Oxidative Decarboxylation and Krebs Cycle

Objectives: Oxidative Decarboxylation

By the end of this lecture, students are expected to:

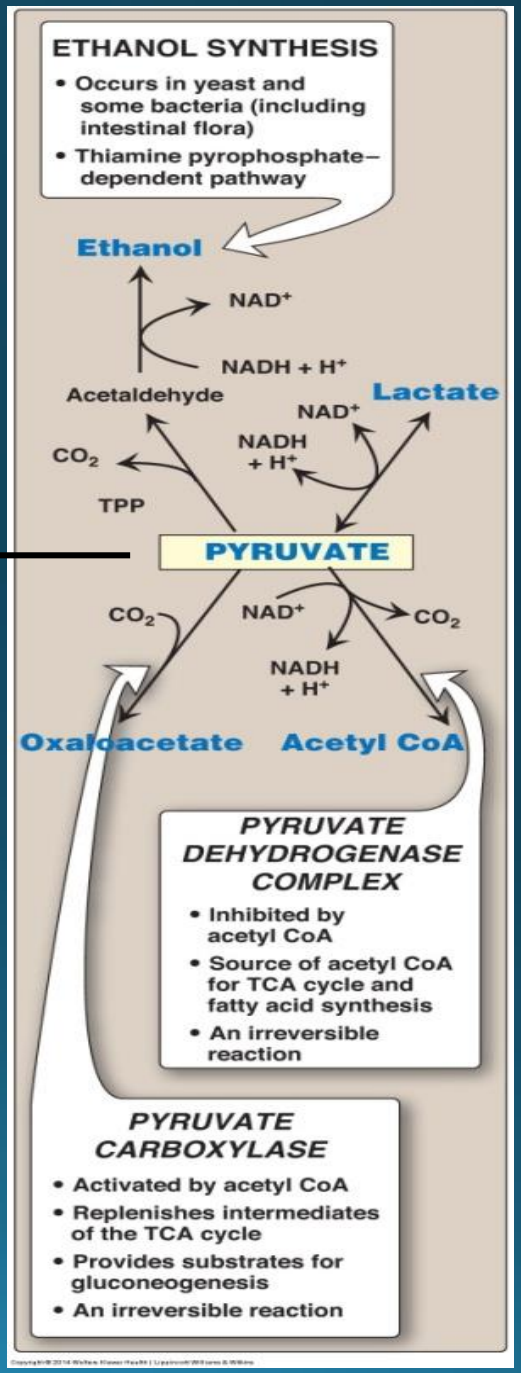
- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoA
- Discuss the major regulatory mechanisms for PDH complex
- Recognize the clinical consequence of abnormal oxidative decarboxylation reactions

Objectives: Krebs Cycle

By the end of this lecture, students are expected to:

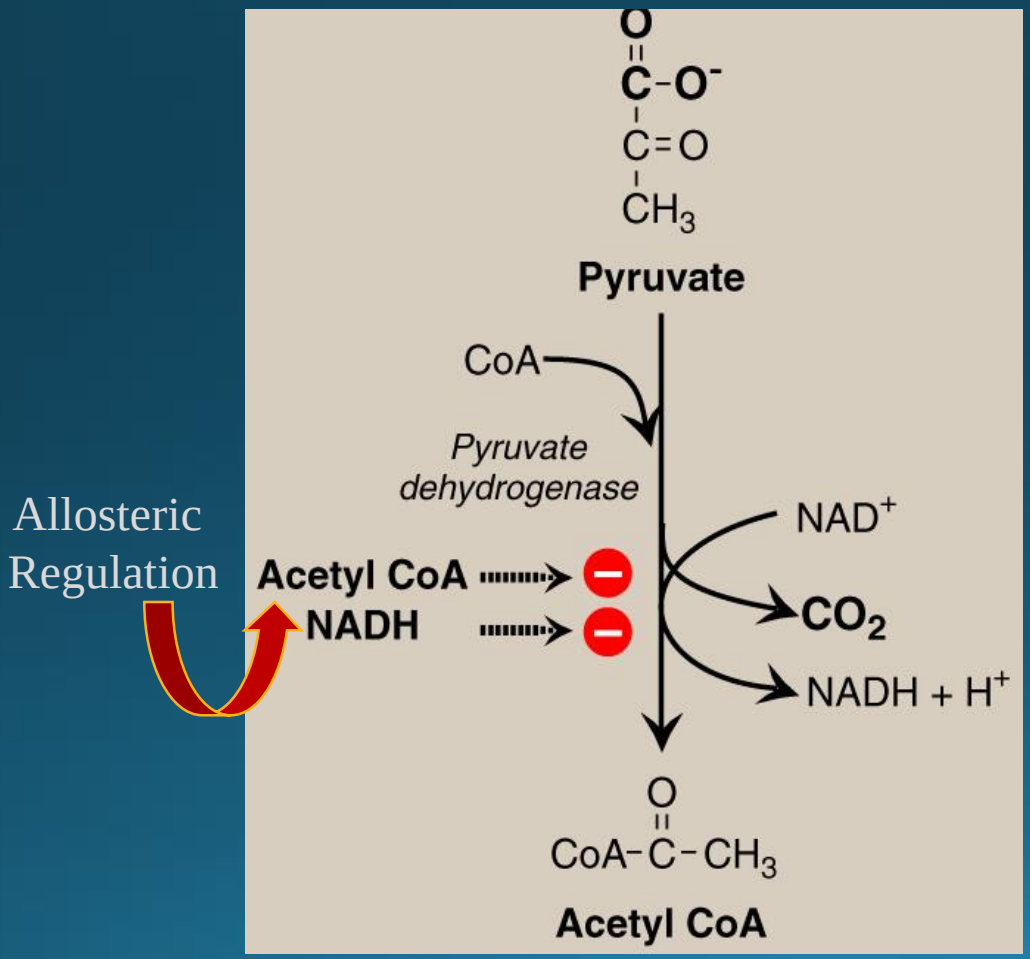
- Recognize the importance of Krebs cycle
- Identify various reactions of Krebs cycle
- Define the regulatory mechanisms of Krebs cycle
- Assess the energy yield of PDH reaction and Krebs cycle's reactions

