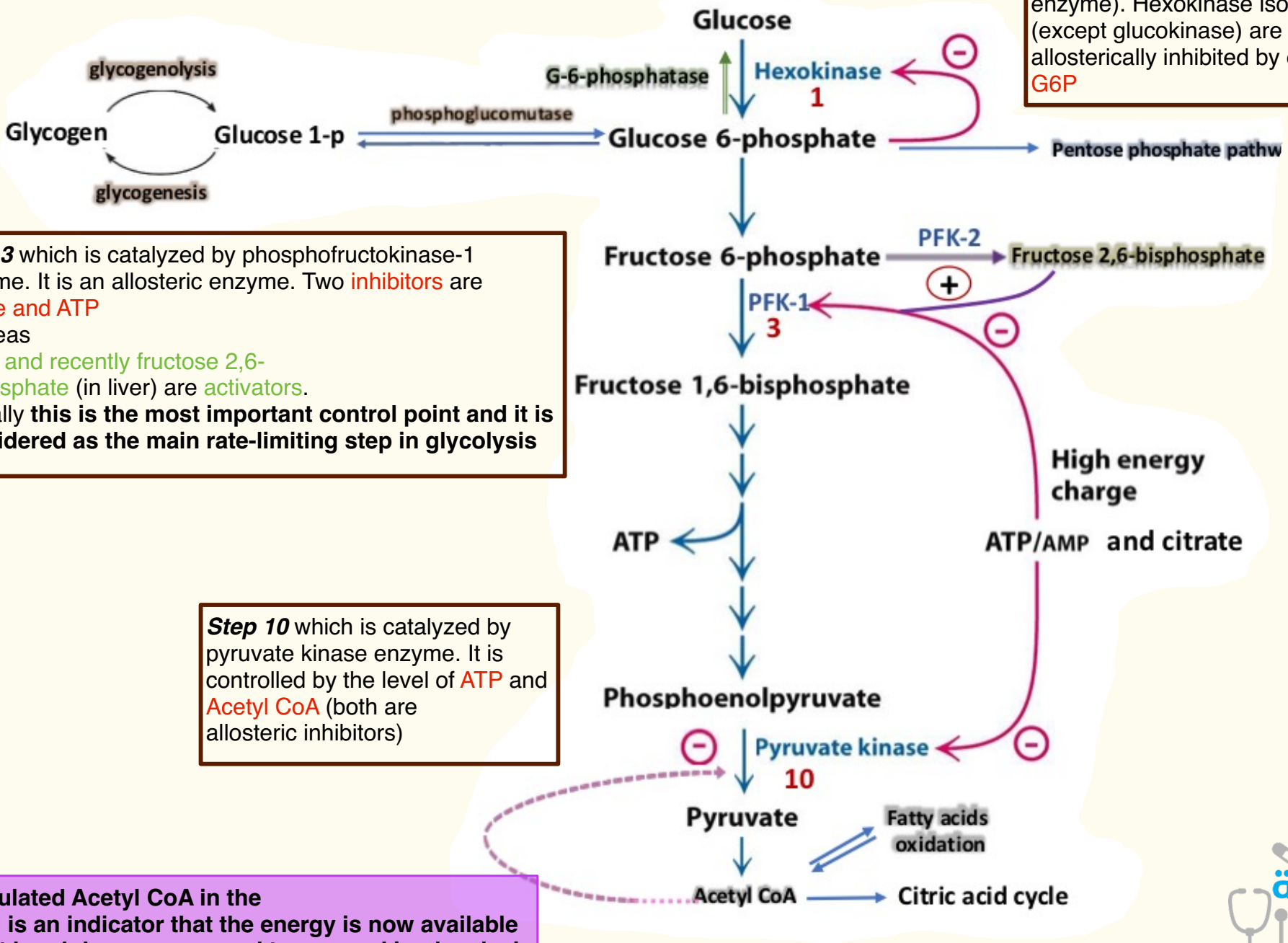
Glycolysis II

لا حول ولا قوة إلا بالله

Glycolysis Regulation

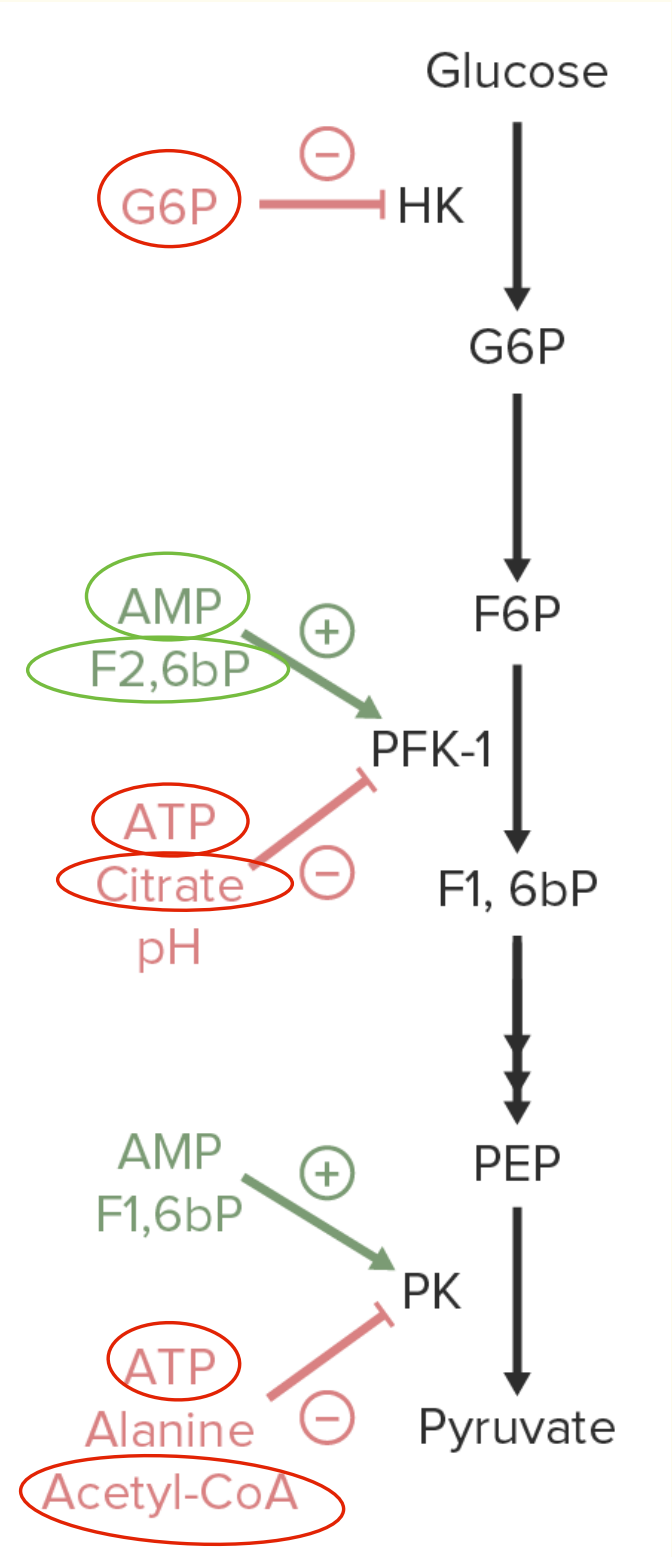
Step 1 which is catalyzed by hexokinase enzyme (allosteric enzyme). Hexokinase isoforms (except glucokinase) are allosterically inhibited by excess G6P

