Biochemistry

Metabolism of Carbohydrates

Dr Jilna Alex N

METABOLISM

GLYCOGENESIS – Biosynthesis of glycogen

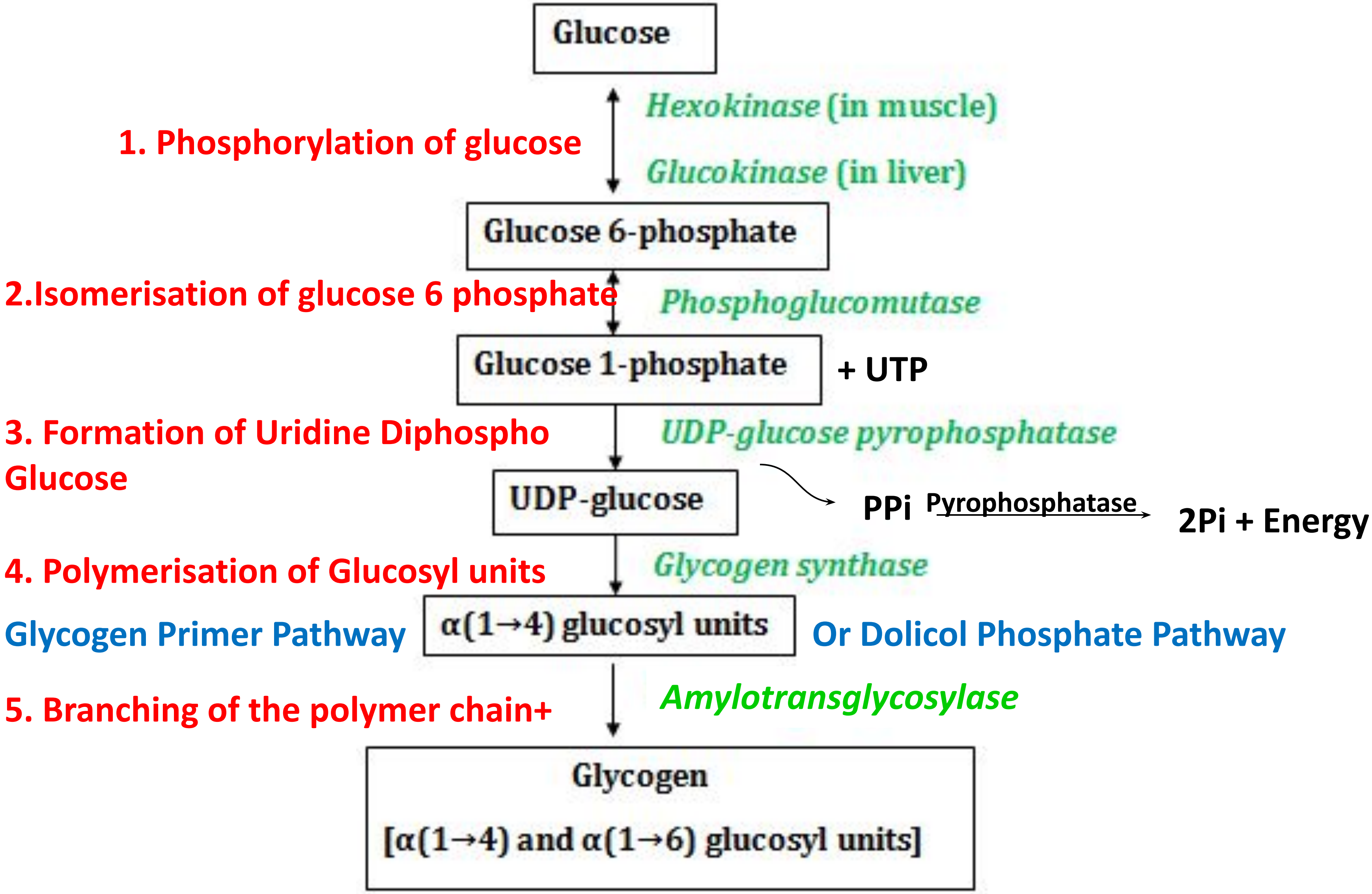
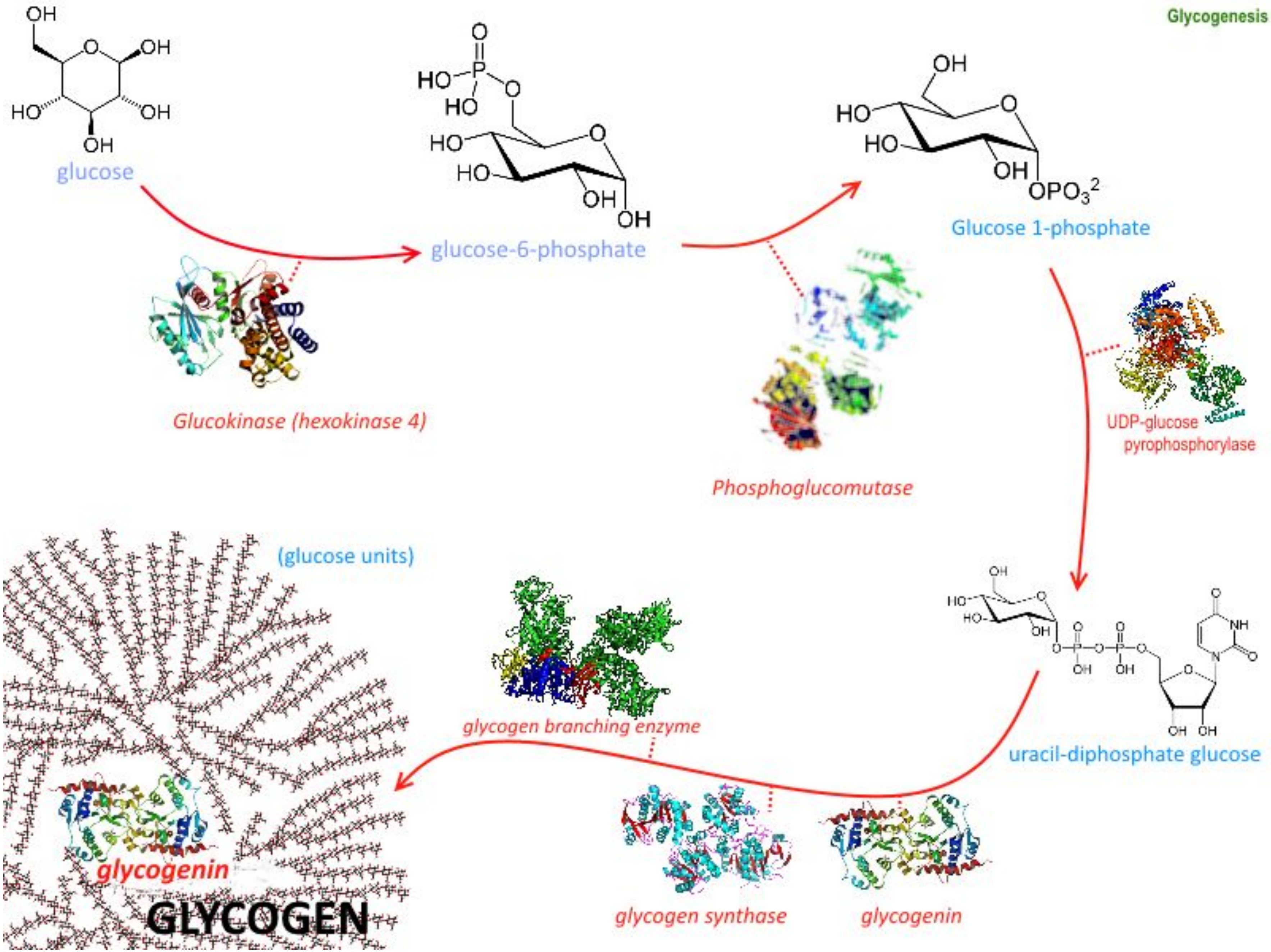


Diagram: Steps of glycogenesis



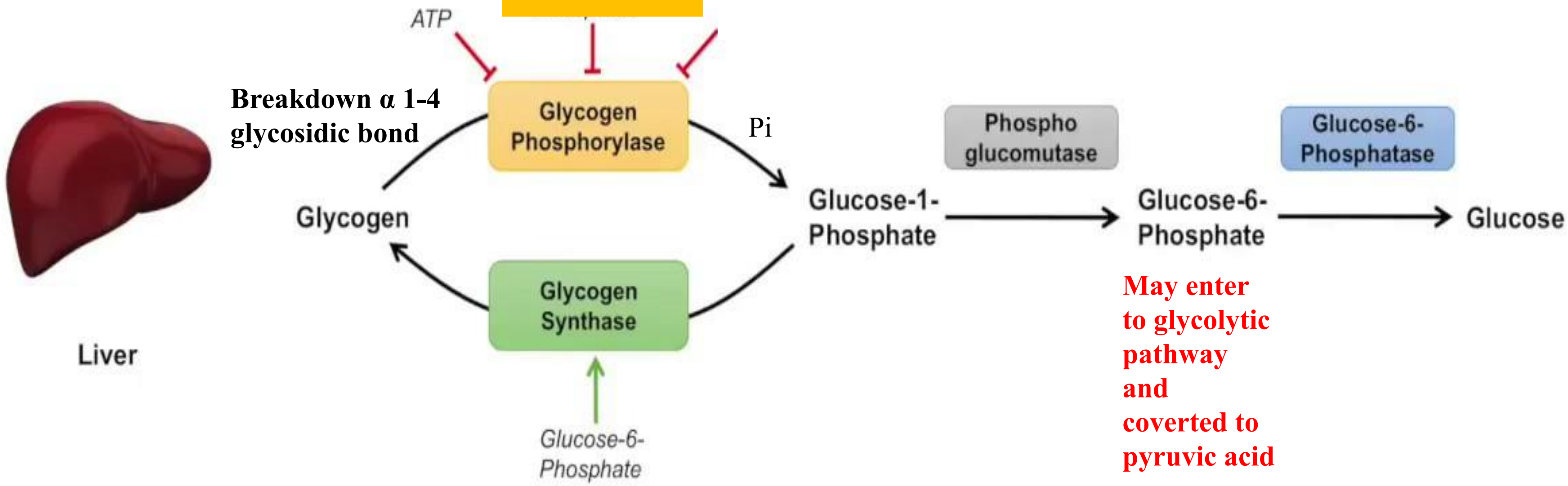
Glycogenesis
glucose
glucose-6-phosphate
Glucose 1-phosphate
Glucokinase (hexokinase 4)
Phosphoglucomutase
UDP-glucose
pyrophosphorylase
uracil-diphosphate glucose
(glucose units)
glycogen branching enzyme
glycogen synthase
glycogenin
glycogenin
GLYCOGEN