Fates of Pyruvate

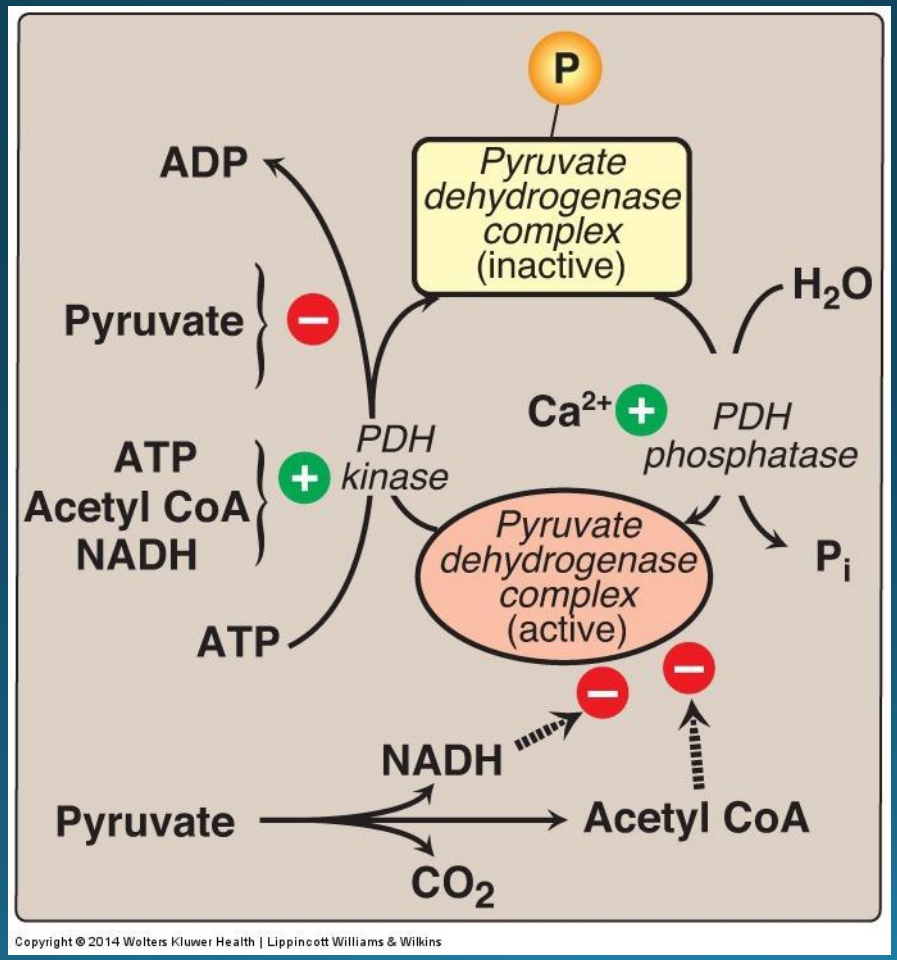


PLP = Pyridoxal Phosphate

Oxidative Decarboxylation of Pyruvate



PDH Complex: Covalent Regulation



PDH Reaction: Clinical application

1. Deficiencies of thiamine or niacin can cause serious CNS problems. **WHY?**

   • Brain cells are unable to produce sufficient ATP if the PDH complex is inactive.

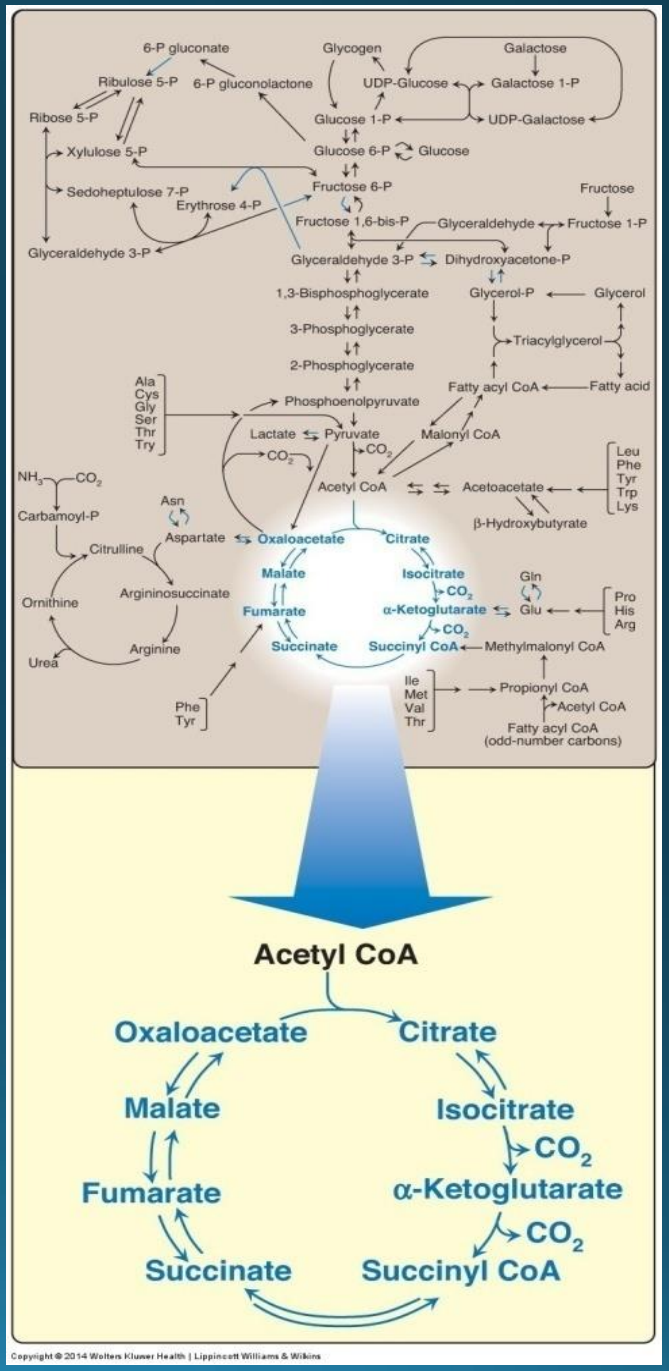
1. **Wernicke-Korsakoff** (encephalopathy-psychosis syndrome) due to thiamine deficiency, may be seen especially with alcohol abuse.

2. PDH complex deficiency is the most common biochemical cause of **congenital lactic acidosis.**

Krebs Cycle

The tricarboxylic acid cycle (Krebs) shown as a part of the essential pathways of energy metabolism.

CoA = coenzyme A.