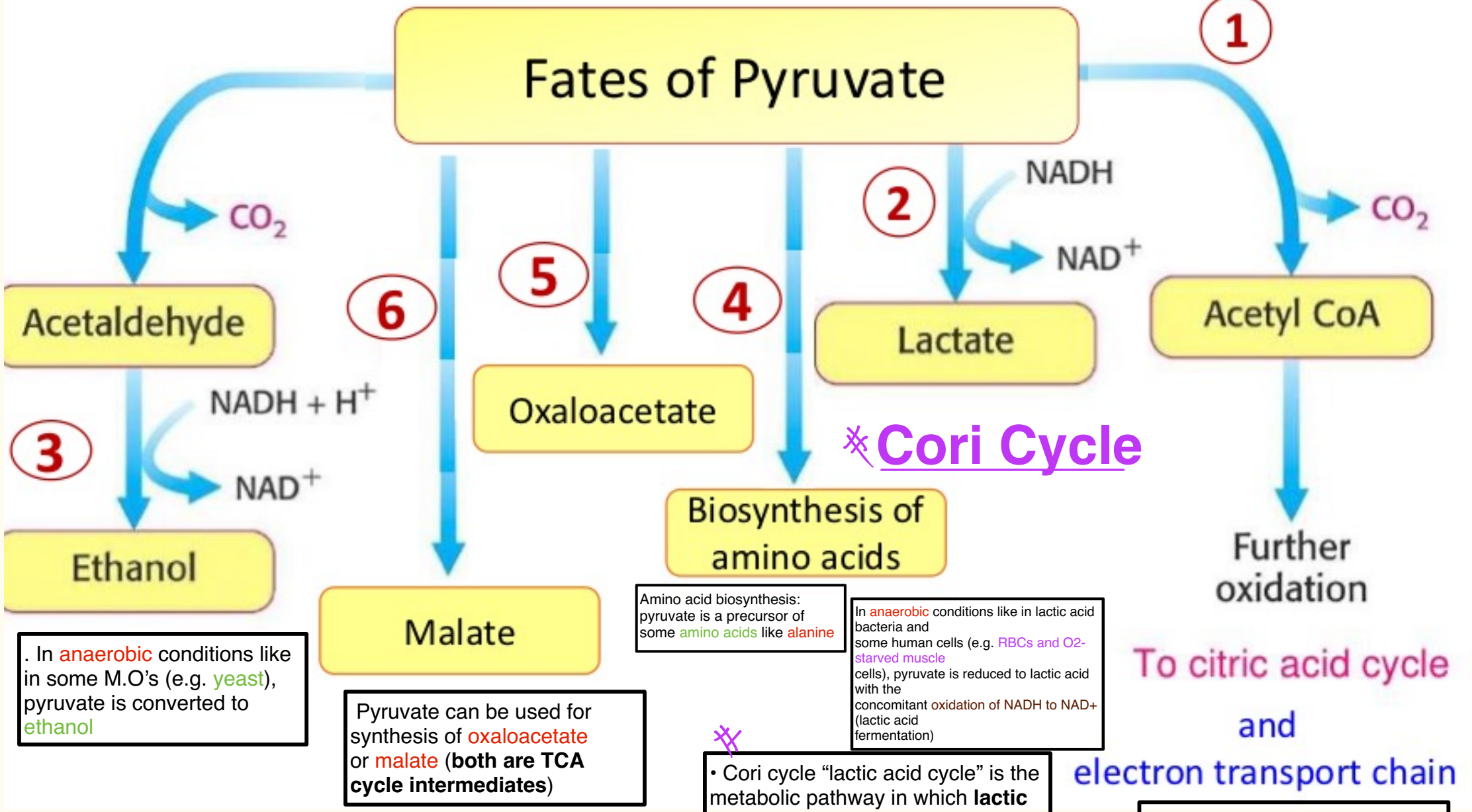


Step 3 which is catalyzed by phosphofructokinase-1 enzyme. It is an allosteric enzyme. Two inhibitors are citrate and ATP
whereas
AMP and recently fructose 2,6-biphosphate (in liver) are activators.
Actually **this is the most important control point and it is considered as the main rate-limiting step in glycolysis**

Step 10 which is catalyzed by pyruvate kinase enzyme. It is controlled by the level of ATP and Acetyl CoA (both are allosteric inhibitors)

