TCA Cycle/Citric acid cycle/Krebs cycle

- Steps
- Bioenergetics
- Regulation
- Significance
- Amphibolic role
- Anaplerotic reactions

TCA Cycle

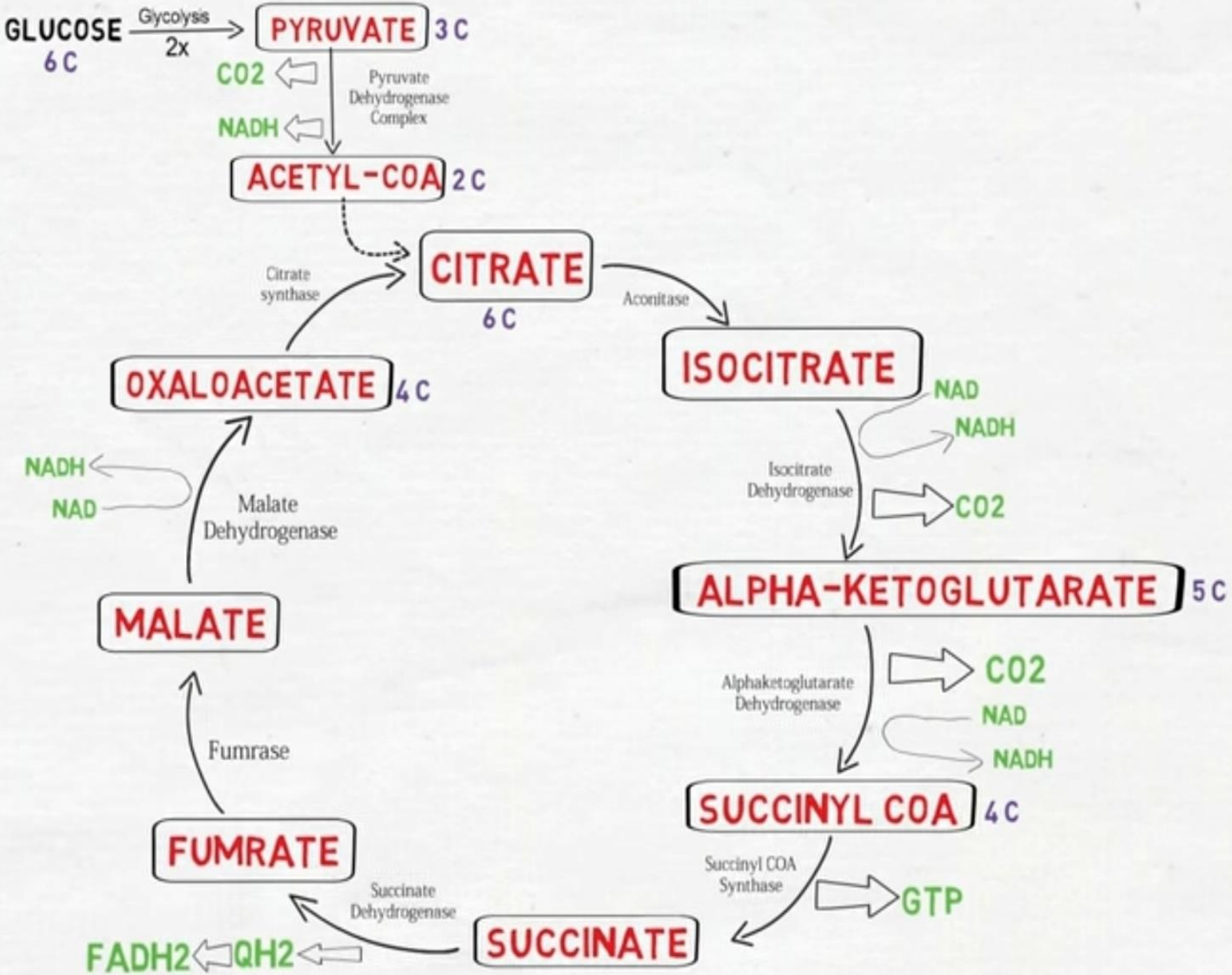
- Also known as Krebs cycle
- TCA cycle essentially involves the oxidation of acetyl CoA to CO_2 and H_2O.
- TCA cycle –the central metabolic pathway
- The TCA cycle is the final common oxidative pathway for carbohydrates, fats, amino acids.