Tricarboxylic Acid Cycle: Krebs Cycle

- Final common pathway for oxidation
- Exclusively in mitochondria
- Major source for ATP
- Mainly catabolic with some anabolic features
- Synthetic reactions (anabolic features):

  Glucose from amino acids

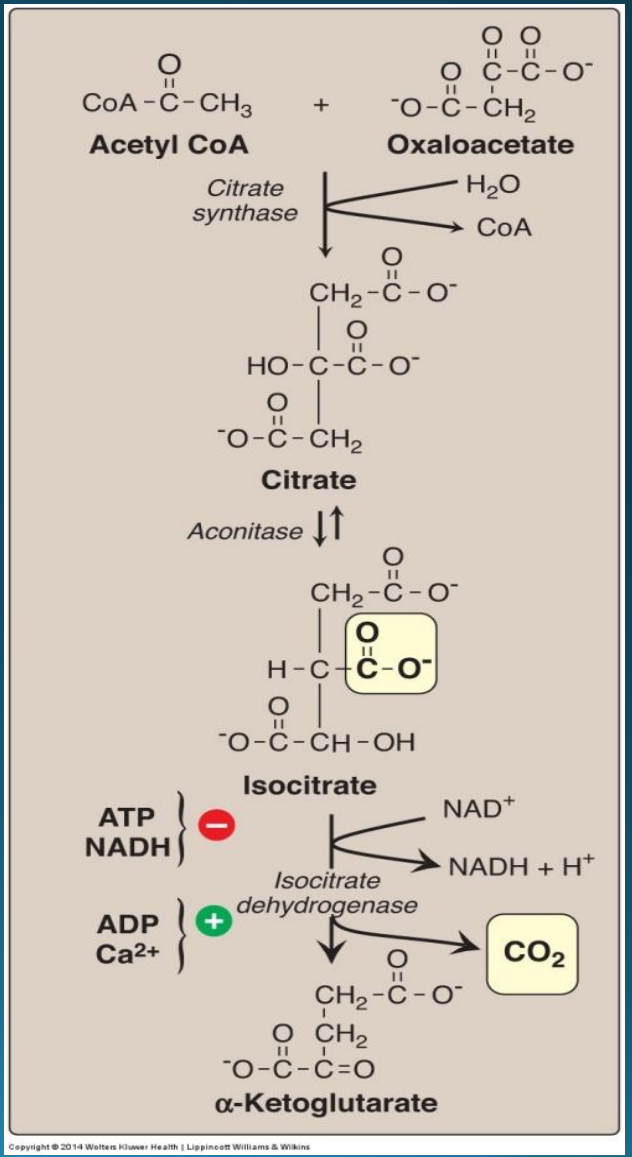
  Nonessential amino acids

  Fatty acids

  Heme

Krebs Cycle Reactions (1)

Formation of α-ketoglutarate from acetyl coenzyme A (CoA) and oxaloacetate.

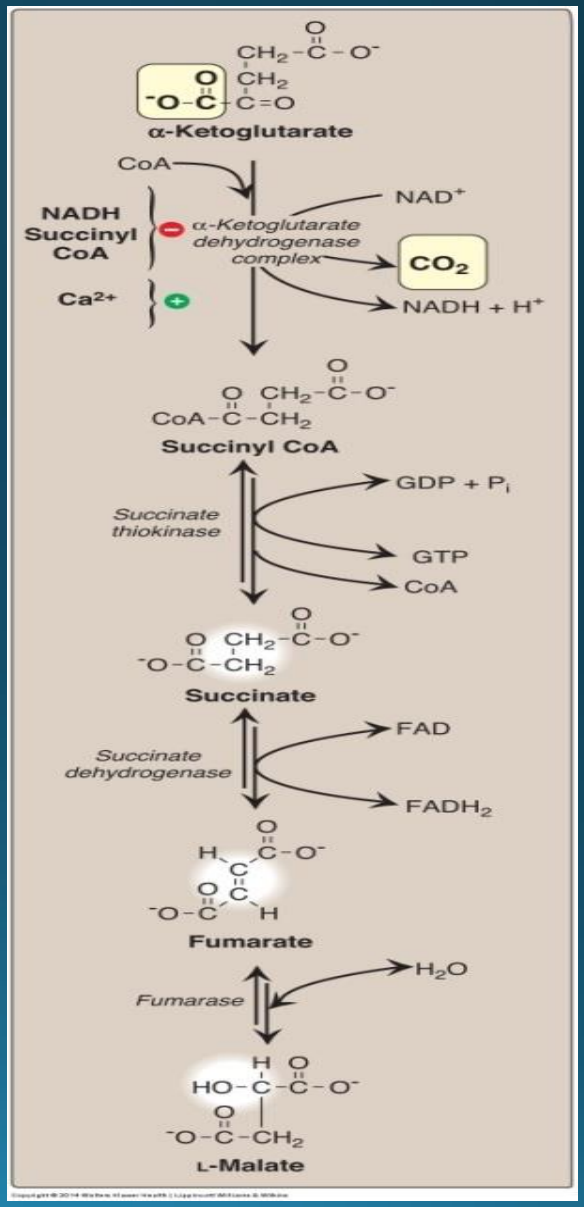


NAD(H) = Nicotinamide adenine dinucleotide.

Krebs Cycle Reactions (2)

Succinate Thiokinase

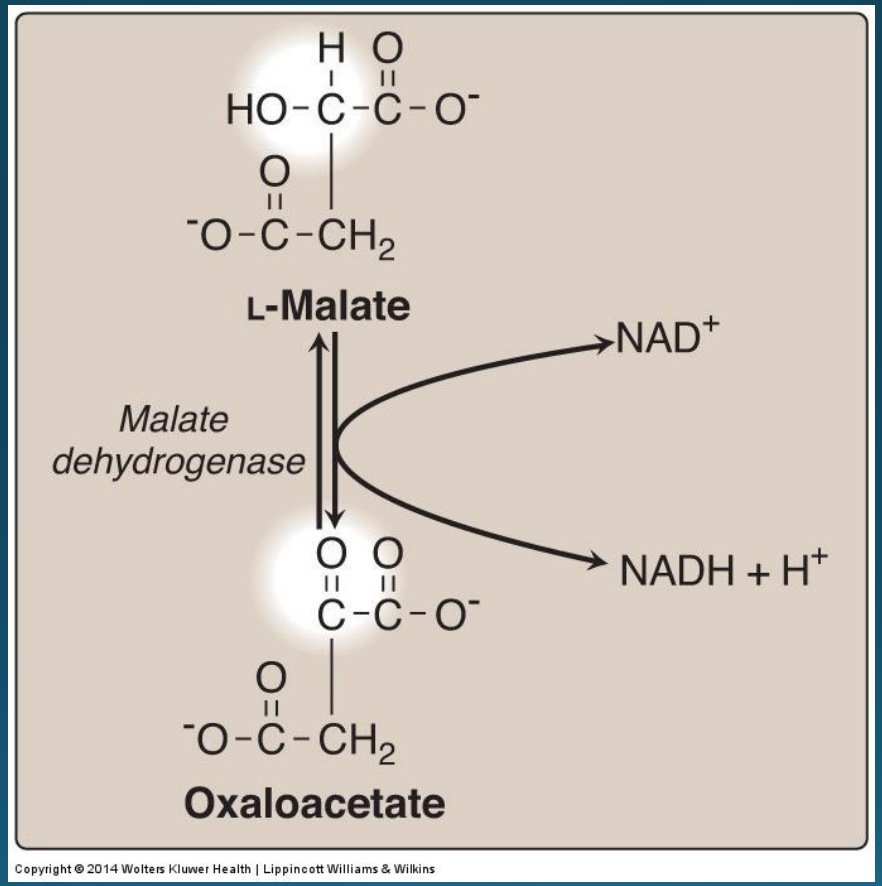
Substrate-Level Phosphorylation



Formation of malate from α-ketoglutarate.

NAD(H) = nicotinamide adenine dinucleotide
GDP = guanosine diphosphate;
P = phosphate
FAD(H_2) = flavin adenine dinucleotide.

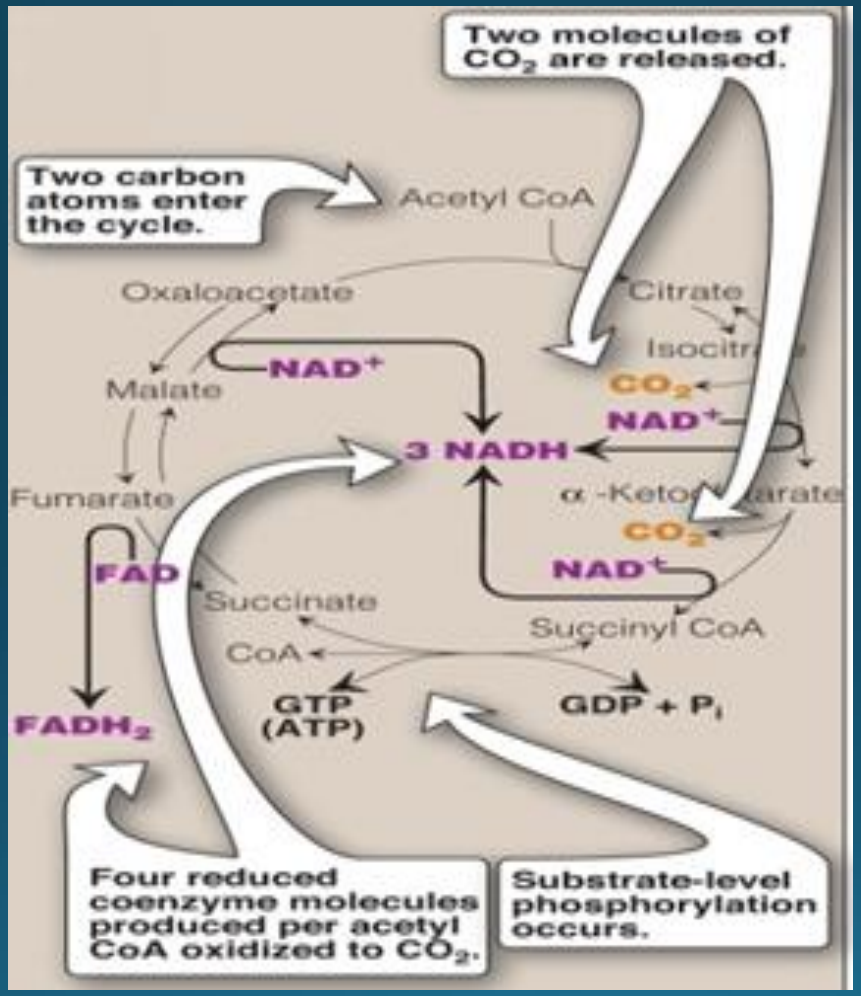
Krebs Cycle Reactions (3)



Formation (regeneration) of oxaloacetate from malate.

NAD(H) = nicotinamide adenine dinucleotide

Krebs Cycle: Energy Yield



Number of ATP molecules produced from the oxidation of one molecule of acetyl coenzyme A (CoA) using both substrate-level and oxidative phosphorylation.

Krebs Cycle: Energy Yield

Energy-producing reaction	Number of ATP produced
$3\ NADH \longrightarrow 3\ NAD^+$	9
$FADH_2 \longrightarrow FAD$	2
$GDP + P_i \longrightarrow GTP$	1
	12 ATP/acetyl CoA oxidized

Number of ATP molecules produced from the oxidation of one molecule of acetyl coenzyme A (CoA) using both substrate-level and oxidative phosphorylation.

Net ATP Production by Complete Glucose Oxidation

Aerobic glycolysis:		8 ATP
Oxidative decarboxylation:	2 X 3 =	6 ATP
Krebs cycle:	2 X 12 =	24 ATP
Net:		38 ATP

Regulation of Oxidative Decarboxylation and Krebs Cycle

- PDH complex and the TCA cycle are both **up-regulated** in response to a **decrease in the ratio** of
  - ATP:ADP
  - NADH:NAD^+
- TCA cycle activators are:
  - ADP
  - Ca^{2+}
- TCA cycle inhibitors are:
  - ATP
  - NADH

Take Home Message

- Pyruvate is oxidatively decarboxylated by PDH to acetyl CoA inside the mitochondria
- Krebs cycle:
  - Final common pathway for the oxidation of carbohydrates, fatty acids and amino acids
  - Occurs in the mitochondria
  - Aerobic
  - Mainly catabolic, with some anabolic reactions
- The complete oxidation of one glucose molecule results in a net production of 38 ATP molecules

Reference

Lippincott Illustrated Review of Biochemistry, 6th edition, 2014, Unit 2, Chapter 9, Pages 109-116.