GLYCOGENOLYSIS

A) PHOPHOROLYSIS

Forms unbranched linear chain **Glucan transferase**

Breakdown α 1-6 glycosidic bond **Glucosidase**



B) HYDROLYSIS / AMYLOSIS

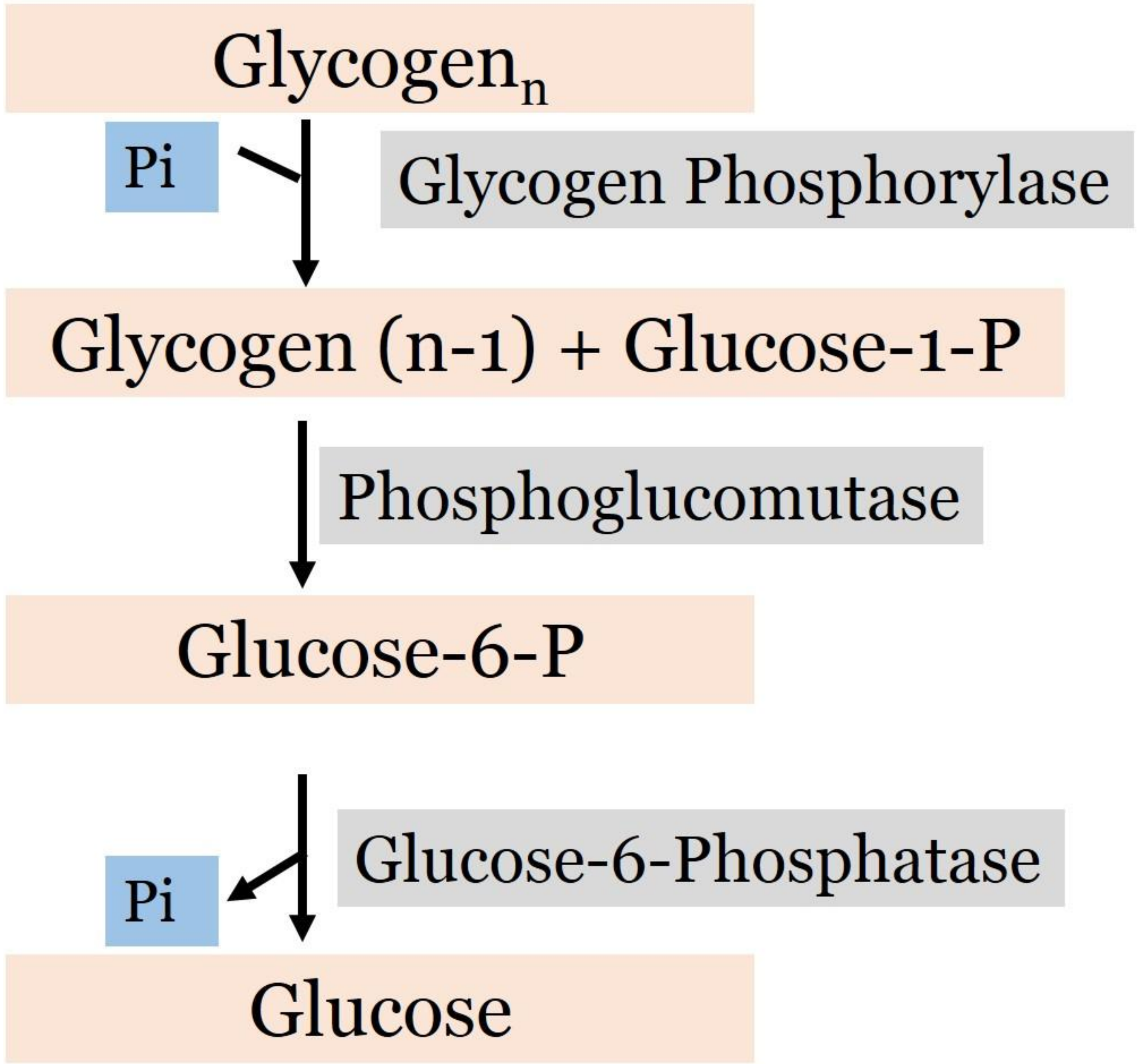
1. Alpha Amylosis

Glycogen --α amylase + H_2O-- Oligosaccharides --α glucosidase-- Glucose

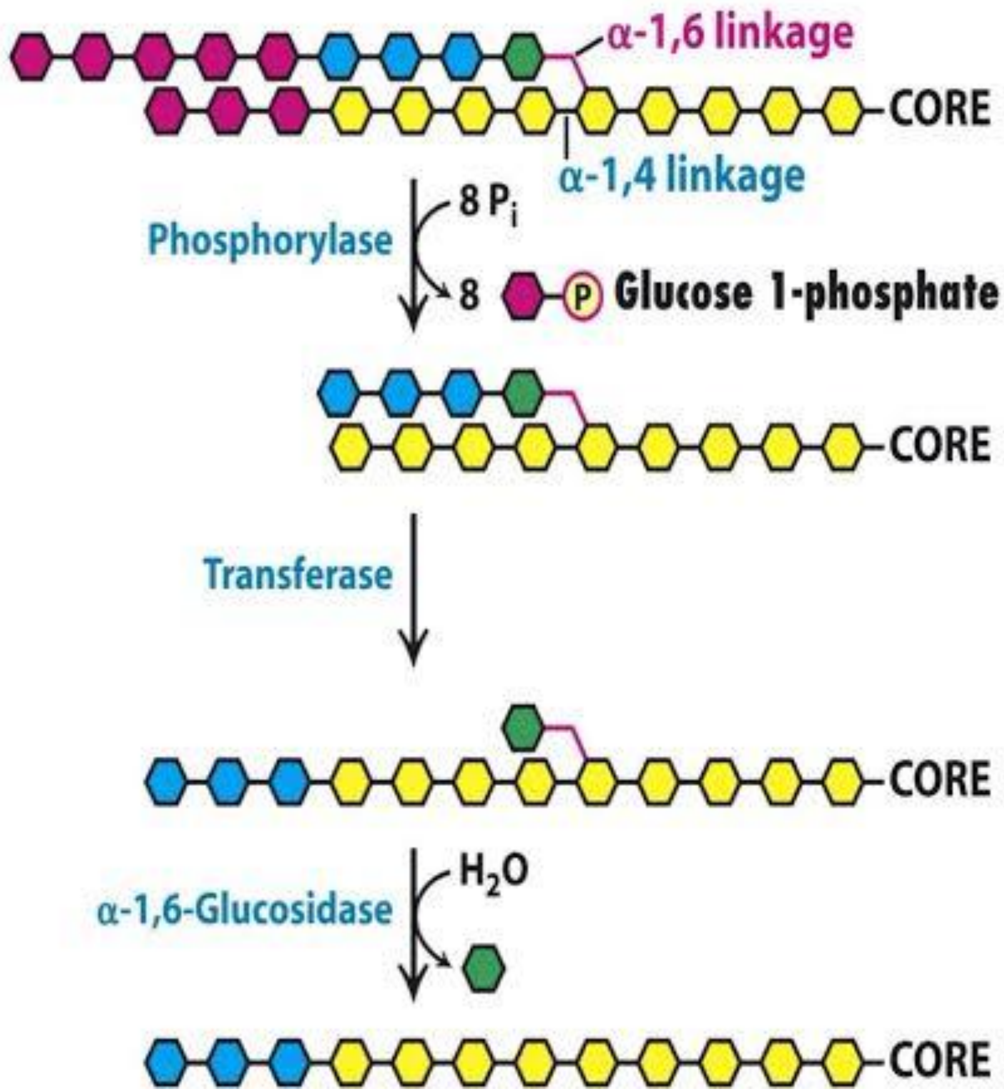
2. Gamma Amylosis

Glycogen --ɾ amylase + H_2O-- ɾ Dextrin + Glucose

ɾ Dextrin --α amylase-- Glucose units

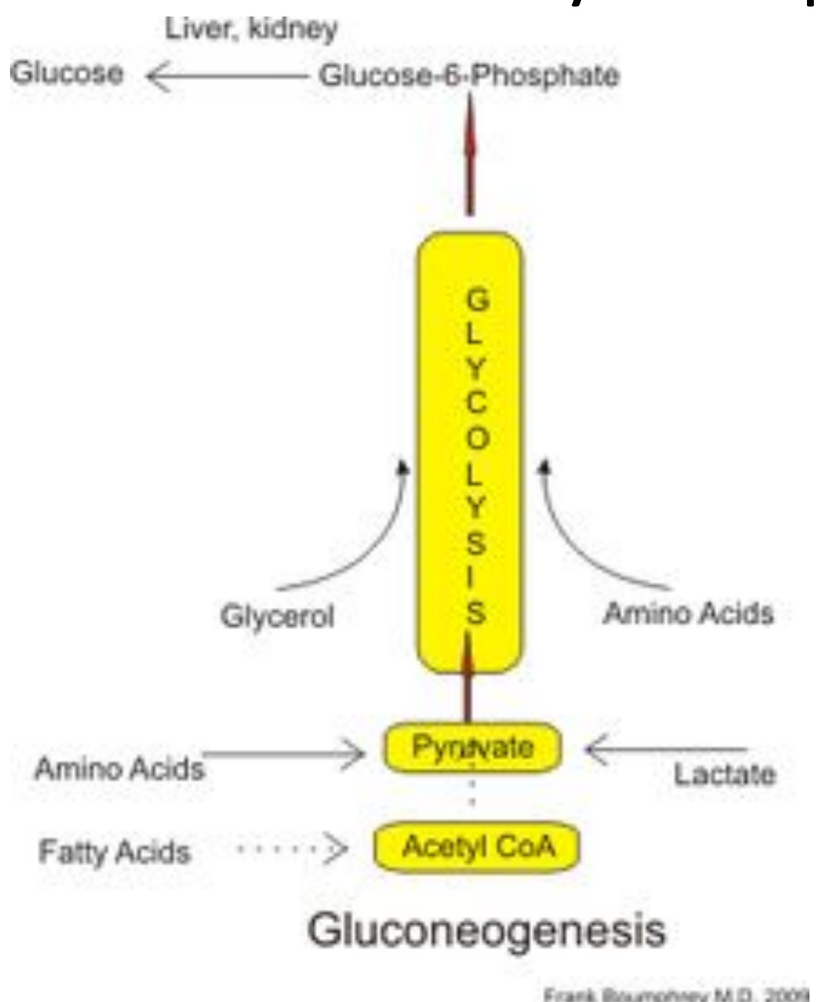

Glycogen$_n$
Pi
Glycogen Phosphorylase
Glycogen (n-1) + Glucose-1-P
Phosphoglucomutase
Glucose-6-P
Glucose-6-Phosphatase
Pi
Glucose

