TRICARBOXYLIC ACID CYCLE :FORMATION OF ACETATE

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CONVERSION OF PYRUVATE TO ACETYL COA

- Glycolysis - a single glucose molecule is split into two smaller, three-carbon molecules called pyruvate. Pyruvate is then converted to acetyl CoA
- Acetyl CoA occupies a pivotal position in intermediary metabolism and it closely integrates the catabolism of sugars fatty acids and amino acids
- Acetyl CoA is produced in the mitochondrial matrix from pyruvic acids, fatty acids and ketogenic amino acids

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- Pyruvic acid is a product of several substrates
- It is mainly a product of glucose oxidation
- It enters into the mitochondrial matrix from cytoplasm with the help of a carrier and converted to the acetyl group of acetyl CoA
- This conversion provides a link between glycolysis and Krebs cycle
- It supplies the energy rich molecule acetyl CoA for turning the wheel of Krebs cycle round and round

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- The conversion of pyruvic acid to acetyl CoA is a complex oxidative decarboxylation process, mediated by a multienzyme complex , known as pyruvic acid dehydrogenase complex

- In this process, a carboxyl group is removed from pyruvic acid as CO_2

- Pyruvic acid dehydrogenase system consists mainly of three enzymes and six cofactors
- The enzymes are pyruvic acid dehydrogenase , dihydroxylipoyl transacetylase (dihydrolipoyil acetyl trasferase) and dihydrolipoyl dehydrogenase (lipoamide dehydrogenase), with multiple copies of each

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- The cofactors include thiamine pyrophosphate (TPP) ,lipoic acid, CoA, NAD, FAD and Mg^{++}
- These enzymes and cofactors are clustered together so that metabolic intermediates will react easily and immediately , without diffusing away from the enzyme system

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- The combined dehydrogenation and decarboxylation of pyruvic acid involves a dehydrogenation process , accompanied by the removal of a carboxyl group as CO_2

- The result is that acetyl group becomes acetyl CoA
- The two hydrogen atoms removed from pyruvic acid appear as NADH + H^+

- NADH later on gives up its electrons to the electron transport chain , which carries them to molecular oxygen

Decarboxylation of pyruvic acid

- Pyruvic acid decarboxylated by the enzyme pyruvic acid dehydrogenase , in combination with TPP and in the presence of Mg^{++}
- This forms acetol – TPP Complex (Activate acetaldehyde) and CO_2

$$\text{Pyruvic acid} \xrightarrow[\text{TPP},Mg^{++}]{\text{Pyruvic acid dehydrogenase}} \text{Acetol – TPP complex} + CO_2$$

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Transfer of acetol group to lipoic acid

- The 2 carbon acetol group is transferred from acetol – TPP to lipoic acid
- This forms S- acetyl lipoic acid complex , which is a high energy thioester
- Lipoic acid remains bound to the enzyme dihydrolipoyl acetyl transferase (dihydro transacetylase),which catalysis this reaction

Acetol – TPP $\xrightarrow[\text{Oxidised lipoic acid}]{\text{Lipoyl acetyl transferase}}$ S- acetyl lipoic acid +TPP

Transfer of acetyl group to CoA and reduction of lipoic acid

- The third reaction involves the transfer of acetyl group from S- acetyl lipoic acid to CoA and also the reduction of lipoic acid , forming acetyl CoA and dihydrolipoic acid (reduced lipoic acid)

- This reaction is catalyzed by the enzyme **acetyl transferase**

Acetyl transferase

Acetyl lipoic acid → Acetyl CoA +Dihydrolipoic acid + TPP

CoA

Oxidation of dihydrolipoic acid

- The catalytic conversion is completed by the oxidation of dihydrolipoic acid to lipoic acid by the enzyme dihydrolipoyl dehydrogenase and its co enzyme FAD
- This forms $FADH_2$ and lipoic acid
- $FADH_2$ gets oxidized by NAD

$$\text{Dihydrolipoic acid} + FAD \xrightarrow{\text{Dihydrolipoyl dehydrogenase}} \text{Lipoic acid} + FADH_2$$

$$FADH_2 + NAD \rightarrow FAD + NADH + H^+$$

THANK YOU