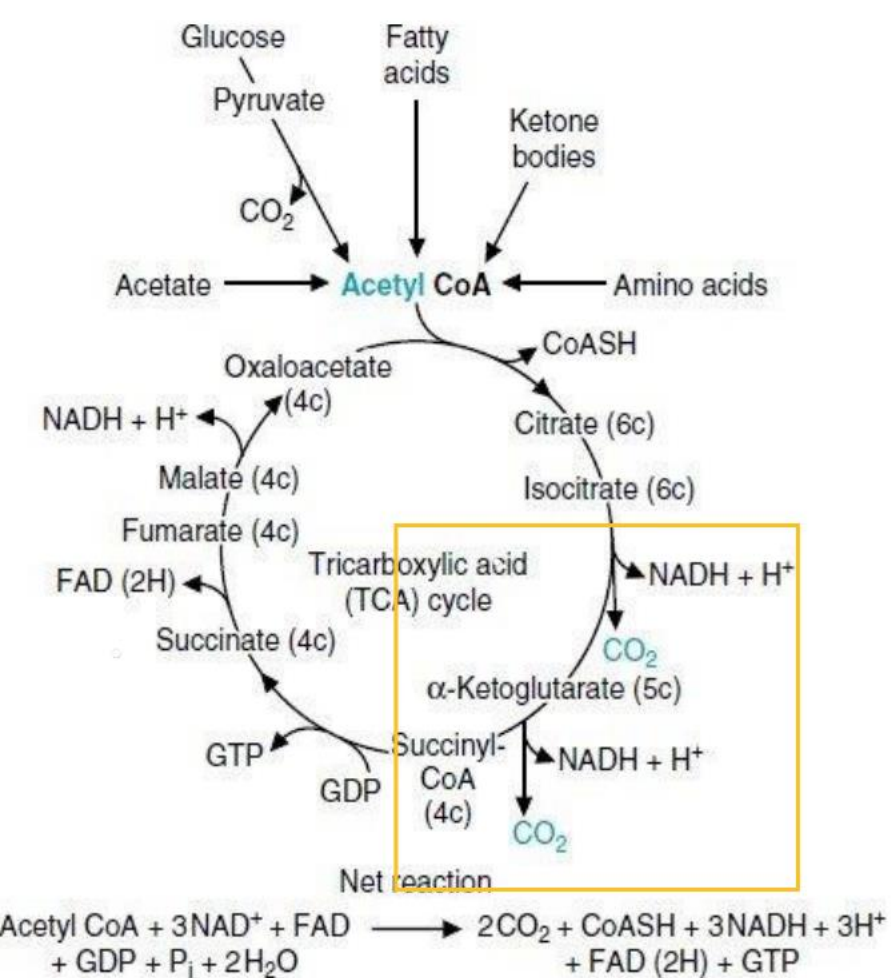
The process requires energy, which is provided by the release of coenzyme A (CoA) from the structure.

2. Conversion of Citrate to Isocitrate

Citrate is converted into **isocitrate**, an isomer that has the same number of carbons but a different structural arrangement.

This rearrangement prepares the molecule for subsequent oxidation steps.

The enzyme responsible for this conversion is **aconitase**, named after the intermediate **cis-aconitate** formed during the reaction.



- **Succinate** is oxidized to **fumarate**,
- **Fumarate** is hydrated to **malate**,
- **Malate** is oxidized to regenerate **oxaloacetate**, completing the cycle.

3. Decarboxylation Steps

Then **isocitrate** would release one carbon unit as **CO₂**, producing a five-carbon unit molecule which is called **alpha-ketoglutarate**

In the subsequent reaction, a four-carbon unit molecule which is called **succinate**, coupled to coenzyme A – this is why it is named **succinyl-CoA** – and one carbon unit is released as **CO₂**

So the two carbon units provided by acetate are released in this half cycle. Now we are with a four-carbon unit molecule coupled to its coenzyme A, and now we should make it **oxaloacetate** again.

As we define cyclic pathways, we must regenerate the first molecule that we started with.