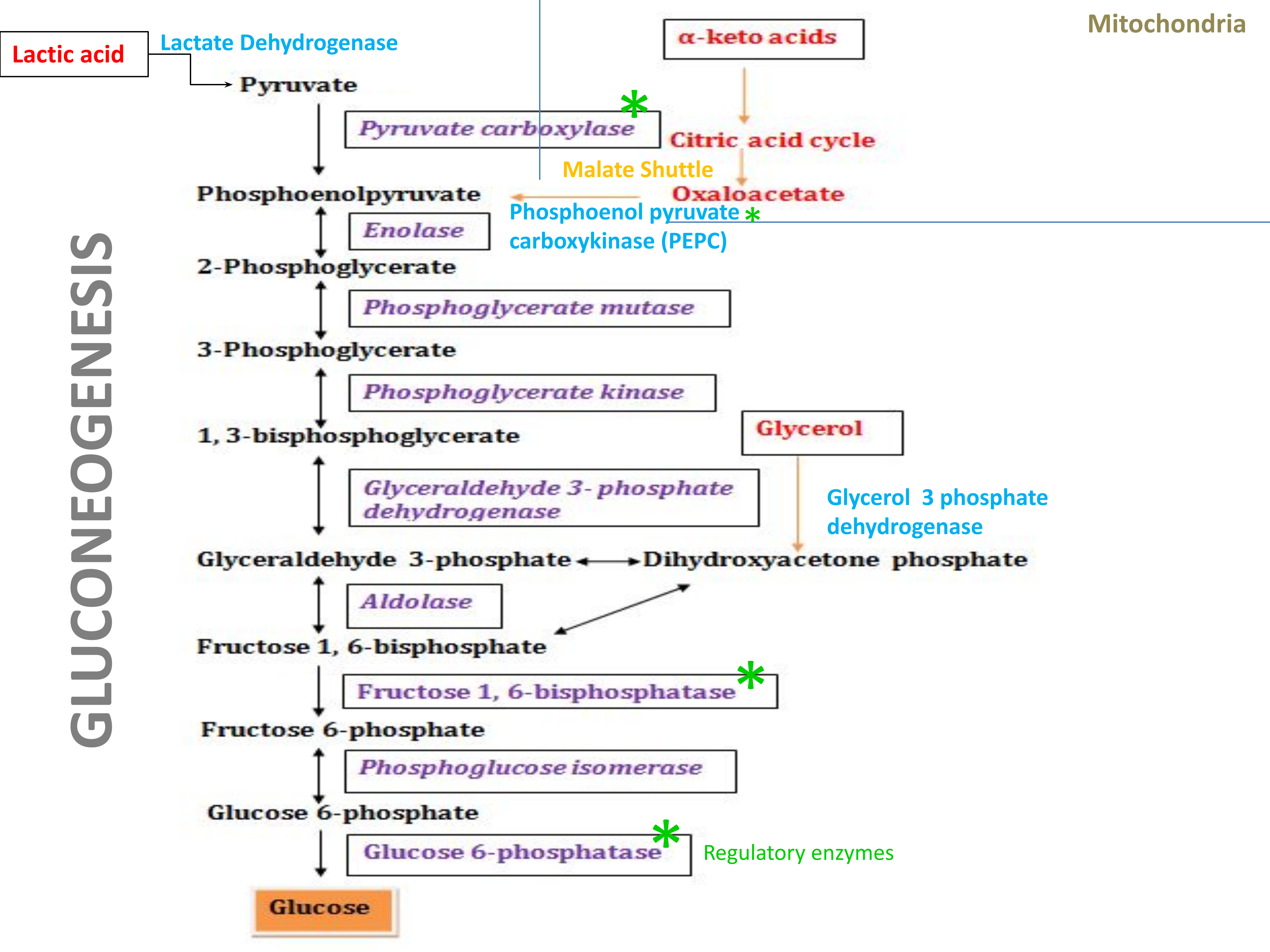
Glycogen degradation cycle



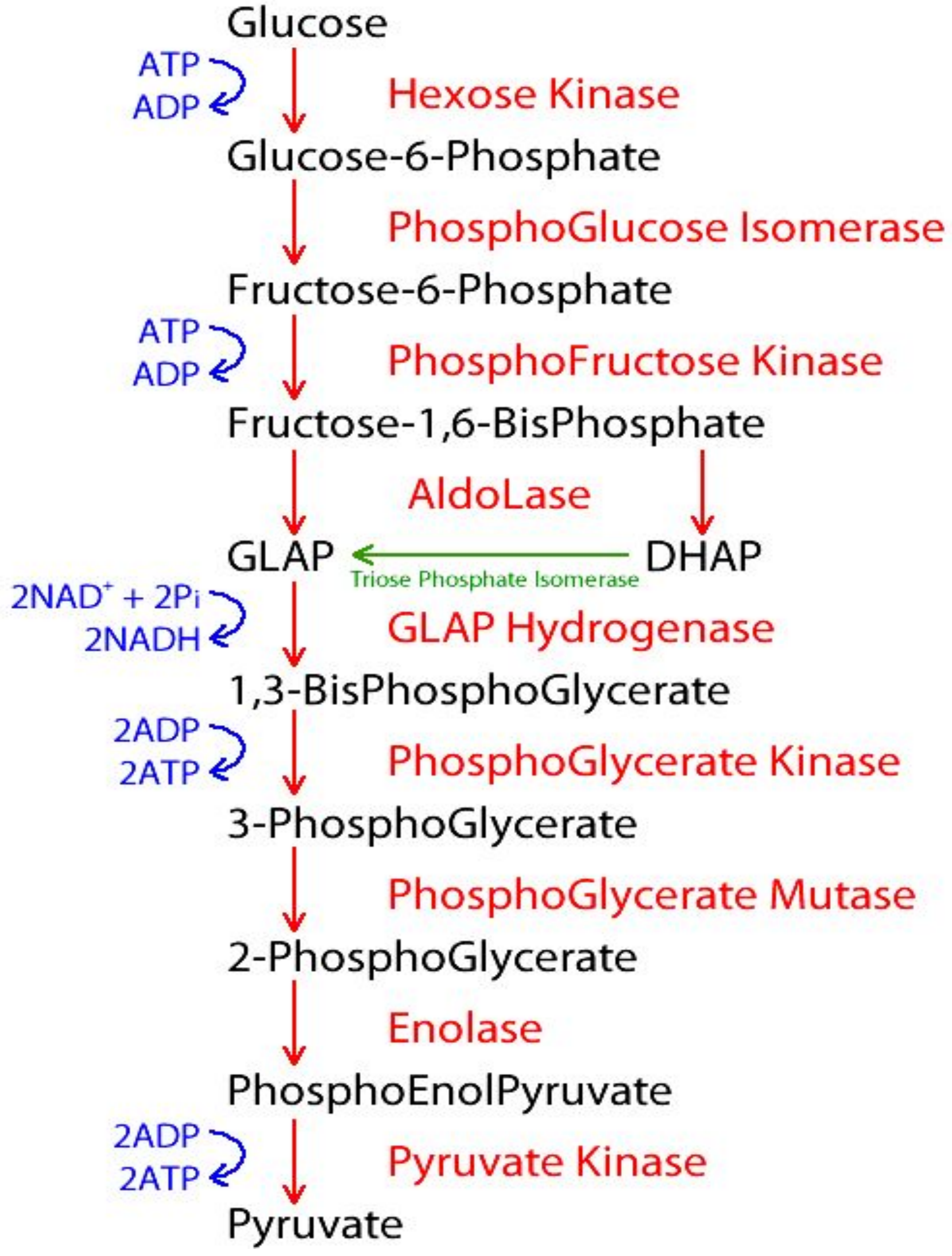
GLUCONEOGENESIS

- Is the metabolic process by which organisms produce sugars (namely glucose) for catabolic reactions from non-carbohydrate precursors




GLUCONEOGENESIS
Mitochondria
Lactic acid
Lactate Dehydrogenase
Pyruvate
Pyruvate carboxylase *
α-keto acids
Citric acid cycle
Malate Shuttle
Oxaloacetate
Phosphoenolpyruvate
Phosphoenol pyruvate carboxykinase (PEPC) *
Enolase
2-Phosphoglycerate
Phosphoglycerate mutase
3-Phosphoglycerate
Phosphoglycerate kinase
1, 3-bisphosphoglycerate
Glycerol
Glyceraldehyde 3- phosphate dehydrogenase
Glycerol 3 phosphate dehydrogenase
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
Aldolase
Fructose 1, 6-bisphosphate
Fructose 1, 6-bisphosphatase *
Fructose 6-phosphate
Phosphoglucose isomerase
Glucose 6-phosphate
Glucose 6-phosphatase *
Regulatory enzymes
Glucose

GLYCOLYSIS

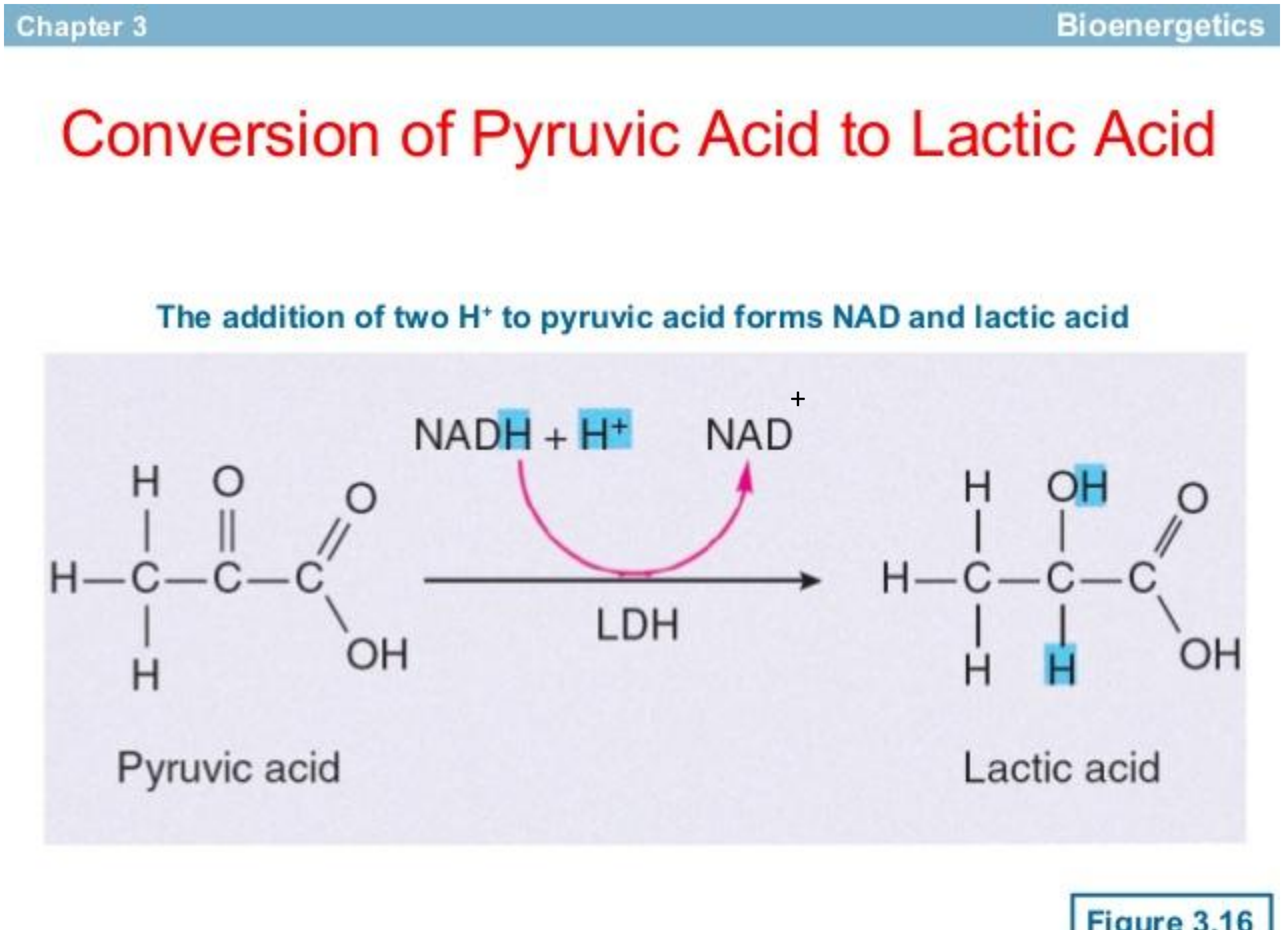


Glucose
ATP
ADP
Hexose Kinase
Glucose-6-Phosphate
PhosphoGlucose Isomerase
Fructose-6-Phosphate
ATP
ADP
PhosphoFructose Kinase
Fructose-1,6-BisPhosphate
AldoLase
GLAP
DHAP
Triose Phosphate Isomerase
2NAD+ + 2Pi
2NADH
GLAP Hydrogenase
1,3-BisPhosphoGlycerate
2ADP
2ATP
PhosphoGlycerate Kinase
3-PhosphoGlycerate
PhosphoGlycerate Mutase
2-PhosphoGlycerate
Enolase
PhosphoEnolPyruvate
2ADP
2ATP
Pyruvate Kinase
Pyruvate

Role of NADH- Bottleneck in glycolysis

- For every glucose molecules in glycolytic pathway 2NAD molecules are reduced to 2NADH + $2H^+$ during oxidative phosphorylation of two molecules of glyceraldehyde 3 phosphate.
- The stock of NAD^+ is within the cell is very much limited.
- This problem is solved by the reconversion of NADH to NAD^+ during mitochondrial oxidative phosphorylation.
- In anaerobiosis this is not possible due to absence of oxygen

- In anaerobiosis NAD^+ is uninterruptedly provided by NADH dependent reduction of pyruvic acid to lactic acid in cytoplasm



Energy balance sheet of Glycolysis

	ATP produced	ATP utilized	Net energy
In absence of oxygen (anaerobic glycolysis)	4 ATP (Substrate level phosphorylation) 2ATP from 1,3 DPG. 2ATP from phosphoenol pyruvate	2ATP From glucose to glucose -6-p. From fructose -6-p to fructose 1,6 p.	2 ATP
In presence of oxygen (aerobic glycolysis)	4 ATP (substrate level phosphorylation) 2ATP from 1,3 BPG. 2ATP from phosphoenol pyruvate.	2ATP -From glucose to glucose -6-p. From fructose -6-p to fructose 1,6 p.	6 ATP Or 8 ATP
	+ 4ATP or 6ATP (from oxidation of 2 NADH + H in mitochondria).		