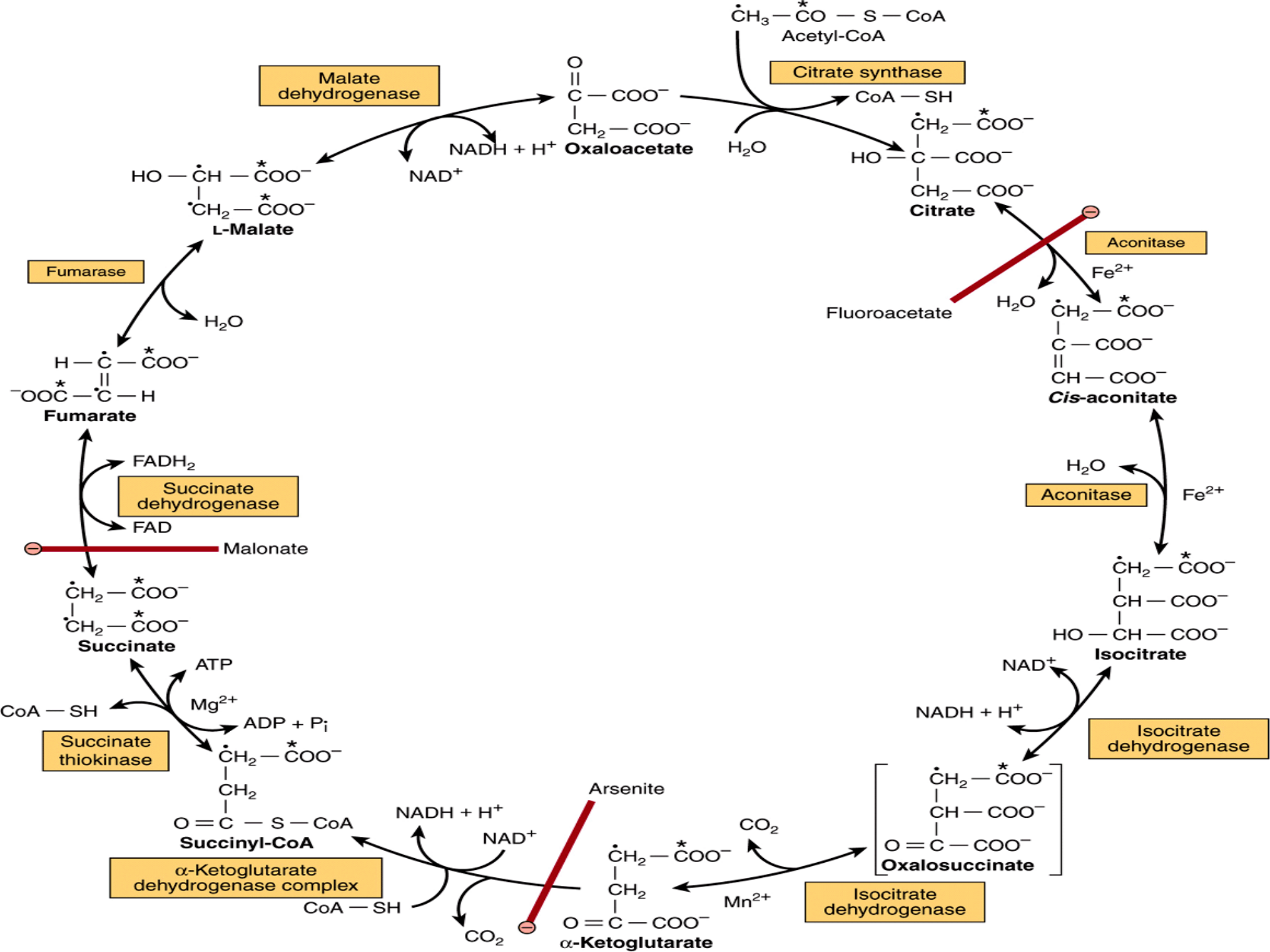
- **TCA cycle supplies energy & also provides many intermediates required for the synthesis of amino acids, glucose, heme etc.**
- **TCA cycle is the most important central pathway connecting almost all the individual metabolic pathways.**

- **Definition**
- **Citric acid cycle or TCA cycle or tricarboxylic acid cycle essentially involves the oxidation of acetyl CoA to CO_2 & H_2O.**
- **Location of the TCA cycle**
- **Reactions of occur in mitochondrial matrix, in close proximity to the ETC.**

Reactions of TCA cycle

- Oxidative decarboxylation of pyruvate to acetyl CoA by PDH complex.
- This step is connecting link between glycolysis and TCA cycle.


