

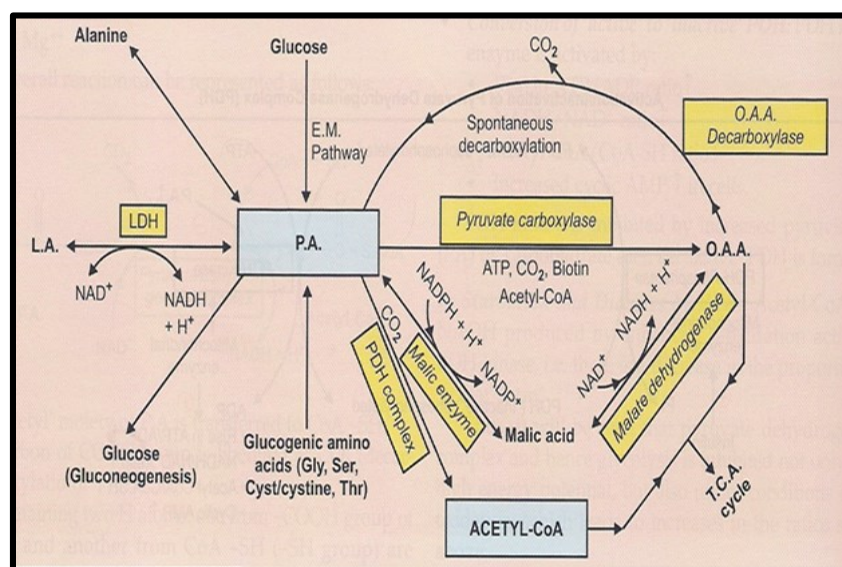
**The citric acid cycle (TCA) cycle
Tricarboxylic acid cycle**

Formation of pyruvic acid (P.A.) in the body:

- 1- From oxidation of glucose (glycolysis).
- 2- From lactic acid by oxidation.
- 3- Deamination of alanine.
- 4- Glucogenic amino acids-pyruvate forming.
- 5- Decarboxylation of oxaloacetic acid (OAA)

Fate of pyruvic acid (P.A.):

- 1- Form acetyl CoA by oxidative decarboxylation (in presence of O₂)
- 2- Forms lactic acid by reduction (in absence of O₂).
- 3- Forms alanine by amination.
- 4- Forms glucose (gluconeogenesis).
- 5- Forms malic acid → to O.A.A (oxaloacetic acid).
- 6- Forms oxaloacetic acid (O.A.A) by CO₂-fixation reaction (carboxylation).



Before pyruvate can enter the TCA cycle, it must be transported into the mitochondria via a special pyruvate transporter that aids its passage across the inner mitochondrial membrane. Within the mitochondria, pyruvate is oxidatively decarboxylated to acetyl-CoA; this reaction is catalyzed by sequentially multienzyme complex (pyruvate dehydrogenase complex).

The citric acid cycle (TCA) cycle

1- TCA cycle (tricarboxylic acid cycle), also known as the citric acid cycle or the Krebs' cycle, is the major energy production pathways in the body.

*The cycle occurs in the mitochondria (Aerobic phase (requires oxygen)).

2- It is a cyclic process.

3-The cycle involves a sequence of compounds inter-related by oxidation reduction and other reactions which finally produces [CO₂ and H₂O].

4- It is the final common pathway of breakdown or catabolism of carbohydrates, fats and proteins.

5-Acetyl CoA derived mainly from oxidation of either glucose or β -oxidation of FA and partly from certain amino acids combines with oxaloacetic acid (OAA) to form "citrate" the first reaction of TCA cycle.

In this reaction acetyl CoA transfers its' acetyl-group' (2 C) to OAA.

6- By stepwise dehydrogenations and loss of two molecules of CO₂, accompanied by internal re-arrangements, the citric acid is reconverted to OAA, which again starts the cycle by taking up another acetyl group from acetyl-CoA.

7-All the enzymes of the TCA cycle are in the mitochondrial matrix, except succinate dehydrogenase which is in the inner mitochondrial membrane.

8-Electrons are transferred by the cycle to NAD⁺ (Nicotinamide Adenine Dinucleotide) and FAD (Flavin Adenine Dinucleotide).

9-As the electrons subsequently are passed to O₂ by the electron transport chain, ATP is generated by the process of oxidative phosphorylation.

10-ATP is also generated from GTP (Guanosine Triphosphate), produced in one reaction of the cycle by substrate level phosphorylation.