Importance

- The only metabolic pathway common to all cells
- Only energy yielding process under oxygen free anaerobic condition
- Supplies Carbon skeleton for synthesis of non essential amino acids and glycerol part of alcohol

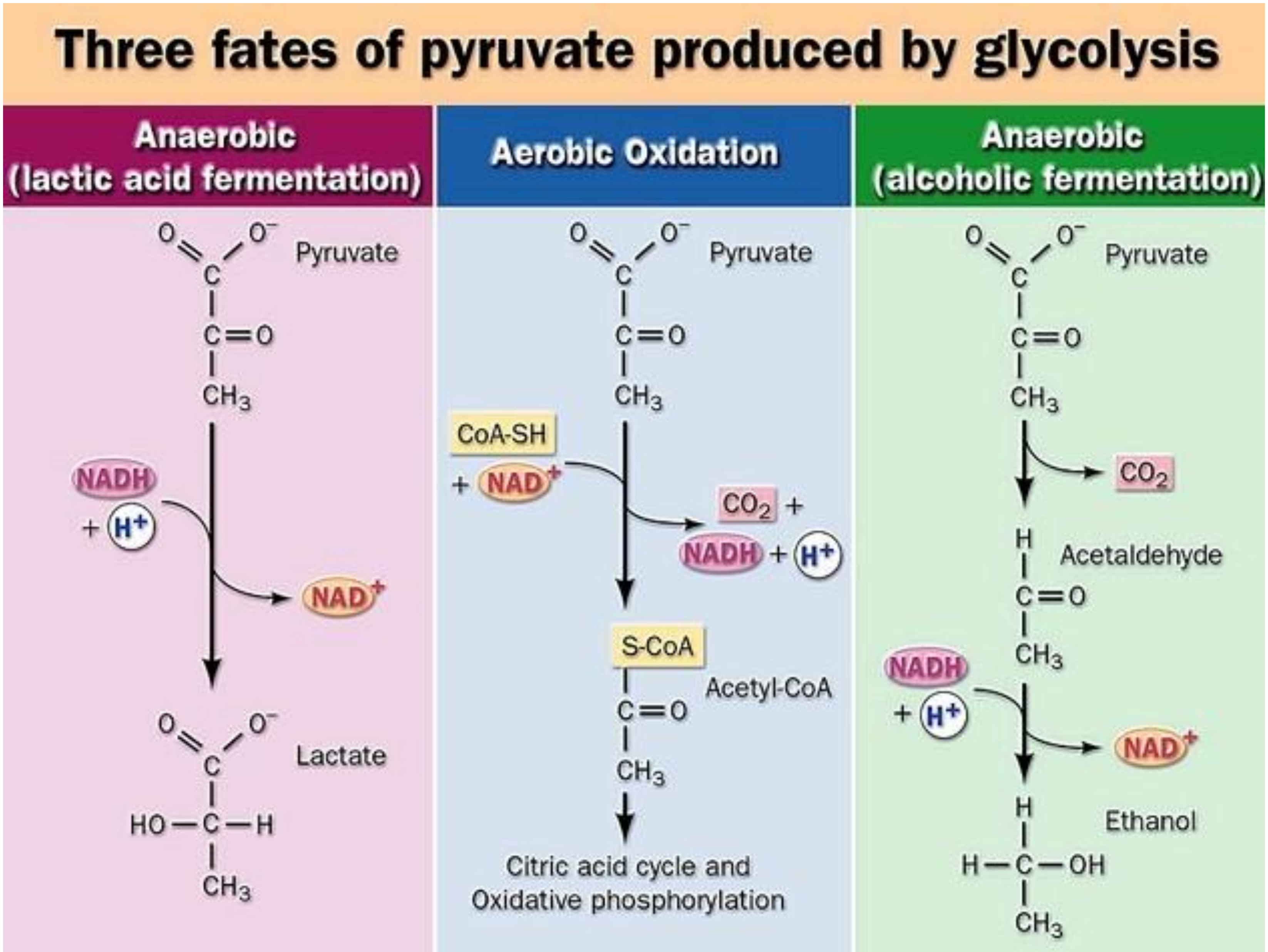
PASTEUR EFFECT

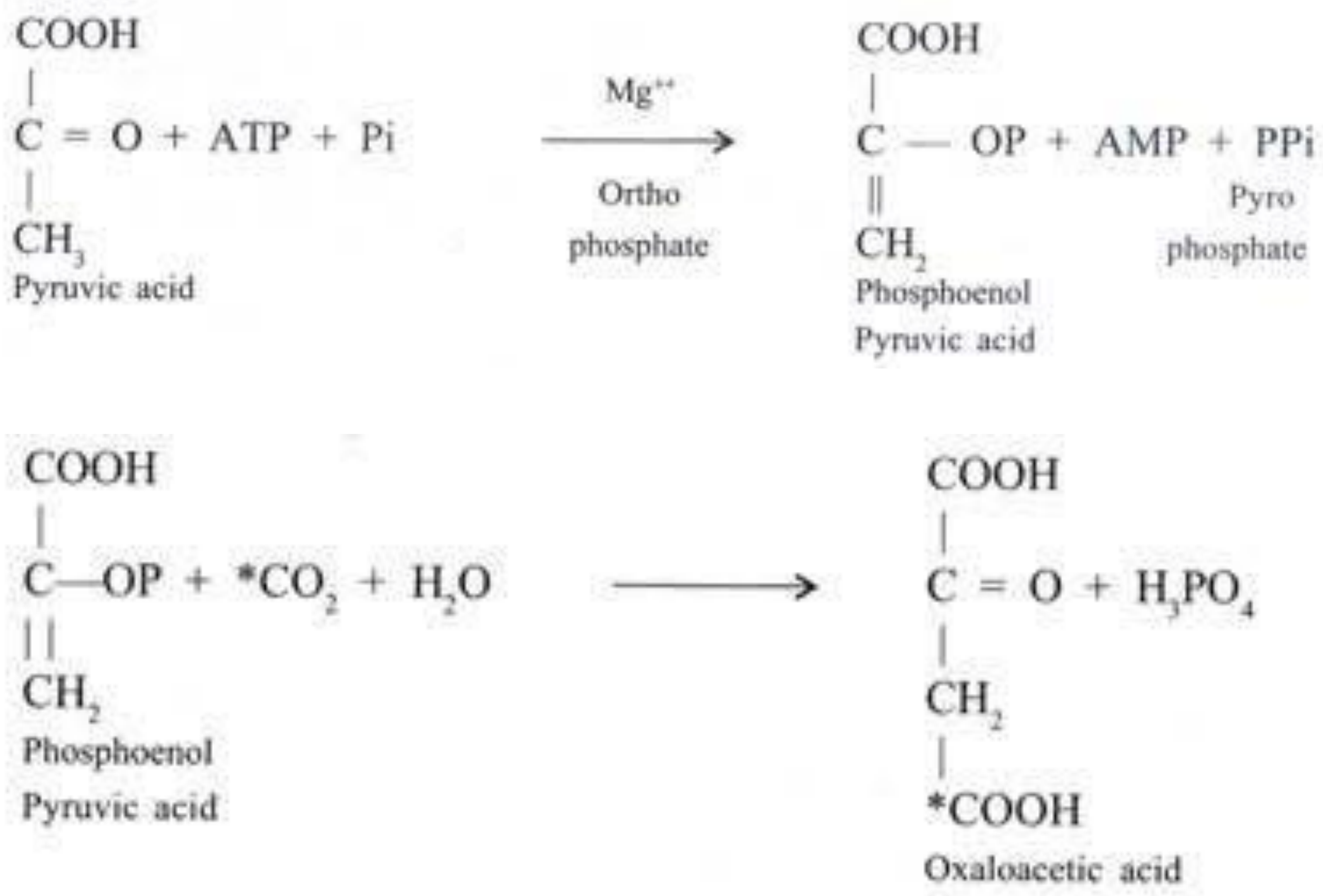
- Suppression of anaerobic respiration by oxygen
- Presence of oxygen increase aerobic respiration – a process that will consume most of the cellular ADP and Pi
- As a result glycolysis and fermentation will not get sufficient supply of them to proceed.
- Further, ADP and Pi are the activators of some glycolytic enzymes and ATP is an allosteric inhibitor of glycolytic enzyme phosphofructo kinase. This all together decrease rate of glycolysis in the cell

CRABTREE EFFECT

- Reversal of Pasteur effect
- Is the suppression of aerobic respiration by high concentration of glucose
- This is due to increased competition between glycolytic and aerobic process for ADP, Pi and Pi