GLUCOSE
6 C
Glycolysis
2x
PYRUVATE
3 C
CO2
NADH
Pyruvate Dehydrogenase Complex
ACETYL-COA
2 C
CITRATE
6 C
Citrate synthase
Aconitase
ISOCITRATE
NAD
NADH
Isocitrate Dehydrogenase
CO2
ALPHA-KETOGLUTARATE
5 C
Alphaketoglutarate Dehydrogenase
CO2
NAD
NADH
SUCCINYL COA
4 C
Succinyl COA Synthase
GTP
SUCCINATE
Succinate Dehydrogenase
FADH2
QH2
FUMRATE
Fumrase
MALATE
NADH
NAD
Malate Dehydrogenase
OXALOACETATE
4 C


Acetyl-CoA
Citrate synthase
CoA — SH
Oxaloacetate
Malate dehydrogenase
NADH + H+
NAD+
H2O
Citrate
L-Malate
Aconitase
Fe2+
Fluoroacetate
Fumarase
H2O
Cis-aconitate
Fumarate
FADH2
Succinate dehydrogenase
FAD
Malonate
H2O
Aconitase
Fe2+
Succinate
Isocitrate
ATP
NAD+
CoA — SH
Mg2+
ADP + Pi
NADH + H+
Isocitrate dehydrogenase
Succinate thiokinase
Succinyl-CoA
Arsenite
NADH + H+
NAD+
CO2
Oxalosuccinate
α-Ketoglutarate dehydrogenase complex
CoA — SH
CO2
Mn2+
Isocitrate dehydrogenase
α-Ketoglutarate

Reactions of TCA Cycle

- **Step:1 Formation of citrate**
- **Oxaloacetate condenses with acetyl CoA to form Citrate, catalysed by the enzyme citrate synthase**
- **Inhibited by:**
- **ATP, NADH, Citrate - competitive inhibitor of oxaloacetate.**

Steps 2 & 3 Citrate is isomerized to isocitrate

- Citrate is isomerized to isocitrate by the enzyme aconitase
- This is achieved in a two stage reaction of dehydration followed by hydration through the formation of an intermediate -cis-aconiase

Steps 4 & 5 Formation of α-ketoglutarate

- Isocitrate dehydrogenase (ICDH) catalyses the conversion of (oxidative decarboxylation) of isocitrate to oxalosuccinate & then to α-ketoglutarate.
- The formation of NADH & the liberation of CO_2 occure at this stage.
- Stimulated (cooperative) by isocitrate, NAD^+, Mg^{2+}, ADP, Ca^{2+} (links with contraction).
- Inhibited by NADH & ATP

Step: 6 Conversion of α-ketoglutarate to succinyl CoA

- Occurs through oxidative decarboxylation, catalysed by α-ketoglutarate dehydrogenase complex.
- α-ketoglutarate dehydrogenase is an multienzyme complex.
- At this stage of TCA cycle, second NADH is produced & the second CO_2 is liberated.

Step: 7 Formation of succinate

- Succinyl CoA is converted to succinate by succinate thiokinase.
- This reaction is coupled with the phosphorylation of GDP to GTP.
- This is a substrate level phosphorylation.
- GTP is converted to ATP by the enzyme nucleoside diphosphate kinase.

Step: 8 Conversion of succinate to fumarate

- Succinate is oxidized by succinate dehydrogenase to fumarate.
- This reaction results in the production of $FADH_2$.
- Step: 9 Formation of malate: The enzyme fumarase catalyses the conversion of fumarate to malate with the addition of H_2O.

Step:10 Conversion of malate to oxaloacetate

- Malate is then oxidized to oxaloacetate by malate dehydrogenase.
- The third & final synthesis of NADH occurs at this stage.
- The oxaloacetate is regenerated which can combine with another molecule of acetyl CoA & continue the cycle.

Regeneration of oxaloacetate

- The TCA cycle basically involves the oxidation of acetyl CoA to CO_2 with the simultaneous regeneration of oxaloacetate.
- There is no net consumption of oxaloacetate or any other intermediate in the cycle.

Significance of TCA cycle

- Complete oxidation of acetyl CoA.
- ATP generation.
- Final common oxidative pathway.
- Integration of major metabolic pathways.
- Fat is burned on the wick of carbohydrates.
- Excess carbohydrates are converted as neutral fat
- No net synthesis of carbohydrates from fat.
- Carbon skeleton of amino acids finally enter the TCA cycle.