11-The whole process is aerobic, requiring O₂ as the final oxidant of the reducing equivalents. Absence of O₂ (anoxia) or partial deficiency of O₂ (hypoxia) causes total or partial inhibition of the cycle.

12-The H atoms removed in the successive dehydrogenations are accepted by corresponding coenzymes. Reduced coenzymes transfer the reducing equivalents to electron-transport system, where oxidative phosphorylation product ATP molecules.

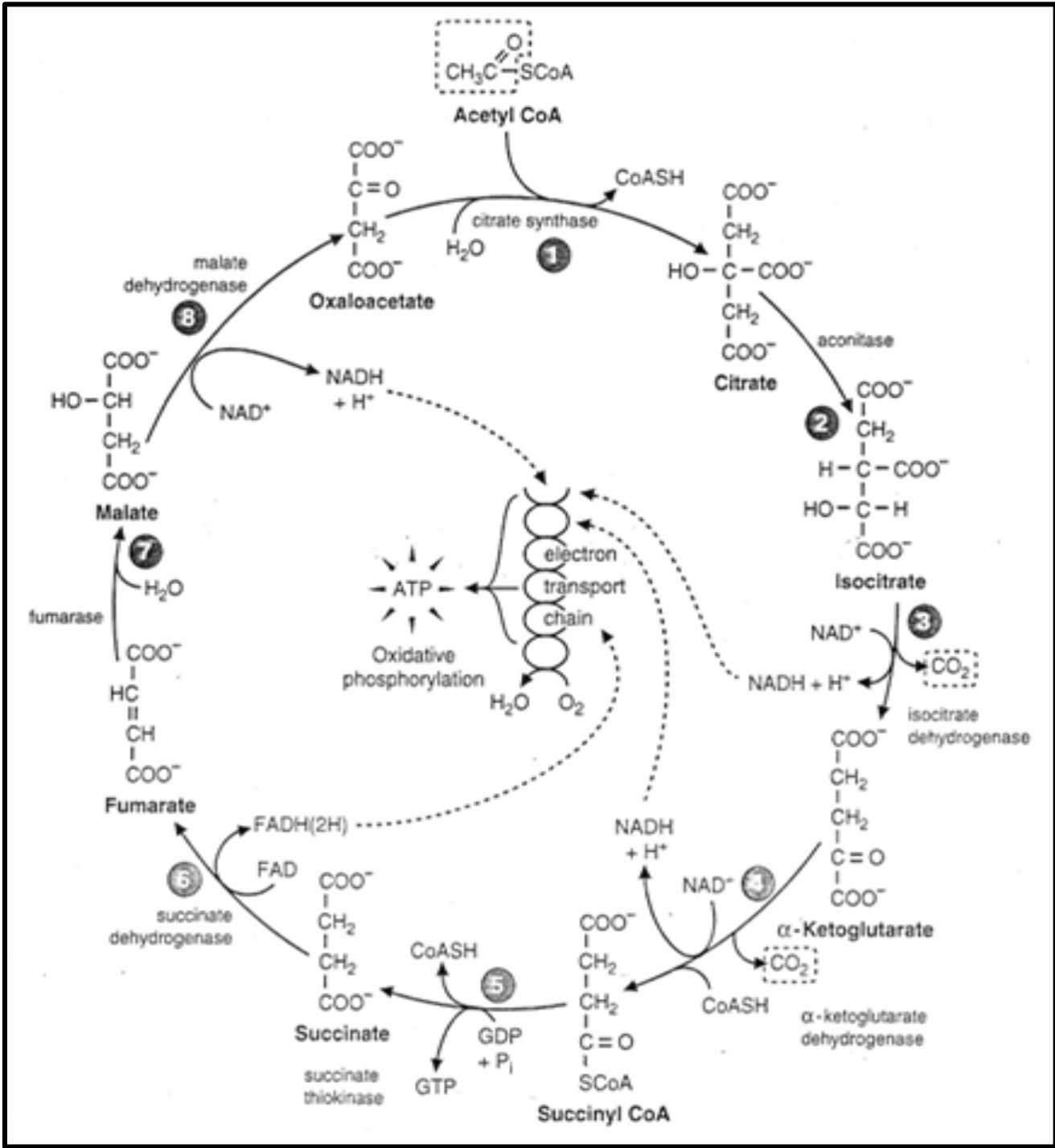
There are three key enzymes in TCA cycle:

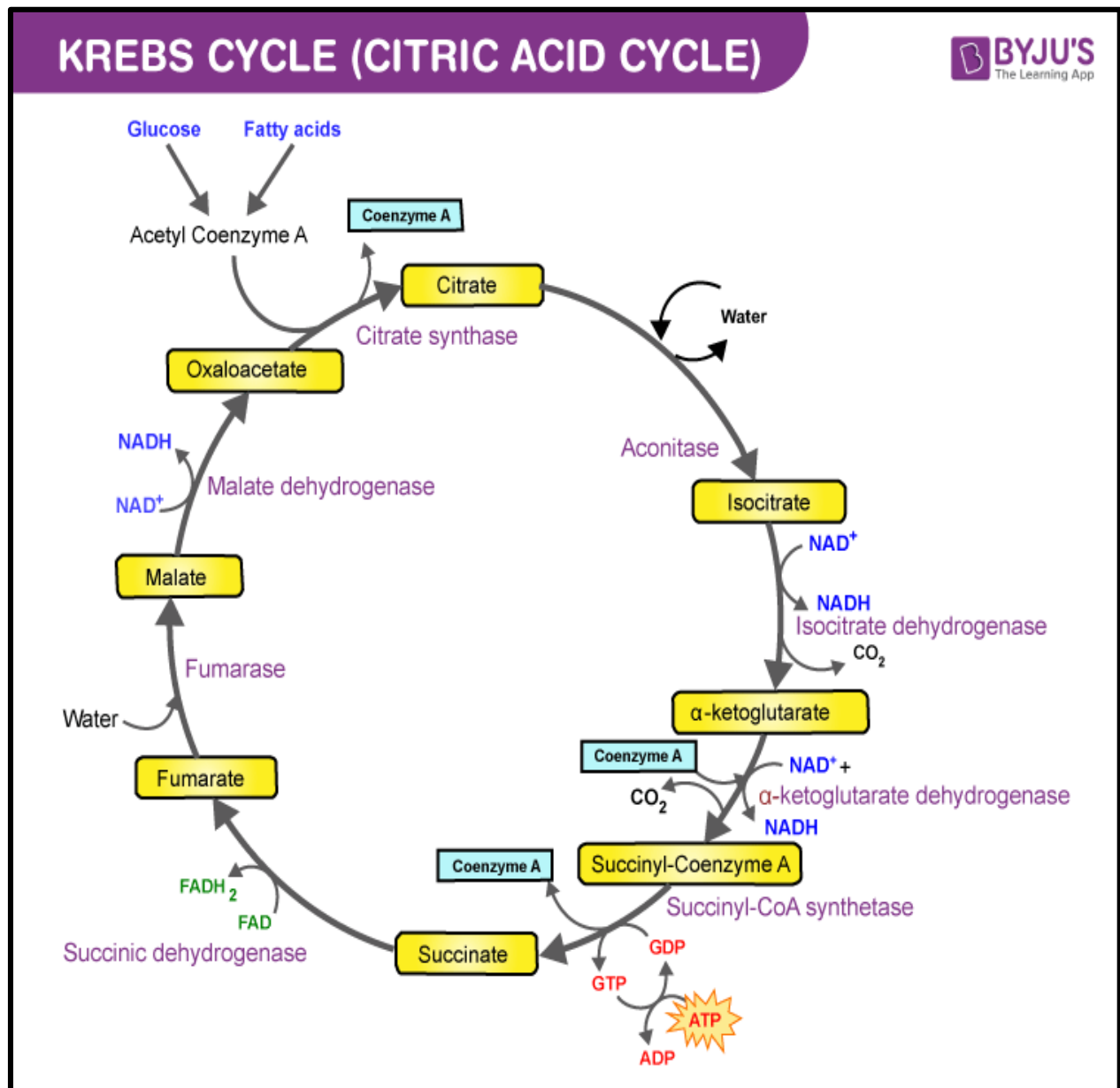
1-Citrate synthase (1)

2- Isocitrate dehydrogenase (I.C.D)