Fate of pyruvic acid

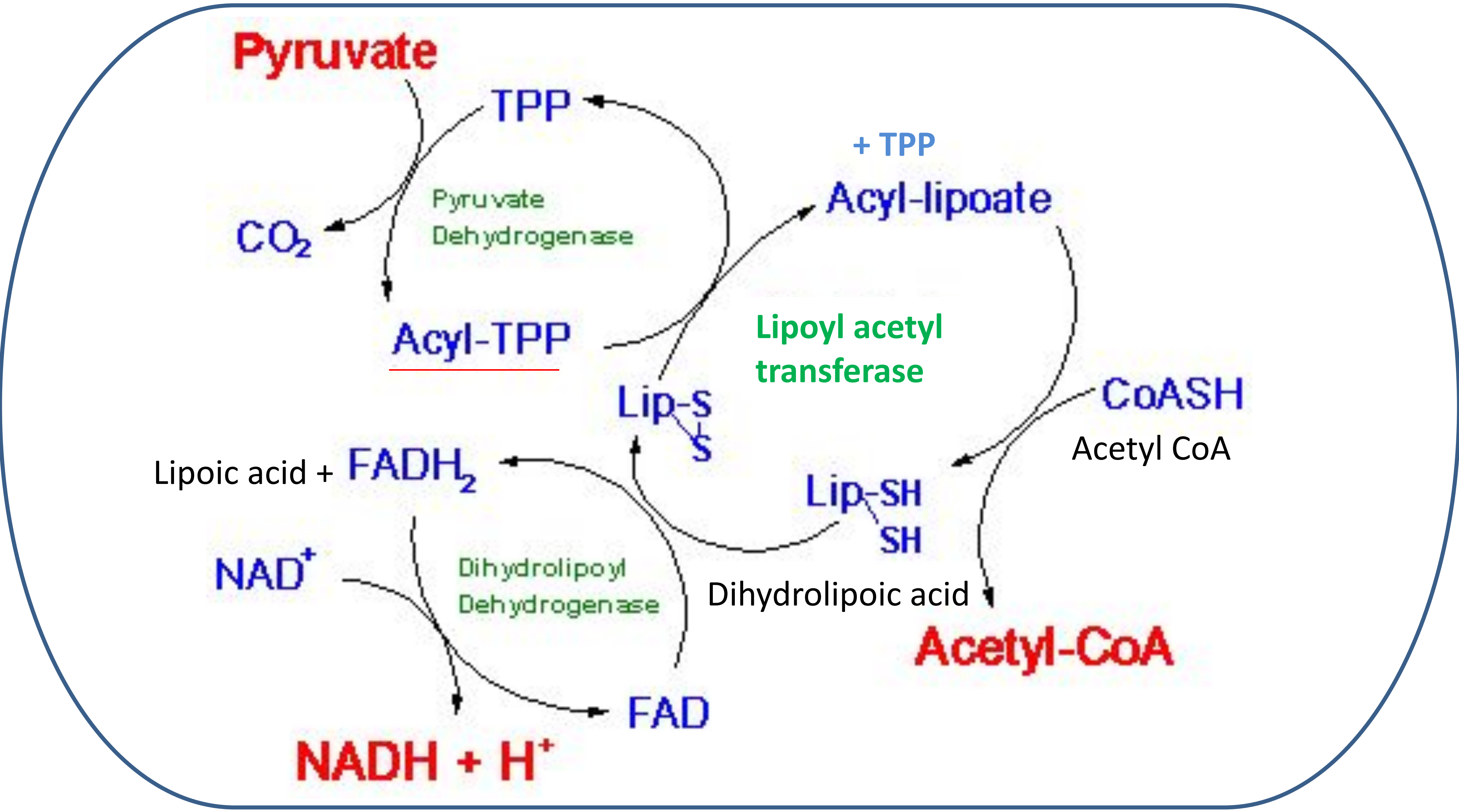




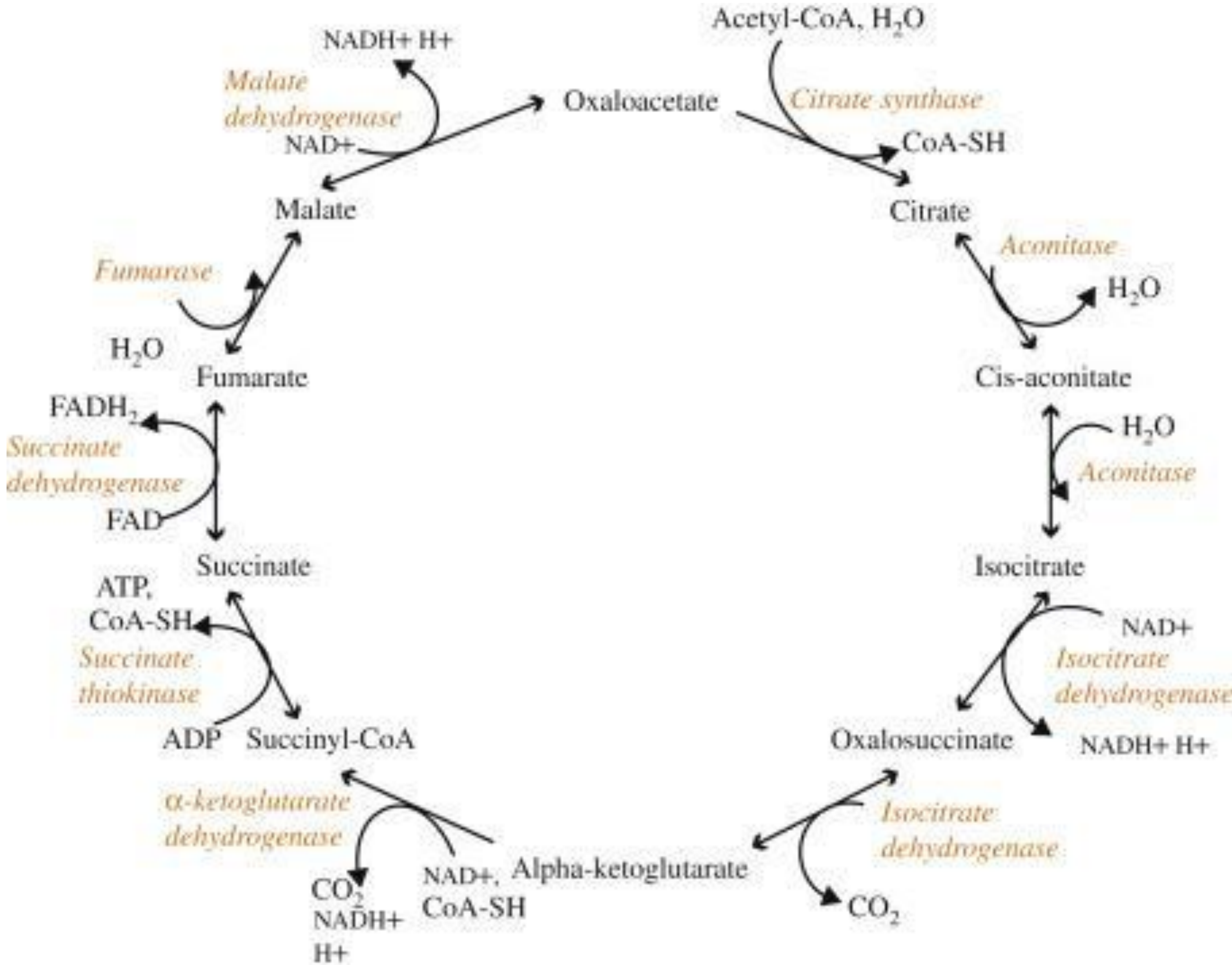
FORMATION OF OXALO ACETIC ACID

Conversion of Pyruvic acid to Acetyl COA

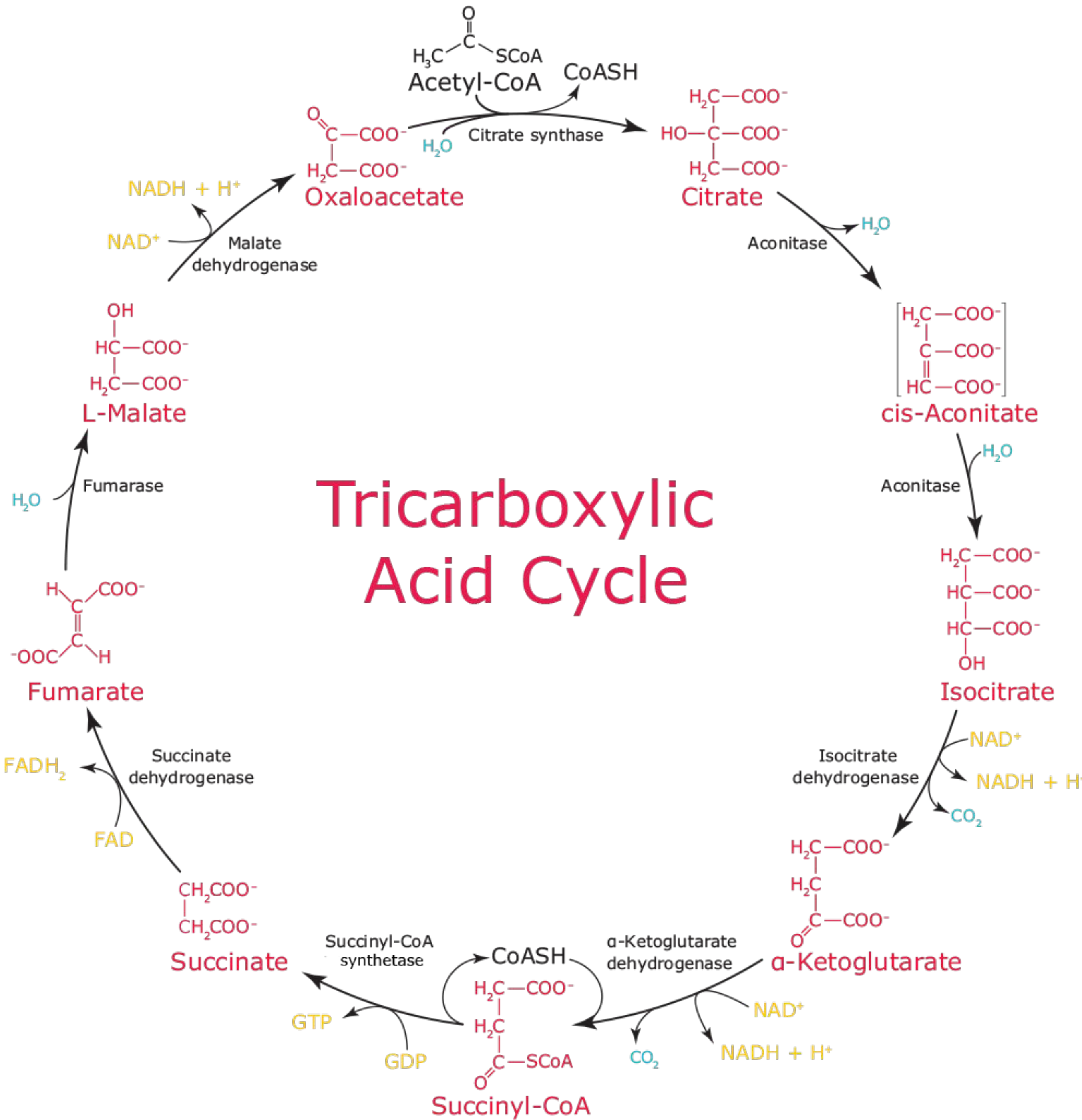
Inside Mitochondria
First step of Krebs cycle