Accumulated Acetyl CoA in the cytosol is an indicator that the energy is now available from fat breakdown so no need to proceed in glycolysis


Glucose
G6P
HK
G6P
F6P
AMP
F2,6bP
PFK-1
ATP
Citrate
pH
F1, 6bP
PEP
AMP
F1,6bP
PK
ATP
Alanine
Acetyl-CoA
Pyruvate



. In anaerobic conditions like in some M.O's (e.g. yeast), pyruvate is converted to ethanol

Pyruvate can be used for synthesis of oxaloacetate or malate (**both are TCA cycle intermediates**)

Amino acid biosynthesis: pyruvate is a precursor of some amino acids like alanine

In anaerobic conditions like in lactic acid bacteria and some human cells (e.g. RBCs and O2-starved muscle cells), pyruvate is reduced to lactic acid with the concomitant oxidation of NADH to NAD+ (lactic acid fermentation)

• Cori cycle "lactic acid cycle" is the metabolic pathway in which **lactic acid produced in muscles during the time of oxygen depletion is converted back to glucose** in the liver by gluconeogenesis process

In aerobic conditions, pyruvate is converted to acetyl CoA which enters the citric acid cycle for further oxidation to CO2 followed by oxidative phosphorylation

Lactic Acid Fermentation: bacteria, RBCs and O2-starved muscle cells

Fluoride as Inhibitor of Enolase

• Oral bacteria depends on the food debris or dietary sugars found on the tooth surface as a primary source of energy. Acids are produced through fermentation process (harmful)

• Fluoride is a competitive inhibitor of enolase enzyme catalyzing **Step 9**

• Drinking fluoridated water or using a toothpaste containing fluoride inhibit the oral bacteria enolase activity. Consequently, this disrupts the bacteria glycolytic pathway and prevents formation of dental caries

• Sodium fluoride is known to have antiglycolytic effect that inhibits glycolysis by **erythrocytes**

• NaF tubes (gray top) are widely used for blood collection for glucose measurement

• Fluoride-containing tubes are suitable for blood collection if there is a long delay in blood separation following collection (false negative result)

Glycolysis as Anabolic Pathway

• Glycolysis acts as catabolic as well as anabolic pathway. Therefore, glycolysis is very important central metabolic pathway

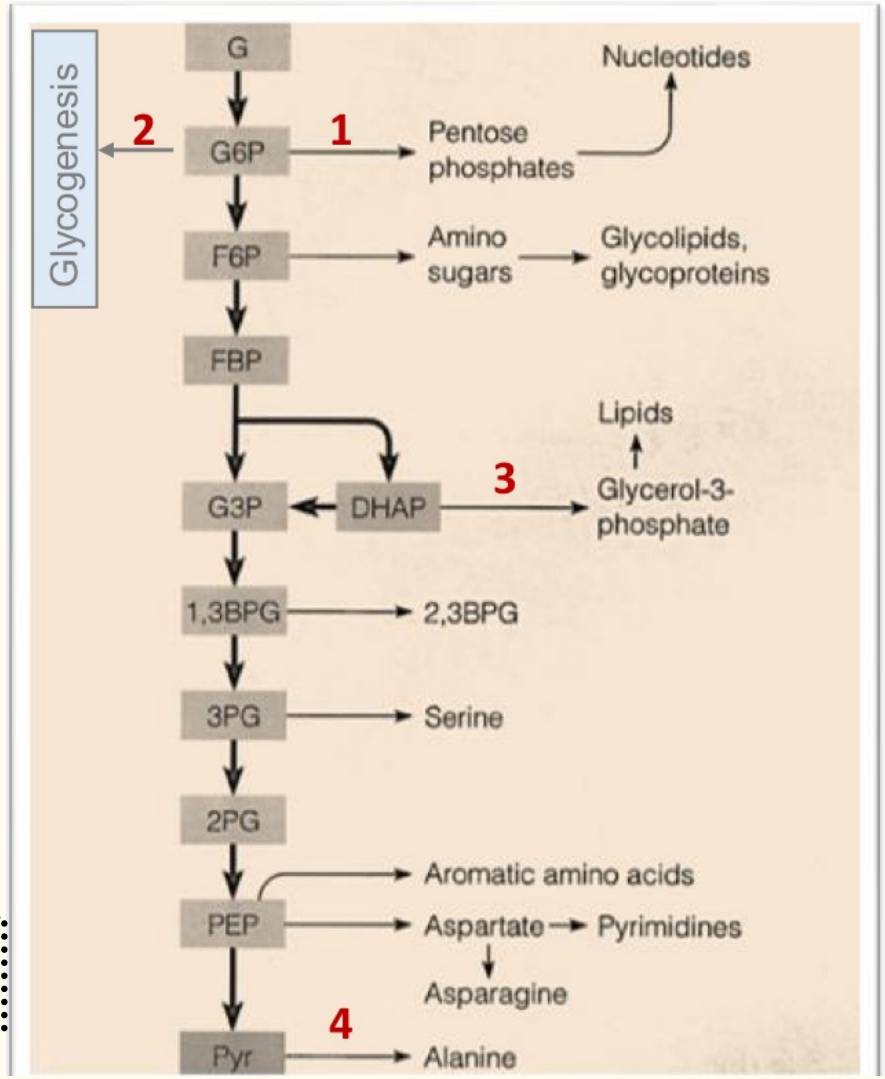
• Glycolysis intermediates with biosynthetic roles:

1. Nucleotides biosynthesis: G6P is an initial substrate in pentose phosphate pathway (metabolic pathway which generates pentoses)

2. Glycogenesis via G6P

3.Lipids biosynthesis: DHAP is converted to glycerol-3-P

4. Amino acids biosynthesis: pyruvate as precursor of alanine

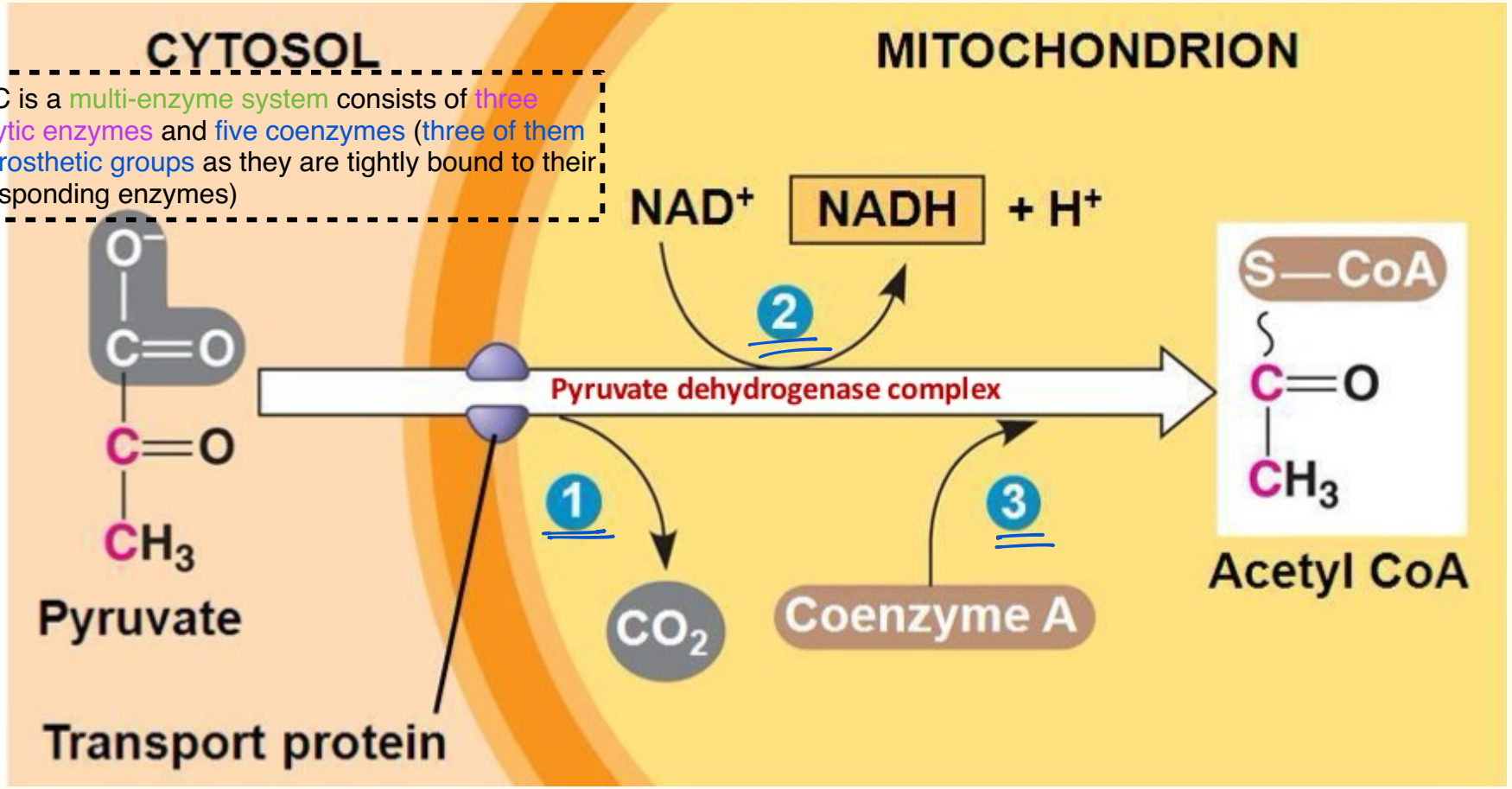


Acetyl CoA Formation

- Energy-rich molecule “NADH” is also produced

- **Coenzyme A** (CoA) acts as acetyl group carrier due to its free sulfhydryl (–SH) end capable of forming thioester bond

- PDC is a multi-enzyme system consists of three catalytic enzymes and five coenzymes (three of them are prosthetic groups as they are tightly bound to their corresponding enzymes)

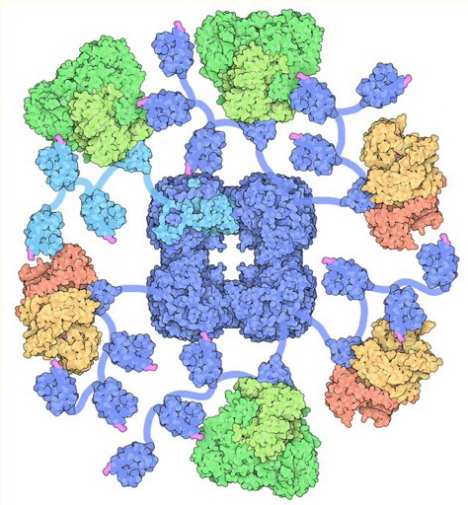


- Pyruvate dehydrogenase complex (PDC) catalyzes the irreversible oxidative decarboxylation of pyruvate into Acetyl CoA with the release of CO2

• In aerobic respiration, pyruvate (3C) joins the citric acid cycle after its conversion to acetyl CoA (2C)

• Citric acid cycle occurs in the mitochondrial matrix. Shuttling of pyruvate from the cytosol is facilitated by a transporter protein embedded in the inner mitochondrial membrane called pyruvate translocase

Pyruvate Dehydrogenase Complex



- E1: pyruvate dehydrogenase
- E2: dihydrolipoamide transacetylase
- E3: dihydrolipoamide dehydrogenase

Coenzymes

- **Thiamine pyrophosphate (TPP) a prosthetic group of E1**
- **Lipoic acid (lipoamide) a prosthetic group of E2**
- **Flavin adenine dinucleotide (FAD) a prosthetic group of E3**

- Coenzyme A (CoA or CoA-SH)
- Nicotinamide adenine dinucleotide (NAD+)