Requirement of O_2 by TCA cycle

- There is no direct participation of O_2 in TCA cycle.
- Operates only under aerobic conditions.
- This is due to, NAD^+ & FAD required for the operation of the cycle can be regenerated in the respiratory chain only in presence of O_2.
- Therefore, citric acid cycle is strictly aerobic.

Energetics of TCA Cycle

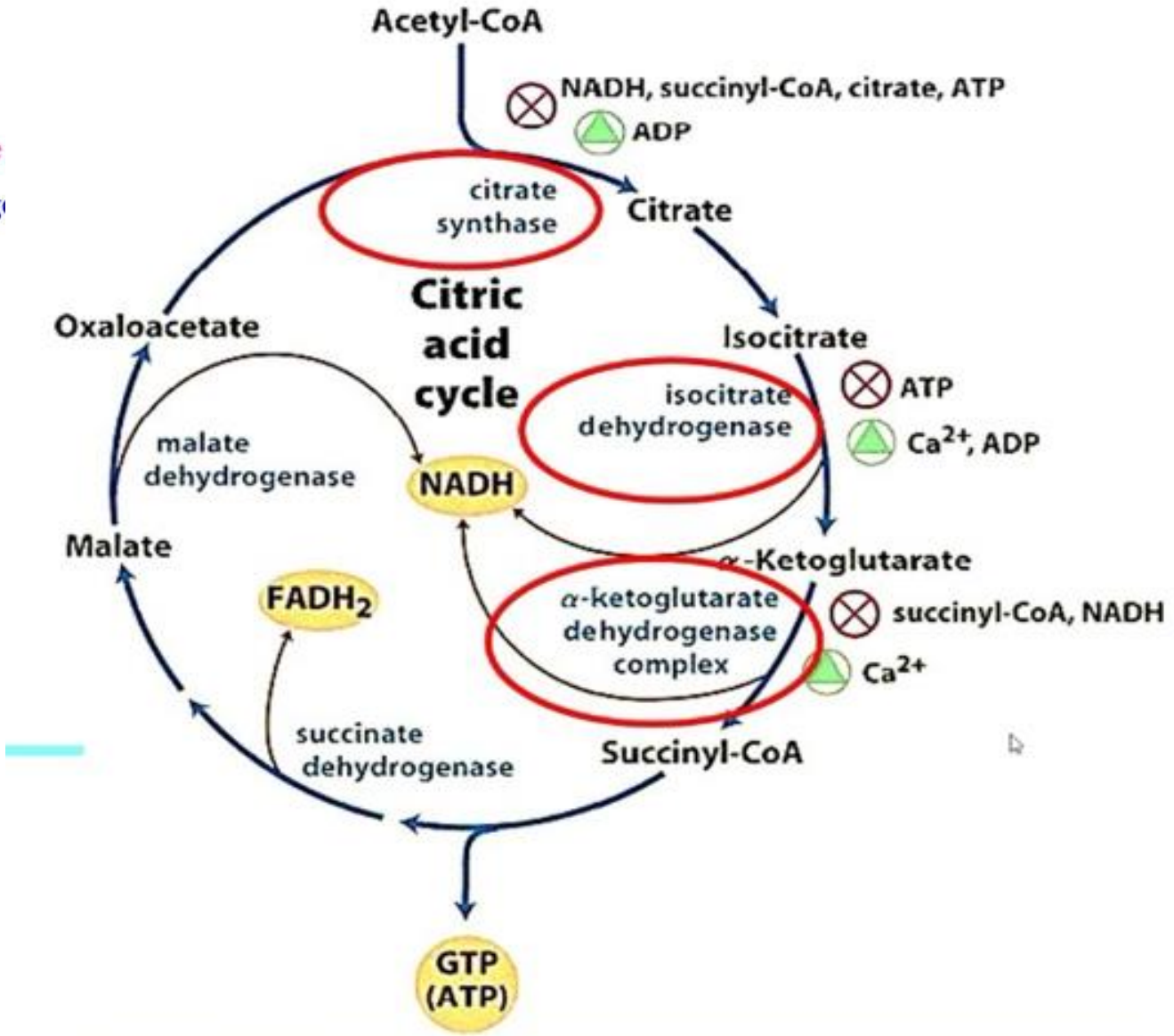
- Oxidation of 3 NADH by ETC coupled with oxidative phosphorylation results in the synthesis of 9ATP.
- $FADH_2$ leads to the formation of 2ATP.
- One substrate level phosphorylation.
- Thus, a total of 12 ATP are produced from one acetyl CoA.