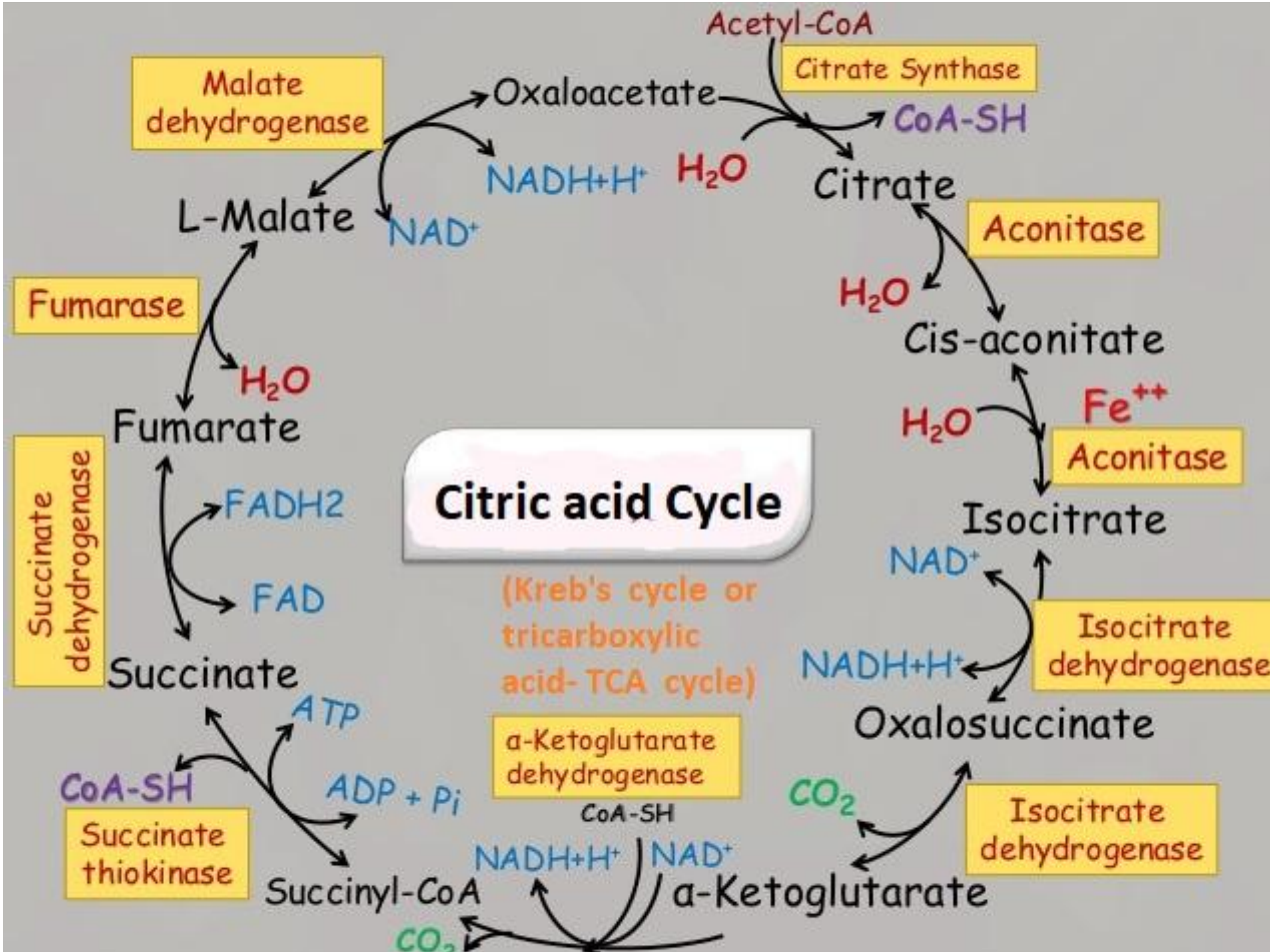


KREBS CYCLE



Acetyl-CoA, H_2O
NADH+ H+
Malate
dehydrogenase
NAD+
Oxaloacetate
Citrate synthase
CoA-SH
Malate
Citrate
Aconitase
H_2O
Fumarase
H_2O
Fumarate
Cis-aconitate
$FADH_2$
Succinate
dehydrogenase
FAD
H_2O
Aconitase
Succinate
Isocitrate
ATP,
CoA-SH
Succinate
thiokinase
ADP
Succinyl-CoA
NAD+
Isocitrate
dehydrogenase
Oxalosuccinate
NADH+ H+
α-ketoglutarate
dehydrogenase
Isocitrate
dehydrogenase
CO_2
NADH+
H+
NAD+,
CoA-SH
Alpha-ketoglutarate
CO_2


Tricarboxylic Acid Cycle
Acetyl-CoA
CoASH
H_2O
Citrate synthase
Oxaloacetate
Citrate
Aconitase
H_2O
cis-Aconitate
Aconitase
H_2O
Isocitrate
Isocitrate dehydrogenase
NAD^+
NADH + H^+
CO_2
α-Ketoglutarate
α-Ketoglutarate dehydrogenase
NAD^+
NADH + H^+
CO_2
CoASH
Succinyl-CoA
Succinyl-CoA synthetase
GTP
GDP
Succinate
Succinate dehydrogenase
$FADH_2$
FAD
Fumarate
Fumarase
H_2O
L-Malate
Malate dehydrogenase
NAD^+
NADH + H^+


Citric acid Cycle
(Kreb's cycle or tricarboxylic acid- TCA cycle)
Acetyl-CoA
Citrate Synthase
Oxaloacetate
CoA-SH
H_2O
Citrate
Aconitase
H_2O
Cis-aconitate
H_2O
Fe^{++}
Aconitase
Isocitrate
NAD^+
Isocitrate dehydrogenase
$NADH+H^+$
Oxalosuccinate
CO_2
Isocitrate dehydrogenase
α-Ketoglutarate
α-Ketoglutarate dehydrogenase
CoA-SH
$NADH+H^+$
NAD^+
Succinyl-CoA
CO_2
Succinate thiokinase
CoA-SH
ADP + Pi
ATP
Succinate
Succinate dehydrogenase
FADH2
FAD
Fumarate
Fumarase
H_2O
L-Malate
Malate dehydrogenase
$NADH+H^+$
NAD^+

3. Krebs Cycle (Citric Acid Cycle)

- **Total net yield (2 turns of krebs cycle)**

1. **2 - ATP (substrate-level phosphorylation)**
2. **6 - NADH**
3. **2 - $FADH_2$**
4. **4 - CO_2**

Energy balance sheet of glucose oxidation

- Old view (theoretical yield)

- **Total ATP Yield**

02 ATP - glycolysis (substrate-level phosphorylation)

06 ATP - converted from 2 NADH - glycolysis

06 ATP - converted from 2 NADH - grooming phase

02 ATP - Krebs cycle (substrate-level phosphorylation)

18 ATP - converted from 6 NADH - Krebs cycle

04 ATP - converted from 2 $FADH_2$ - Krebs cycle

38 ATP - TOTAL

The ATP Totals

Glycolysis

- 2 Pyruvate molecules
- 2NADH
- Four ATP (-2ATP) : Net Gain 2ATP

Citric Acid production/ Krebs Cycle

- 6 molecules of CO_2
- 2 molecules of ATP
- 8 molecules of NADP
- 2 $FADH_2$ Total: 2ATP

The Electron Transport Chain

- 10NADH =30 ATP
- 2 $FADH_2$ = 4ATP

Total:34

More ATP produced in the ETC

1 NADH : 3 ATP

1 FADH2 : 2 ATP

Totals

- 38 ATP for every glucose

- To pass the electrons from NADH to last Oxygen acceptor, total of 10 protons are transported from matrix to inter mitochondrial membrane
- 4 protons via complex I, 4 via complex III and 2 via complex IV. And to make 1 ATP, 4 protons move from inter mitochondrial membrane to matrix via ATPase
- Thus for NADH— 10/4=**2.5** ATP is produced actually. Similarly for 1 FADH2, 6 protons are moved so 6/4= **1.5** ATP is produced.

The ATP Totals

Glycolysis

- 2 Pyruvate molecules
- 2NADH
- Four ATP (-2ATP) : Net Gain 2ATP

Citric Acid production/ Krebs Cycle

- 6 molecules of CO_2
- 2 molecules of ATP
- 8 molecules of NADP
- 2 $FADH_2$ Total: 2ATP