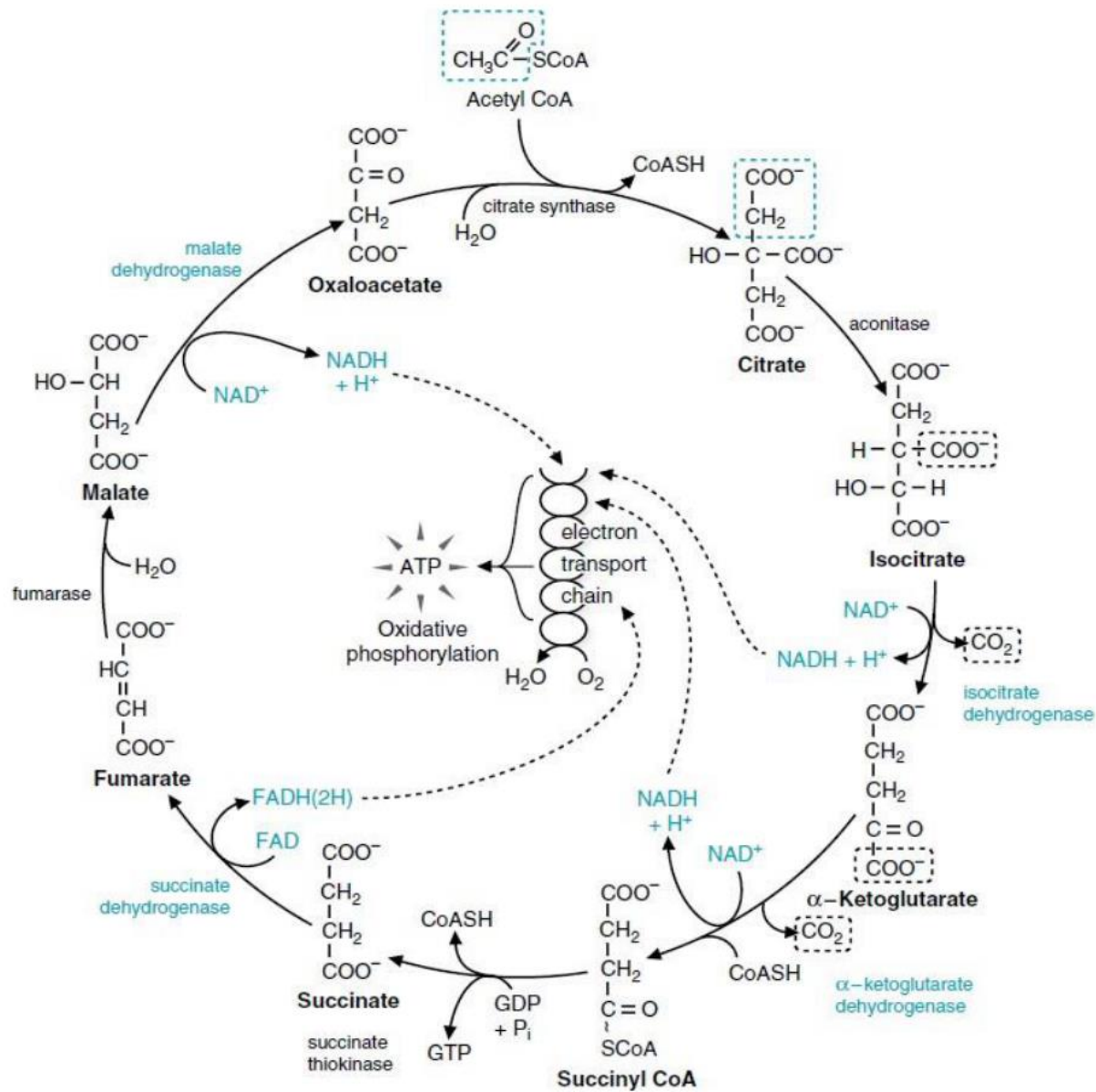
4. Regeneration of Oxaloacetate

So, the first step is to remove coenzyme A, and when coenzyme A is released, it will release its energy.

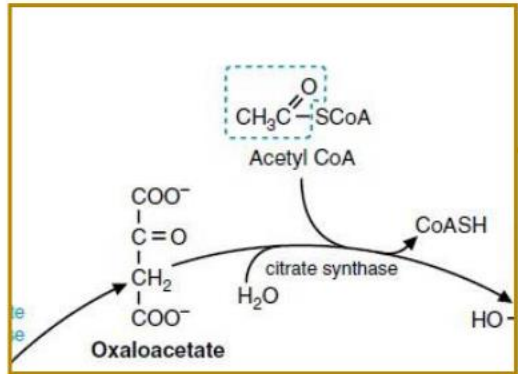
This energy is used to couple inorganic phosphate with GDP to produce GTP as a high-energy molecule, leaving succinate behind – as you can see with a four-carbon unit molecule.