Energetics of TCA cycle

Step No.	Enzyme	Coenzyme	ATPs generated
4	Isocitrate dehydrogenase	NADH	3
6	α-Ketoglutarate dehydrogenase	NADH	3
7	Succinic thiokinase	GTP	1
8	Succinate dehydrogenase	FADH2	2
10	Malate dehydrogenase	NADH	3
Total ATPs generated			12

Regulation of TCA Cycle

- **Three regulatory enzymes**
  1. **Citrate synthase**
  2. **Isocitrate dehydrogenase**
  3. **α-ketoglutarate dehydrog**

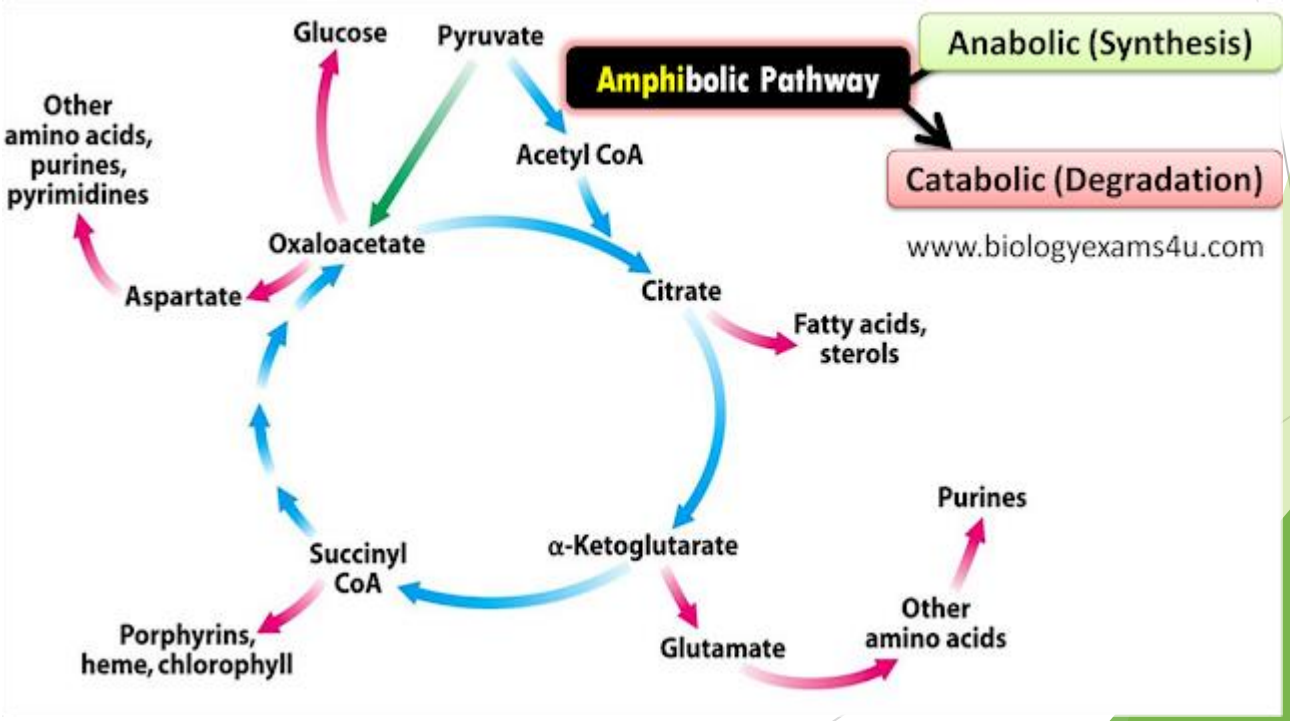


Inhibitors of TCA Cycle

- Aconitase is inhibited by fluoro-acetate.
- This is a non-competitive inhibition.
- Alpha ketoglutarate is inhibited by Arsenite.
- This is also a non-competitive.
- Succinate dehydrogenase is inhibited by malonate.
- This is competitive inhibition.

Amphibolic nature of the TCA cycle

- **TCA cycle is both catabolic & anabolic in nature, called as amphibolic.**
- **Since various compounds enter into or leave from TCA cycle, it is sometimes called as metabolic traffic circle.**



Anaplerosis or anaplerotic reactions

- **The reactions concerned to replenish or to fill up the intermediates of citric acid cycle are called anaplerotic reactions or Anaplerosis**

(Glucose, Fatty Acids, Amino Acids)