The Electron Transport Chain

- 10NADH = 25 ATP
- 2 $FADH_2$ = 3 ATP

Total:34

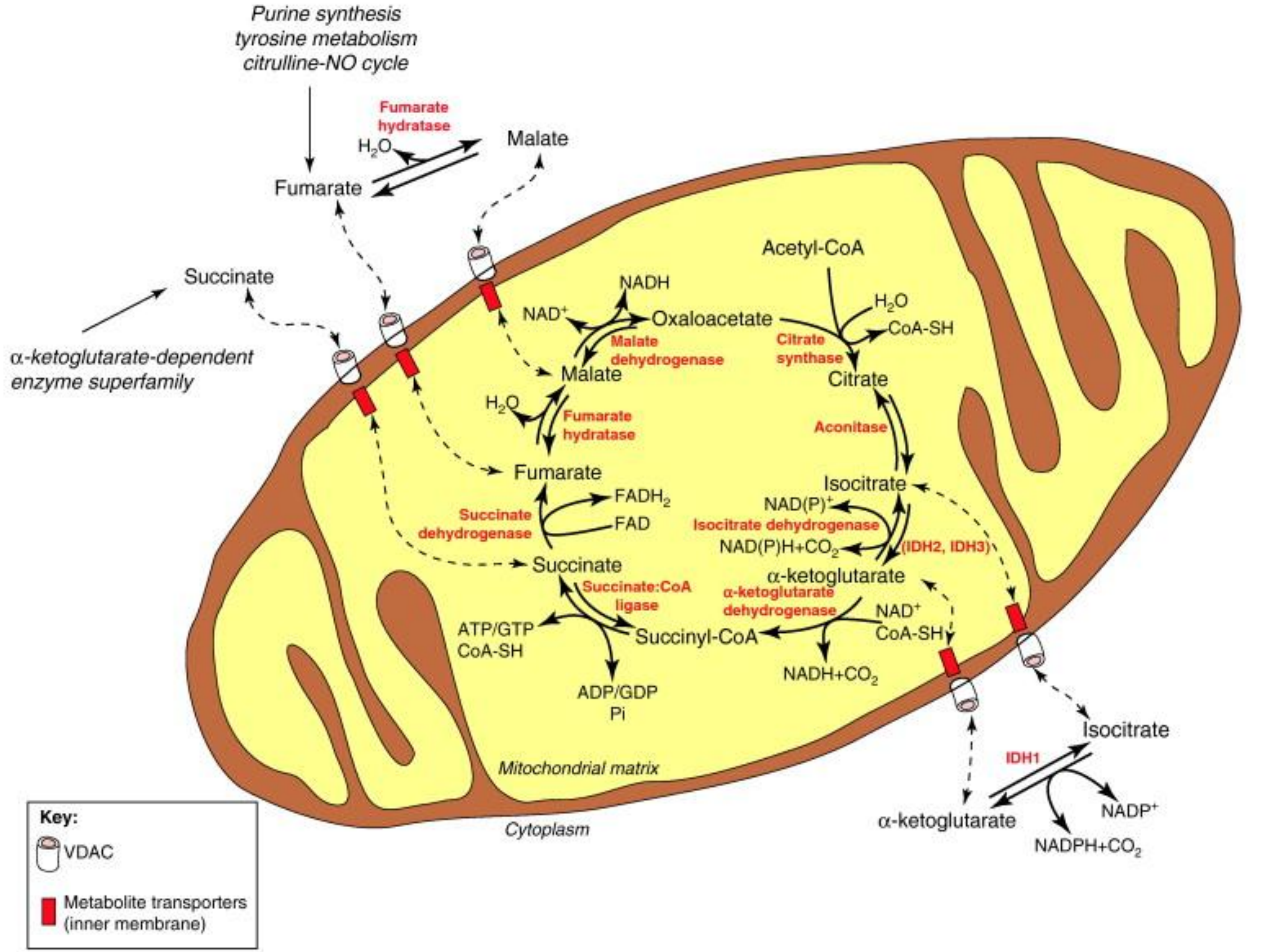
More ATP produced in the ETC

1 NADH : 2.5 ATP

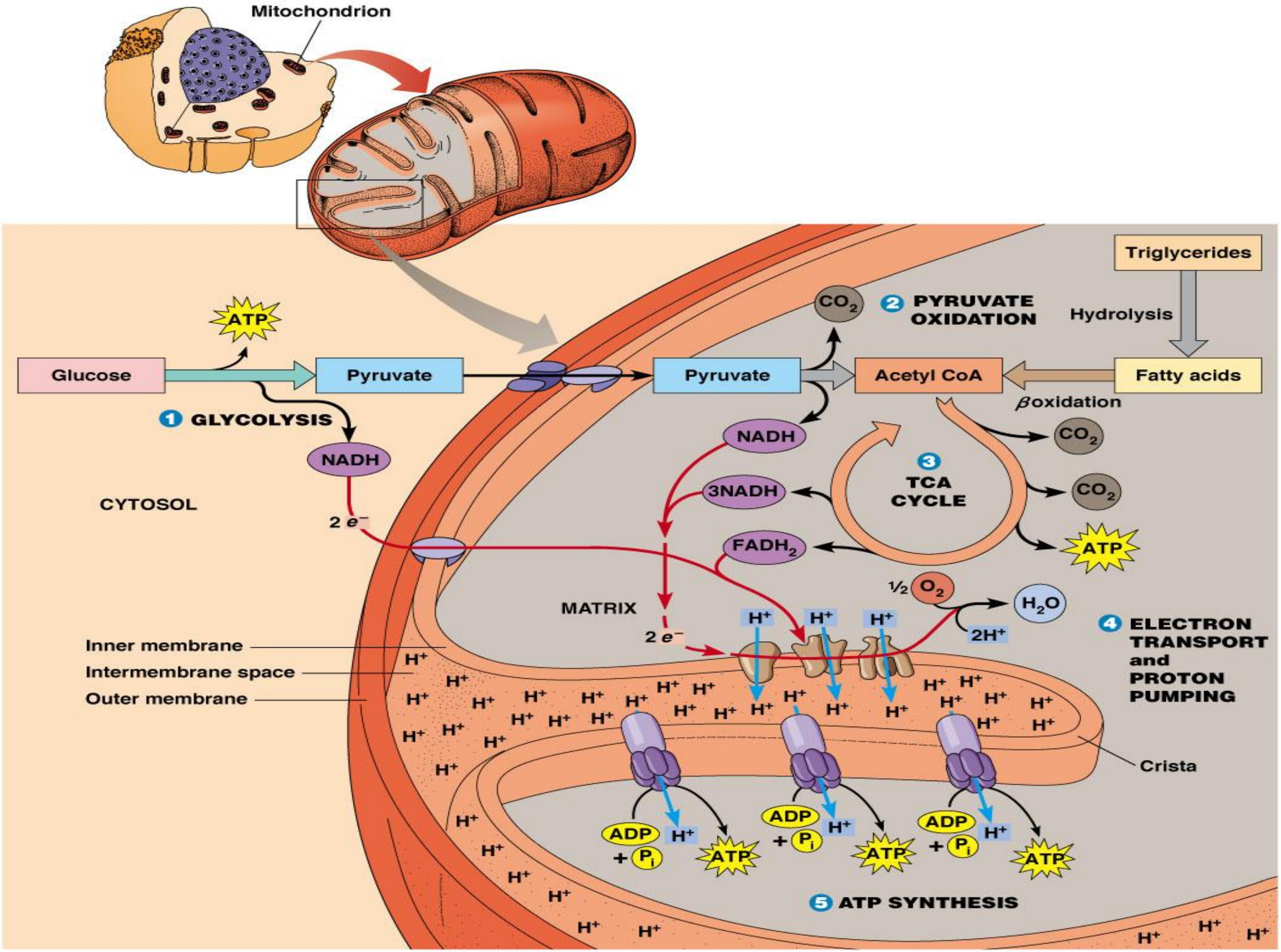
1 FADH2 : 1.5 ATP

Totals

32 ATP for every glucose



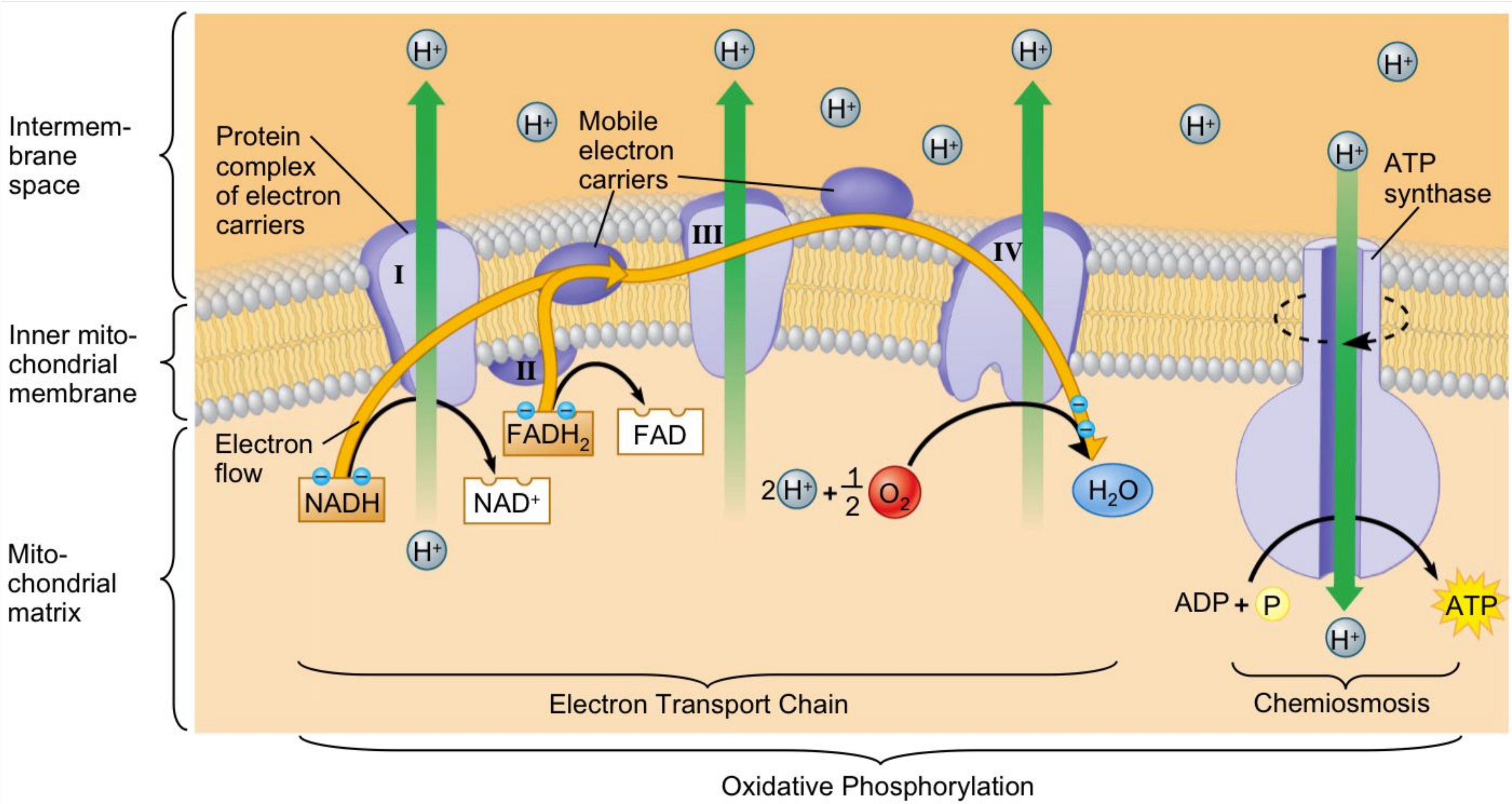
TRENDS in Molecular Medicine

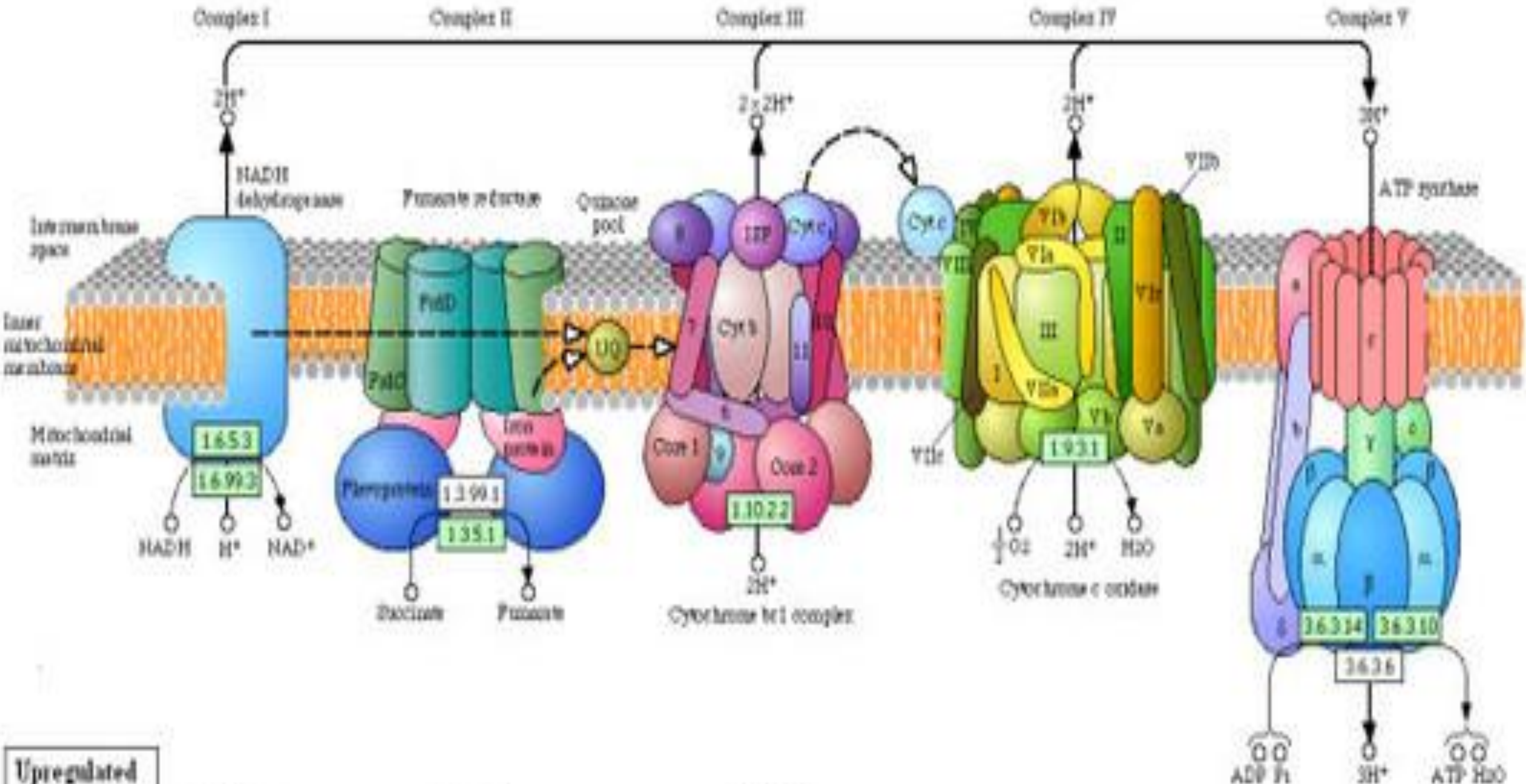


Mitochondrion
Triglycerides
Hydrolysis
CO2
2 PYRUVATE OXIDATION
ATP
Glucose
Pyruvate
Pyruvate
Acetyl CoA
Fatty acids
β oxidation
1 GLYCOLYSIS
NADH
NADH
CO2
3 TCA CYCLE
3NADH
CO2
CYTOSOL
2 e−
FADH2
ATP
½ O2
H2O
MATRIX
H+
2 e−
2H+
4 ELECTRON TRANSPORT and PROTON PUMPING
Inner membrane
Intermembrane space
Outer membrane
Crista
ADP + Pi
ATP
5 ATP SYNTHESIS