Succinate is oxidized to become fumarate, fumarate is hydrated to become malate, and malate is oxidized to become oxaloacetate again. This regeneration step is crucial because it allows the cycle to continue repeatedly.

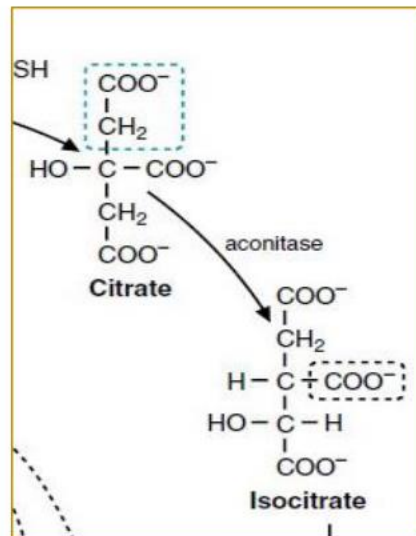
COMPONENTS & STEPWISE REACTIONS



COMPONENTS & STEPWISE REACTIONS

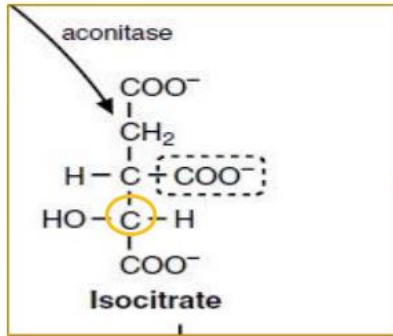


- Structure-wise, as you can see, the acetate molecule is a two-carbon unit molecule that joins oxaloacetate.
- Oxaloacetate is a four-carbon unit molecule, where it has two carboxylates on its terminals, and the two carbons in the middle – one of them is CH₂ and the other is a carbonyl group.
- It will join these two carbon units to become citrate by the action of citrate synthase.



- This citrate carries, as the name implies, TCA – tricarboxylic acid – one carboxylic group, second carboxylic group, and this is the third carboxylic group.
- If you look at the structure of citrate – and since energy production is a process of oxidation – if you look at the carbon units, none of them can be oxidized.
- You will have three carboxylic groups, which are the highest state of oxidation out of these functional groups, and we have a hydroxyl group representing an alcoholic group, which is in a tertiary form – tertiary alcohol which also can't be oxidised.
- So this one (OH) also cannot be oxidized since the carbon is connected to three carbon units.

And this is why citrate is converted to isocitrate – the isomer form of citrate – where this hydroxyl group is translocated to another carbon.



- The isomer form of citrate where this hydroxyl group is transformed to is replaced to join this carbon unit translocated .
- This isocitrate is the product, and the enzyme that converts citrate to isocitrate, catalyzing this isomerization reaction, is called aconitase, which does not imply the action of the enzyme, but an intermediate step instead.
- It is named after an intermediate in the process of conversion of citrate to isocitrate, which is called cis-aconitate.
- So the enzyme is named after the intermediate in between citrate and isocitrate.

we have to split the citric acid cycle into two halves.

- There are eight-step reactions, so we will take the first four as one unit and the other four as another unit.
- In the first half of the cycle, the citric acid cycle is engaged in converting the six-carbon unit molecule into a four-carbon unit molecule.

- So in the first half of the cycle we have four reactions.