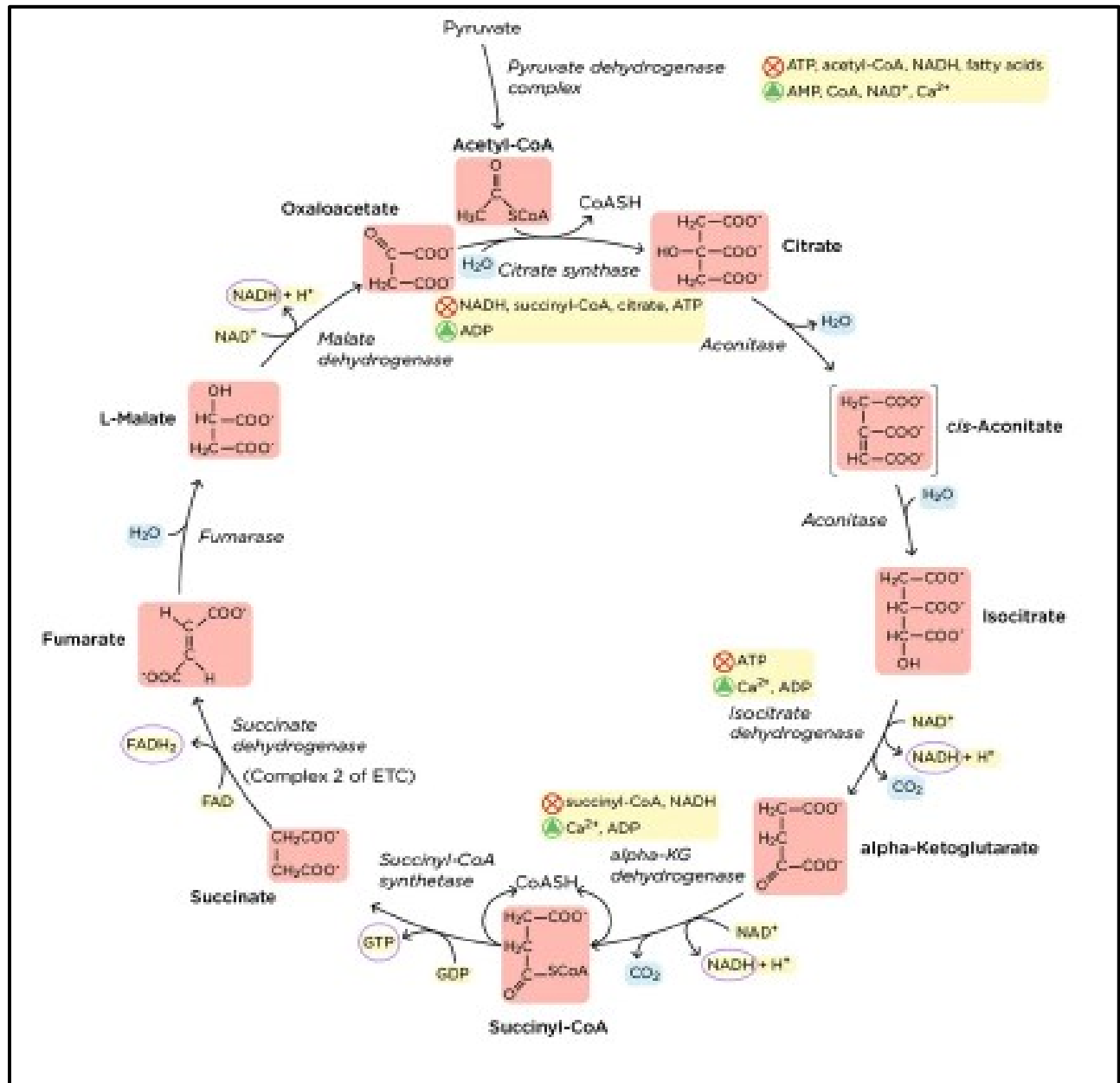
3- α -ketoglutarate dehydrogenase or named α -oxoglutarate dehydrogenase

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Energy produced by the TCA cycle:

NOTE: 1NADH = 3ATP

1GPT = 1ATP

1FADH₂ = 2ATP

Reactions	No. of ATP formed
1. 2 isocitrate → 2 α-ketoglutarate (2 NADH + 2H ⁺) (2 × 3)	6
2. 2 α-ketoglutarate → 2 succinyl CoA (2 NADH + 2H ⁺) (2 × 3)	6
3. 2 succinyl CoA → 2 succinate (2 GTP = 2ATP)	2
4. 2 succinate → 2 Fumarate (2 FADH ₂) (2 × 2)	4
5. 2 malate → 2 oxaloacetate (2 NADH + 2H ⁺) (2 × 3)	6
Total No. of ATP formed	24

Biomedical importance of TCA cycle:

1- Final common pathway for carbohydrates, proteins and fats, through formation of

2- Carbon unit acetyl-CoA.

- Acetyl-CoA is oxidized to CO₂ and H₂O giving out energy (Catabolic role).

- Intermediates of TCA cycle play a major role in synthesis also like heme formation, formation of non essential amino acids, FA synthesis, cholesterol and steroid synthesis (anabolic role).

- TCA cycle is called Amphibolic in nature because TCA cycle has dual role catabolic and anabolic.