ELECTRON TRANSPORT CHAIN

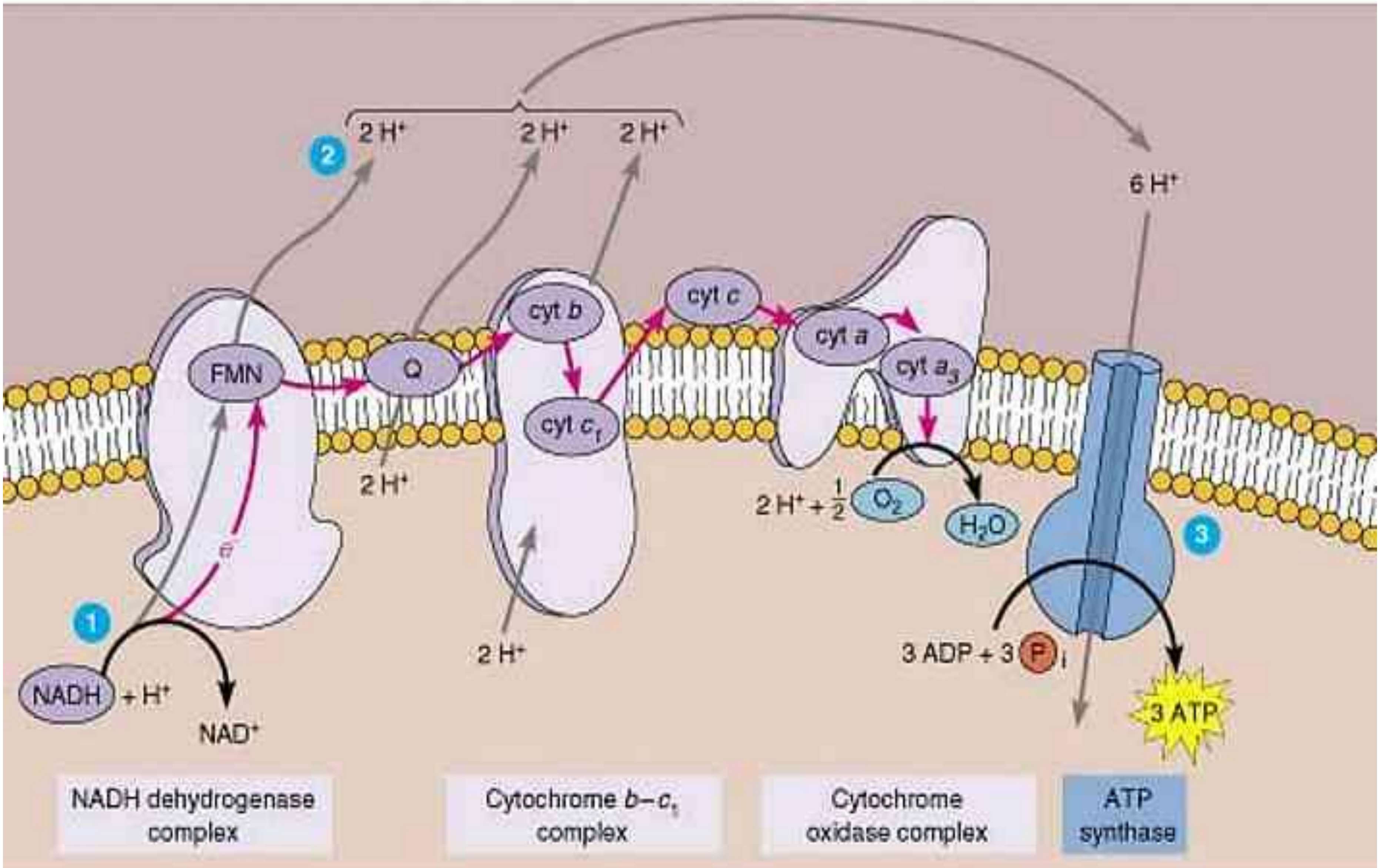
Figure 6.10



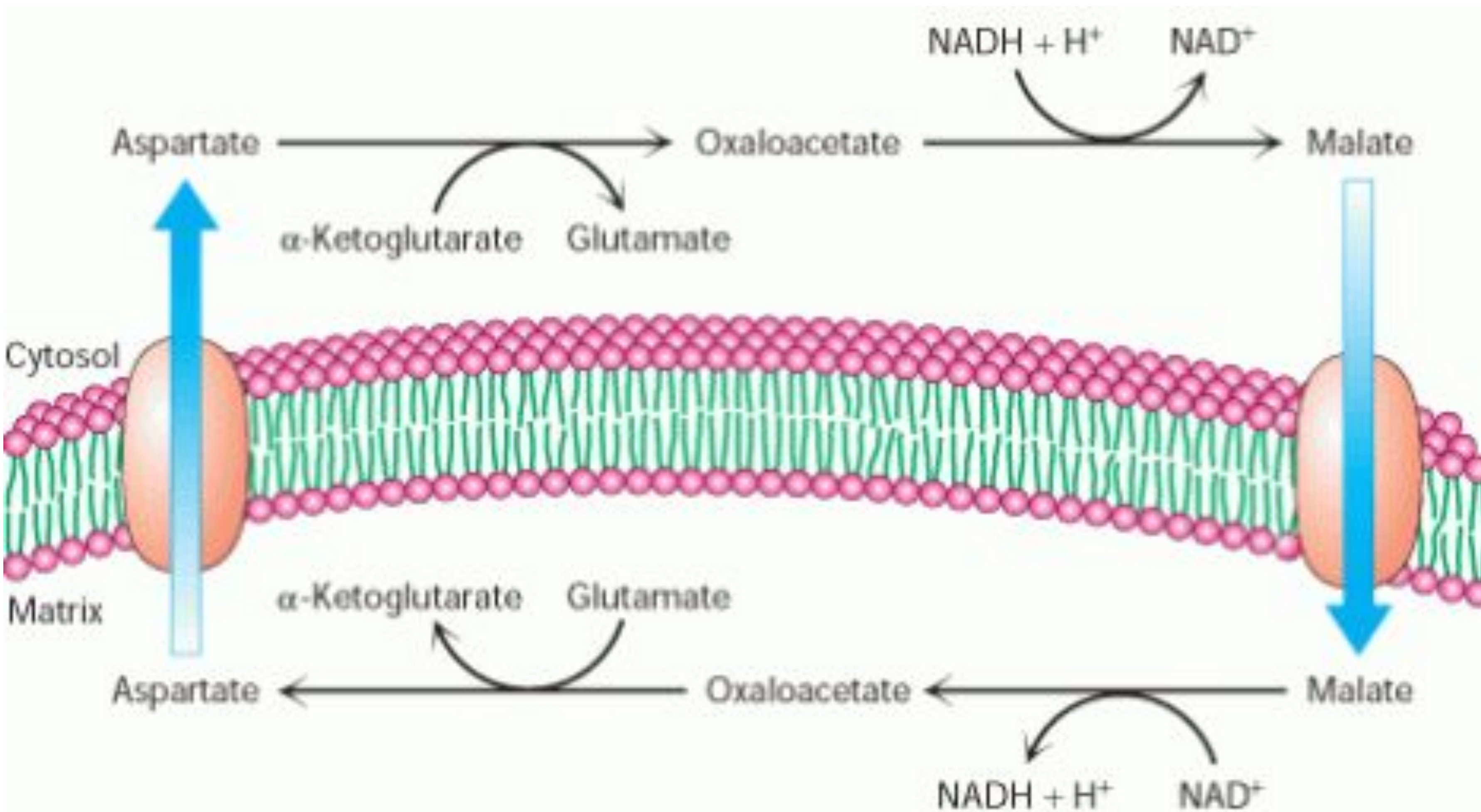


Upregulated genes in VEGF d/d mice	Ndufv2	Uqcrc2	Cox5b Surf1		ATP5a1 ATP5g3

ELECTRON TRANSPORT CHAIN

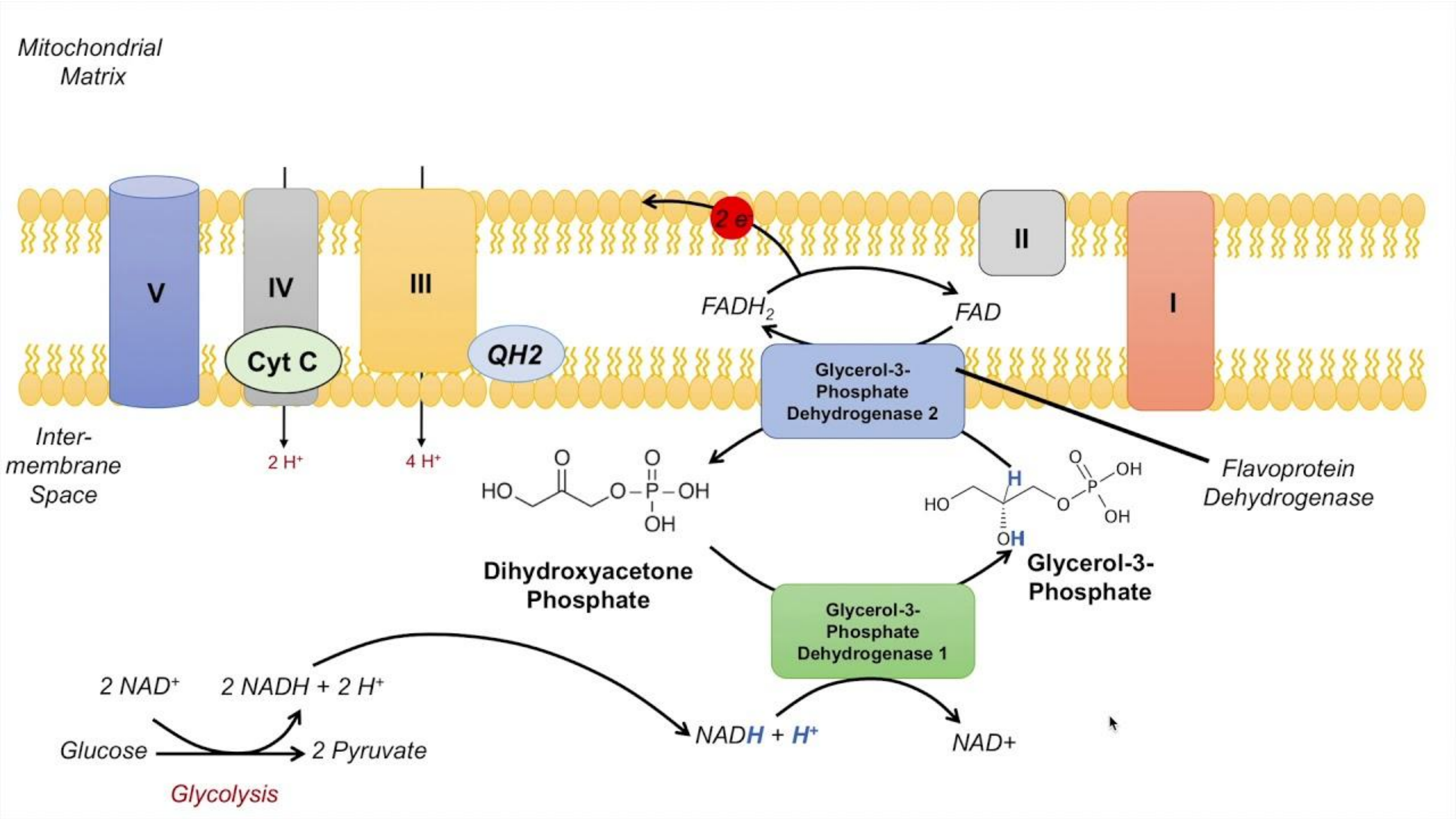


SHUTTLE PATHWAY
(i) Malate- aspartate shuttle



Transport of NADH across inner mitochondrial membrane

(ii) Glycerol 3 phosphate shuttle system



For transport of NADH produced in cytosol by glycolysis