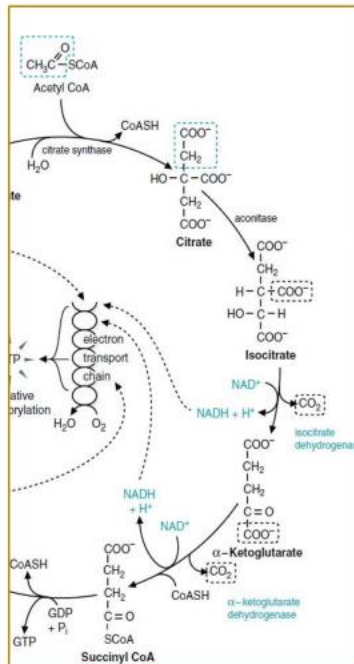
In the first one, we make **citrate**

In the second one, we **isomerize citrate into isocitrate**

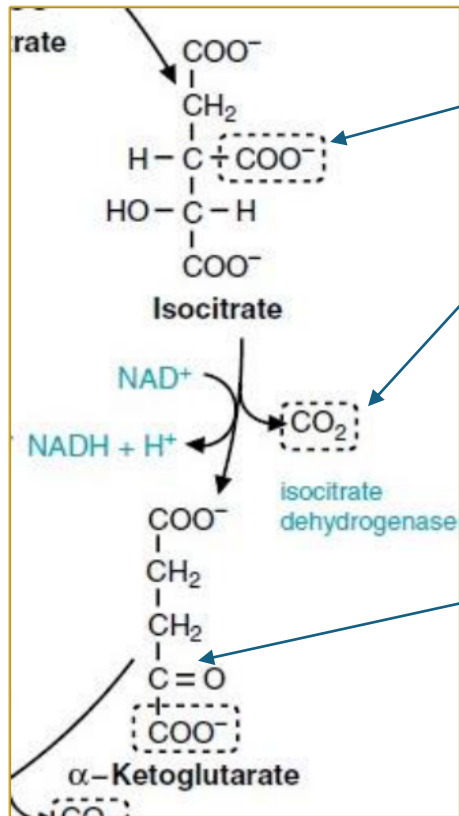
We are left with two other reactions.

These two reactions should release two carbon units – because we got to the cycle with two carbon units, so we have to remove them to preserve the nature of a cycle.

Otherwise, molecules will keep enlarging in their structure.



In the other half, citric acid cycle is engaged in reformulating this four-carbon molecule to become **oxaloacetate** again.



- So, in this reaction, **CO₂ should leave** , and it is dashed representing the carboxylic groups that are leaving the structure.

So this carbon, this carboxylic group, is leaving as **CO₂-** and always carboxylic groups leave the structures as CO₂. And CO₂ gets to the structures as carboxylic groups.

- So this carboxylic group leaves as CO₂.

And why did we convert citrate to isocitrate?
For the purpose of oxidation.

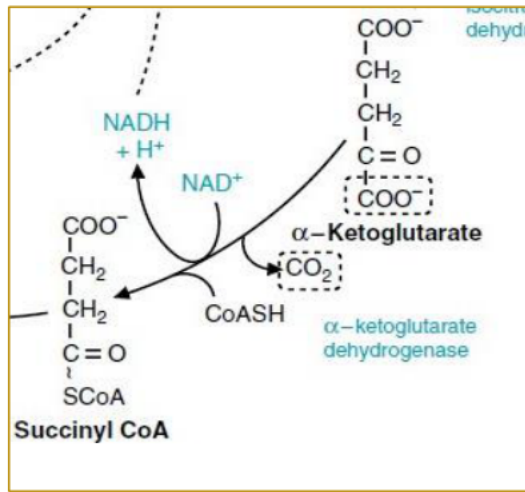
- So, at this level, this proton leaves, producing **the NADH molecule** inside the cycle
After the hydrogens leave, there will be a double bond between the carbon and the oxygen – a keto group.

- And this is why the molecule is named “**keto.**”

It's a **five-carbon unit** molecule, represented by the word “glutarate,” and “-ate” represents the acidic nature of the molecule.

- So **alpha-ketoglutarate** is the molecule produced by the oxidation of isocitrate.

- And the enzyme that catalyzes this conversion is an oxido-reductase called **isocitrate dehydrogenase**

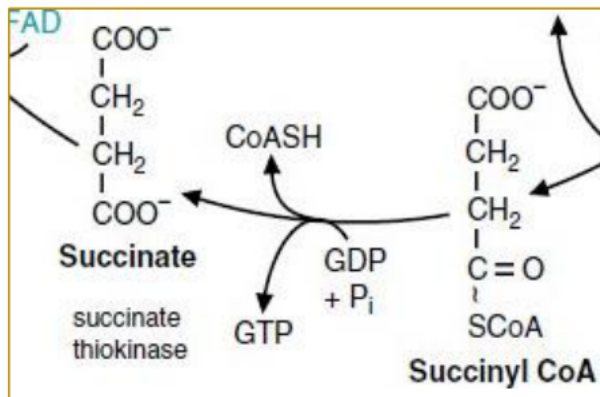


After that, **α -ketoglutarate** undergoes another decarboxylation and oxidation, producing **succinyl CoA**, a four-carbon compound coupled with CoA. The carbon lost in this step is the second CO_2 – meaning the two carbons that entered the cycle as acetyl CoA are now released.

And here we finish the first half of the reaction, four reactions are done

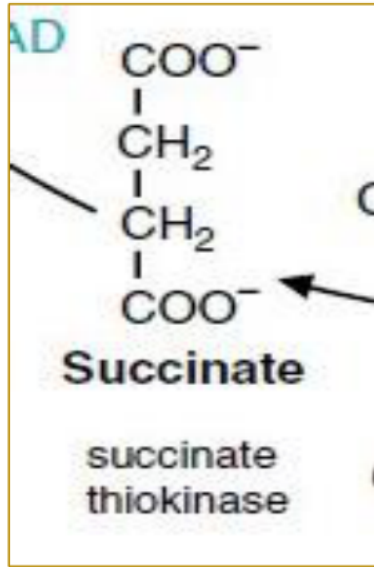
During the conversion of alpha-ketoglutarate, CO_2 is released, and the remaining four-carbon group attaches to coenzyme A, forming succinyl-CoA.

Here, coenzyme A is released, and when it's released, it gives off its energy. This energy is used to bind inorganic phosphate with **GDP** to form **GTP**, a high-energy molecule. GTP has the same amount of energy loaded on ATP and This is why you see it sometimes in text box here as ATP. So, from this step, we produce a high-energy molecule **–without the need for oxygen** or oxidative phosphorylation.



This process is called **substrate-level phosphorylation** – we produce energy directly from the substrate.

There are three substrate-level phosphorylation reactions in our body. This is one of them, and the other two occur in glycolysis, which you'll take in carbohydrate metabolism.



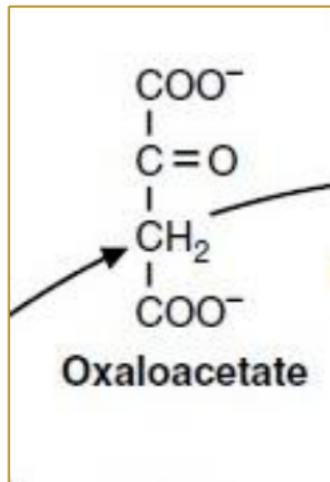
So, leaving this four-carbon unit molecule which is the succinate with some reformulation this succinate molecule has a very nice structure two carboxylic groups on terminals and two CH_2 groups in the middle (you can read it from the top you can read it from the bottom the same way).

The enzyme that catalyses this step (the conversion of succinyl CoA into succinate) it has a three names :

- **Succinyl-CoA synthetase**
- **Succinyl-CoA thiokinase**
- **Succinate thiokinase**

the enzyme that the doctor required is **succinate thiokinase** and this enzyme represents the reaction happening. Where succinate represents either succinate in reactants or in the products Thio represents the presence of a coenzyme in the structure, because the active group is the thiol group

kinase because it phosphorylates GDP so it tells me what's going on inside the reaction and we are now ended up by succinate



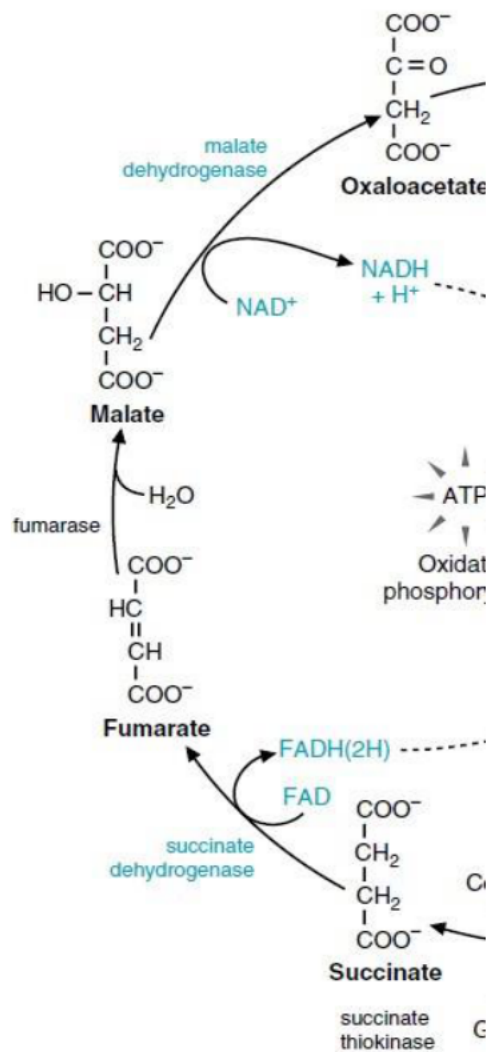
If you look at the structure of succinate and compare it to oxaloacetate, we have two carboxylates on the terminals the same. We have CH_2 in both .

So, what's different is that we have a carbonyl group on one of the carbons while it is here as CH_2 .

Both are 4-carbon dicarboxylic acids.

The difference: oxaloacetate has a carbonyl ($\text{C}=\text{O}$) instead of CH_2 .

This means oxaloacetate is the oxidized form of succinate.



If you take it backward, it will make understanding better... How can I make a carbonyl group?
From a secondary alcohol.”

A carbonyl is formed by oxidizing a secondary alcohol.
So to form oxaloacetate, we oxidize malate.

Reaction: Malate → Oxaloacetate + NADH + ⁺H

Enzyme: Malate dehydrogenase

– Hydration Step

“How do I produce this alcoholic group? By hydration of an alkene... this one will take a hydrogen and this one a hydroxyl group.”

Fumarate has a double bond (C=C).

By adding water across it, we form malate.

Reaction: Fumarate + H₂O → Malate

Enzyme: Fumarase

– Oxidation Step

“If I remove hydrogens, I’m making oxidation... The enzyme succinate dehydrogenase.”

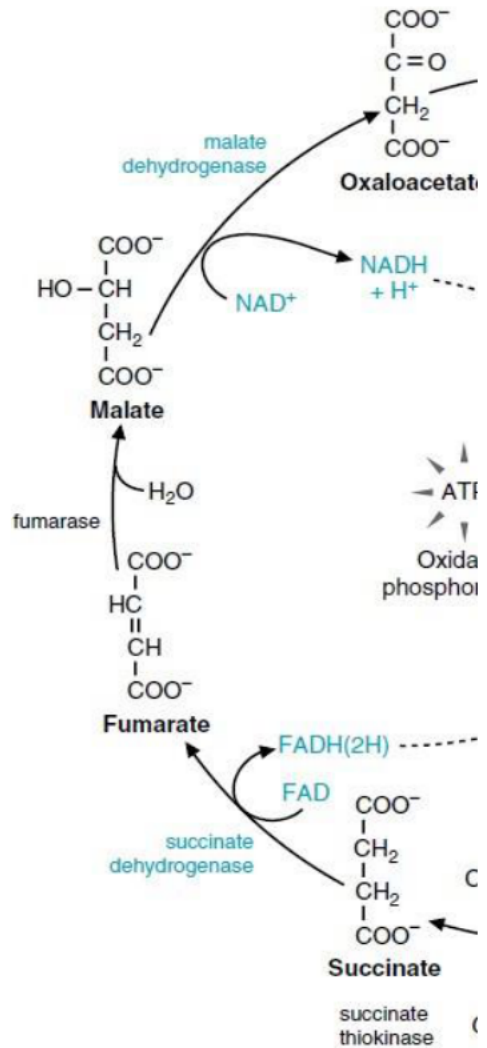
Removing two hydrogens from succinate forms fumarate.

Reaction: Succinate + FAD → Fumarate + FADH₂

Enzyme: Succinate dehydrogenase

Cofactor: FAD (not NAD⁺)

Fumarate will be hydrated to become malate, and malate will be oxidized to become oxaloacetate



Step	Substrate	Product	Enzyme	Cofactor	Reaction Name
1	Succinate	Fumarate	Succinate dehydrogenase	FAD → FADH ₂	Oxidation reaction
2	Fumarate	Malate	Fumarase	H ₂ O	Hydration reaction
3	Malate	Oxaloacetate	Malate dehydrogenase	NAD ⁺ → NADH	Oxidation reaction

For any feedback, scan the code or click on it.



Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional resources

Reference Used:

Prof. Nafez Abutarbosh recorded lecture

Extra References for the Reader to Use:

