The Pentose Phosphate Pathway (HMP) and Gluconeogenesis(糖异生）

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Outline

- Pentose Phosphate Pathway

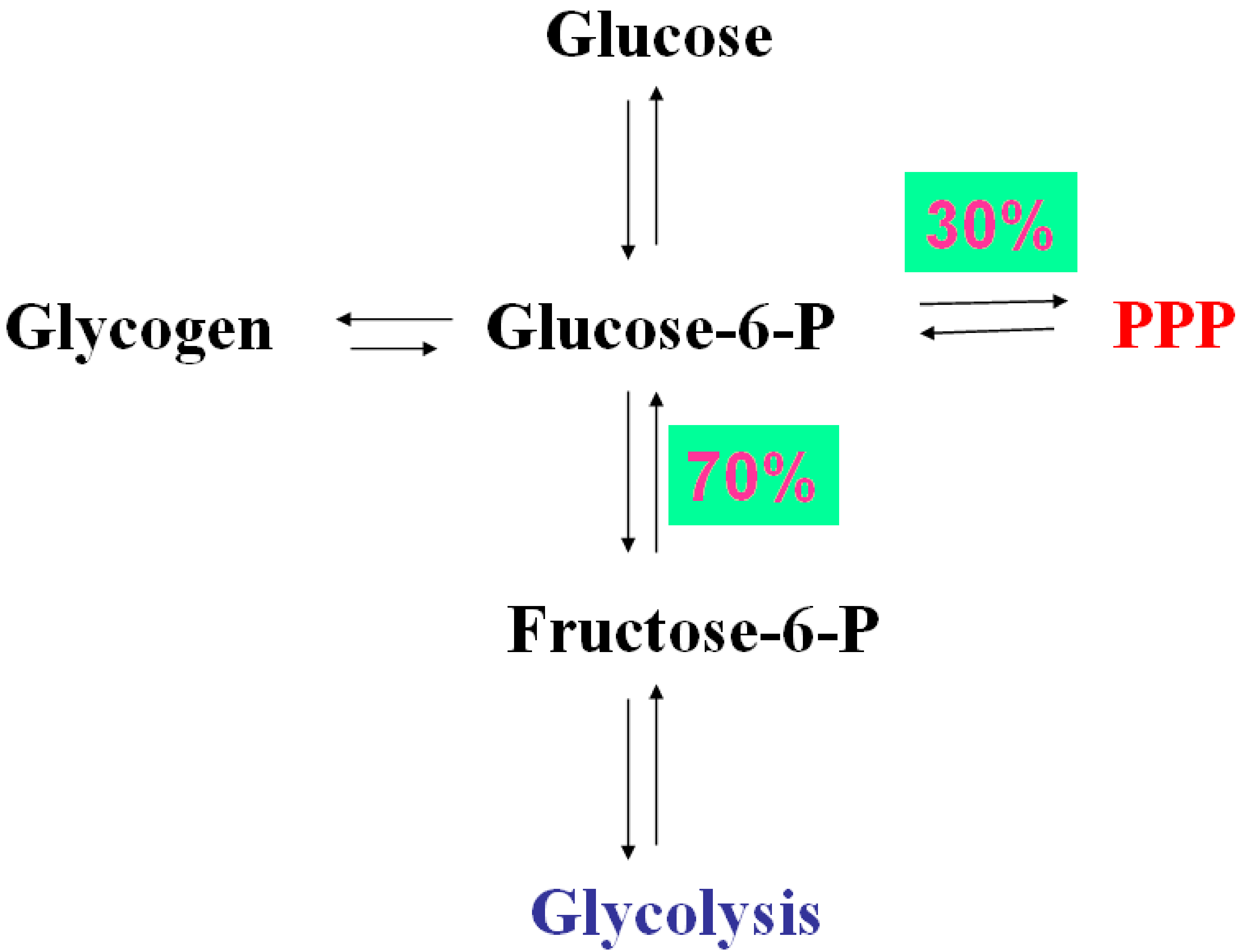
    --The Oxidative Phase

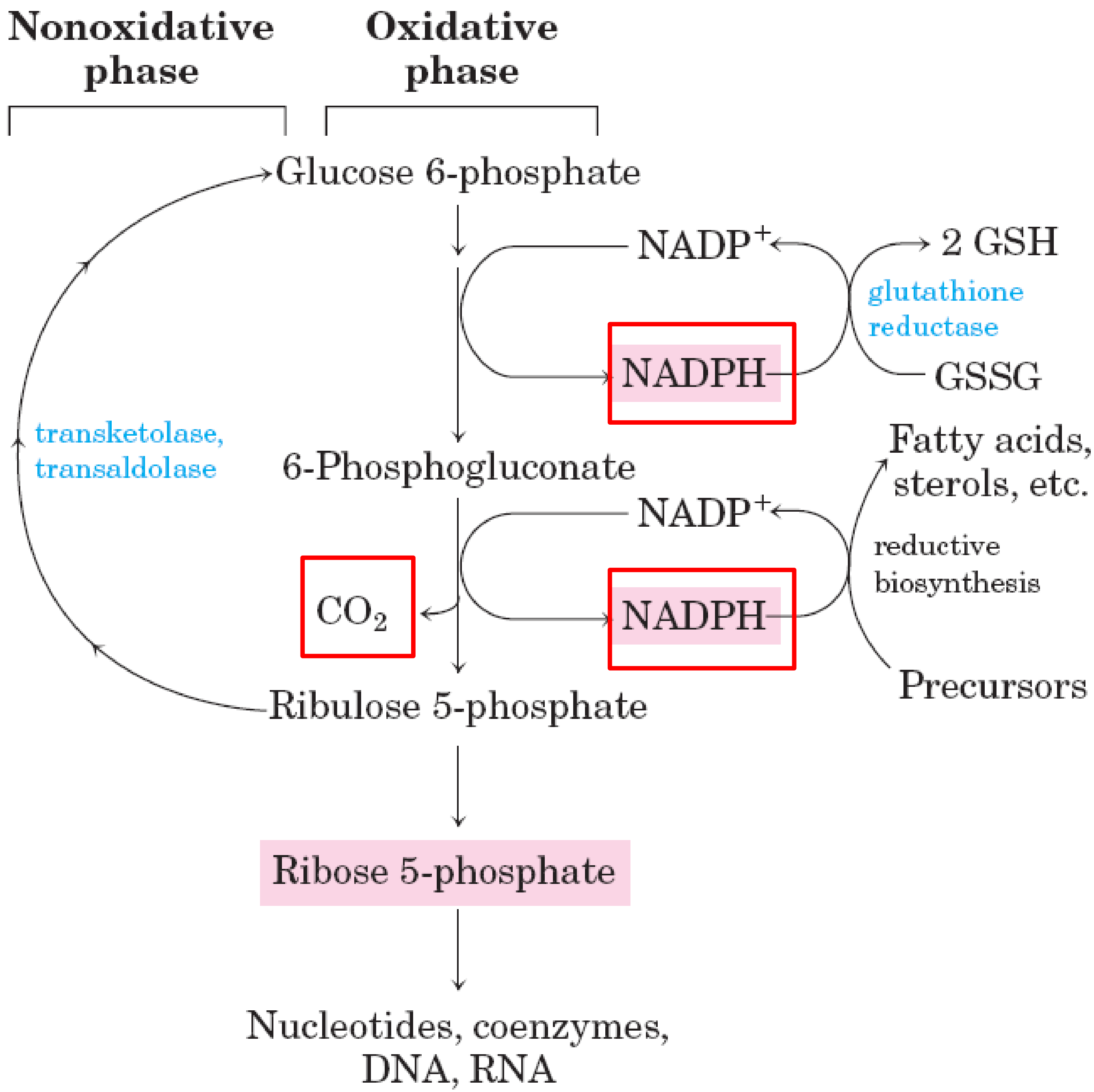
    --The Nonoxidative phase

- Gluconeogenesis
- Regulation of Gluconeogenes

1. Pentose Phosphate Pathway（PPP）

- Mostly in **cytoplasm** of **liver** and **adipose** cells
- Begin with **G-6-P**
- Provides **NADPH**, 3-, 4-, 5-, 6-, 7-C sugars
- **Three** oxidative processes followed by **five** non-oxidative steps

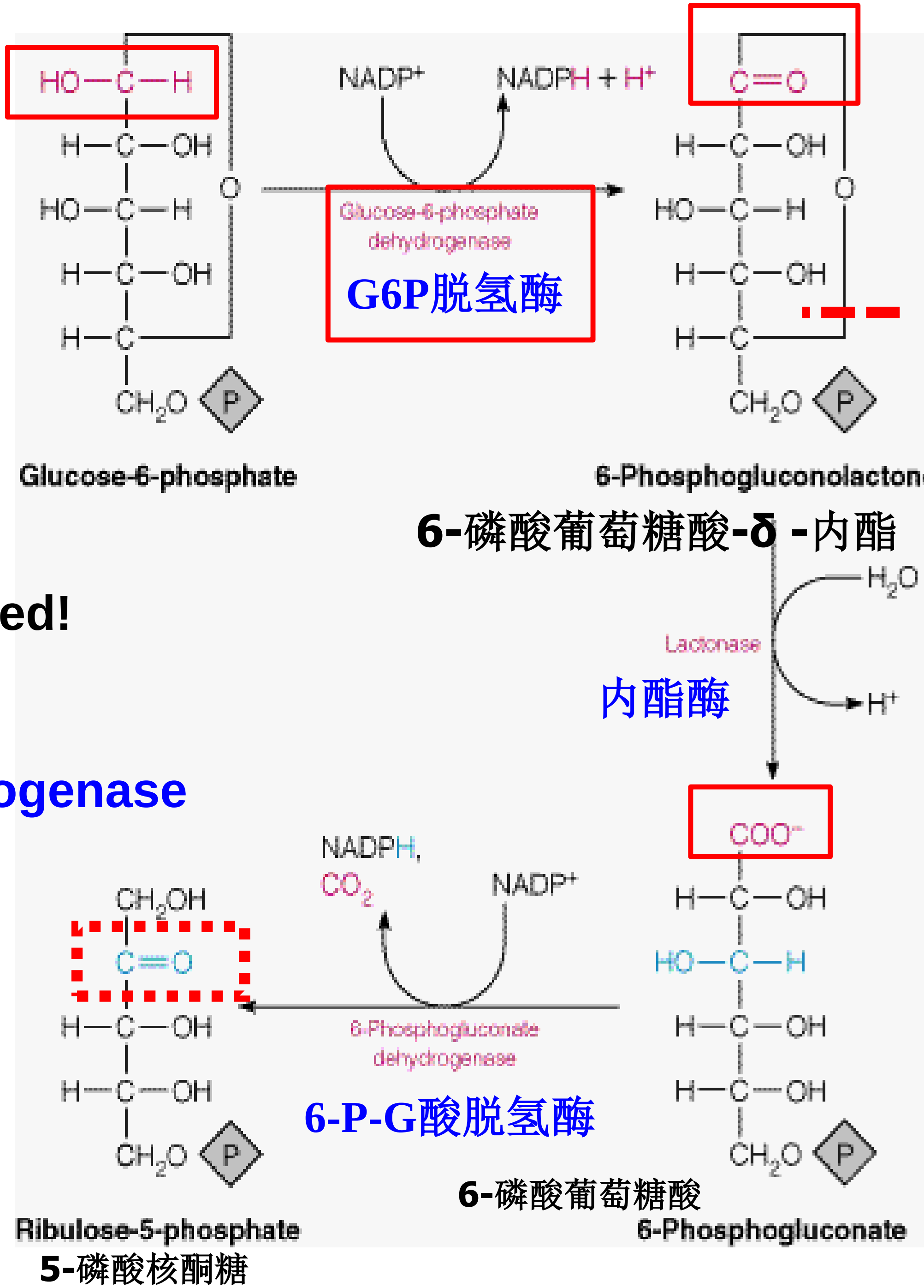

Glucose
30%
Glycogen
Glucose-6-P
PPP
70%
Fructose-6-P
Glycolysis



Nonoxidative phase
Oxidative phase
Glucose 6-phosphate
NADP$^+$
NADPH
2 GSH
glutathione reductase
GSSG
transketolase, transaldolase
6-Phosphogluconate
Fatty acids, sterols, etc.
NADP$^+$
reductive biosynthesis
CO_2
NADPH
Precursors
Ribulose 5-phosphate
Ribose 5-phosphate
Nucleotides, coenzymes, DNA, RNA

1.1 The Oxidative Phase

Generation of NADPH



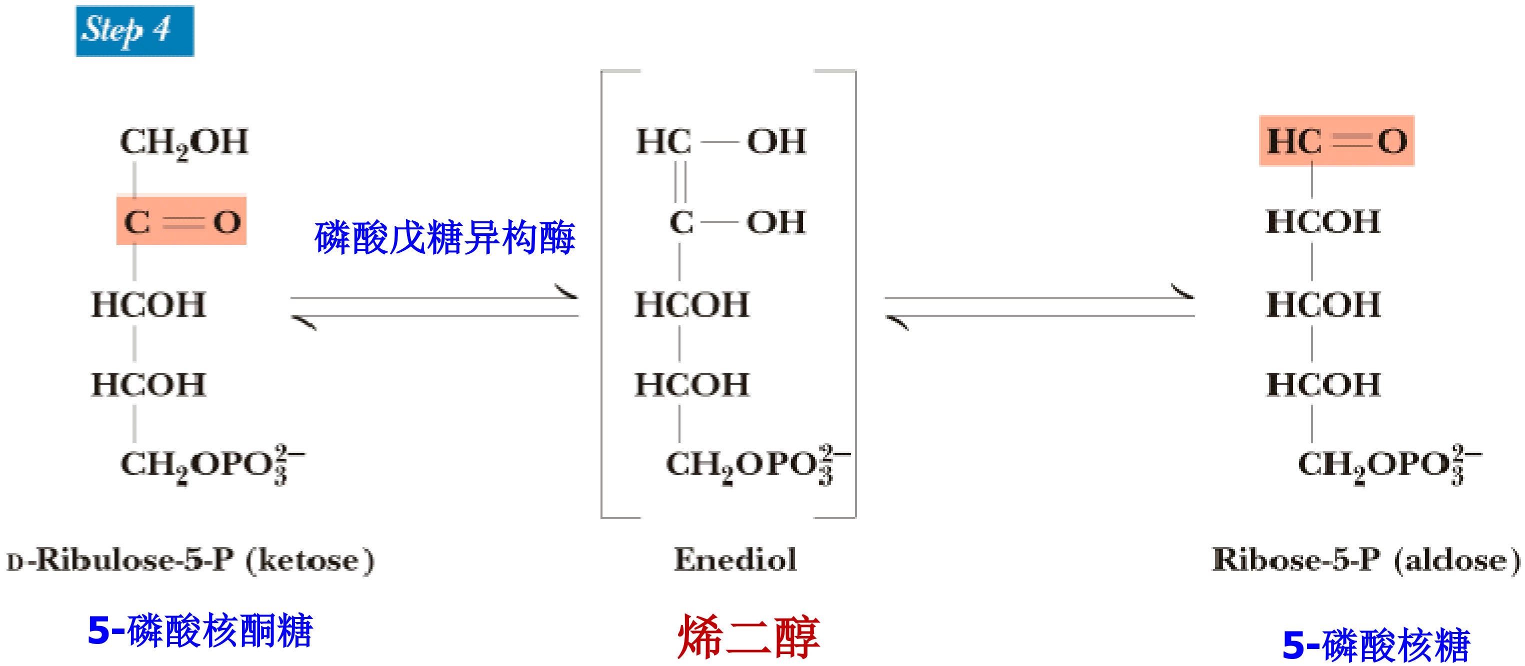
- **Glucose-6-P Dehydrogenase**
  - **– Irreversible-highly regulated!**
- **Gluconolactonase**
- **6-Phosphogluconate Dehydrogenase**

1.2 The Nonoxidative phase

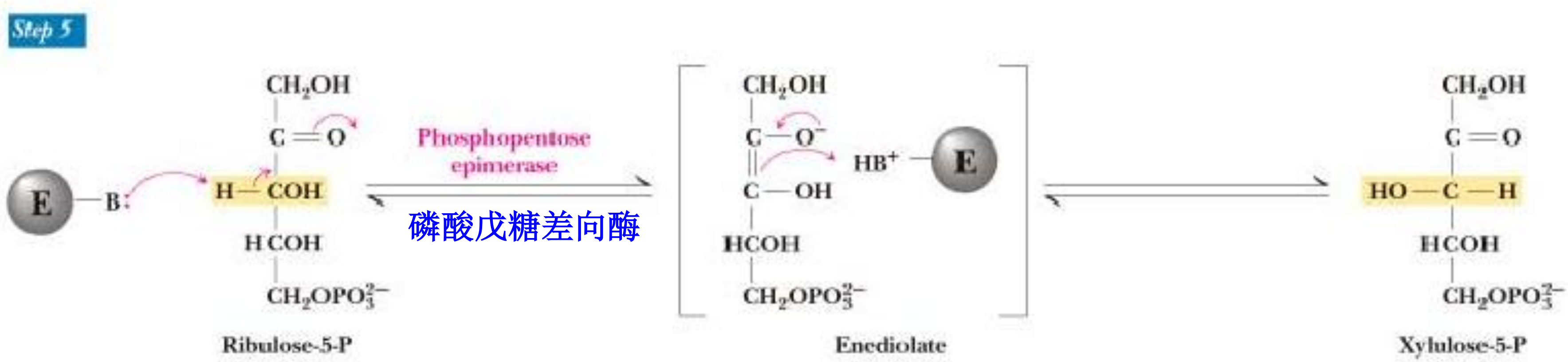
Five steps, 4 types of reaction

- **Phosphopentose isomerase（异构酶）**
  - converts ketose (酮糖) to aldose (醛糖)
- **Phosphopentose Epimerase（差向酶）**
  - epimerizes at C-3
- **Transketolase (TPP-dependent)（转酮酶）**
  - transfer of two-carbon units
- **Transaldolase (Schiff base mechanism)（转醛酶）**
  - transfers a three-carbon unit

The phosphopentose isomerase reaction involves an enediol intermediate

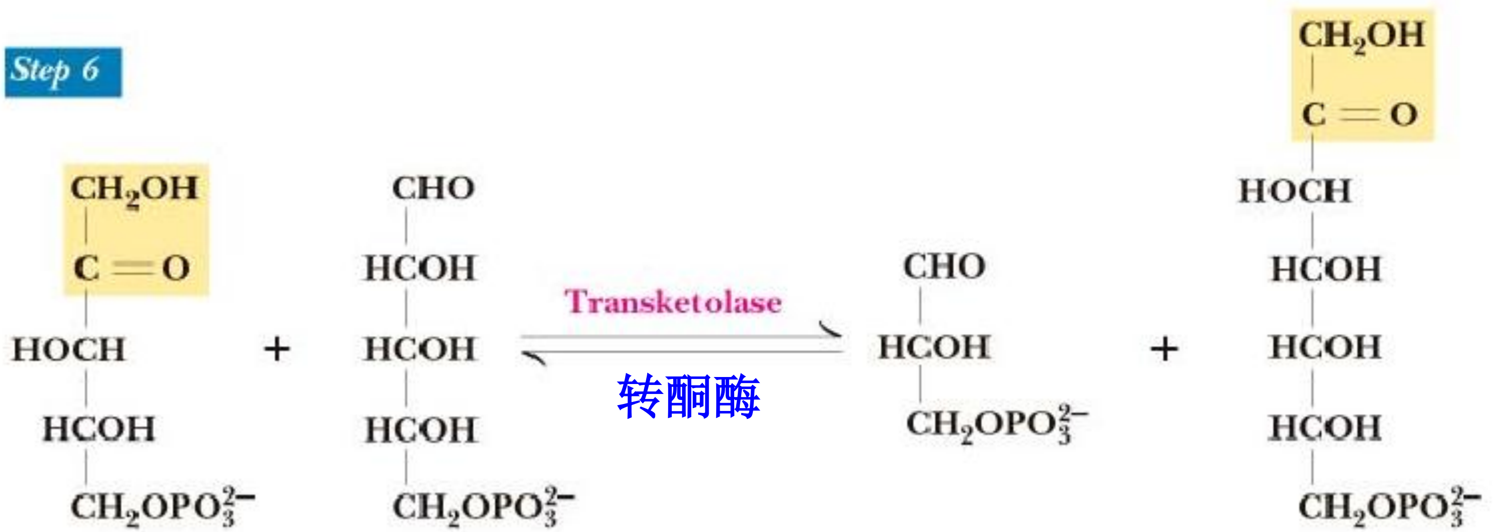


The phosphopentose epimerase reaction interconverts ribulose-5-P and xylulose-5-phosphate



5-磷酸核酮糖　　烯二醇　　5-磷酸木酮糖

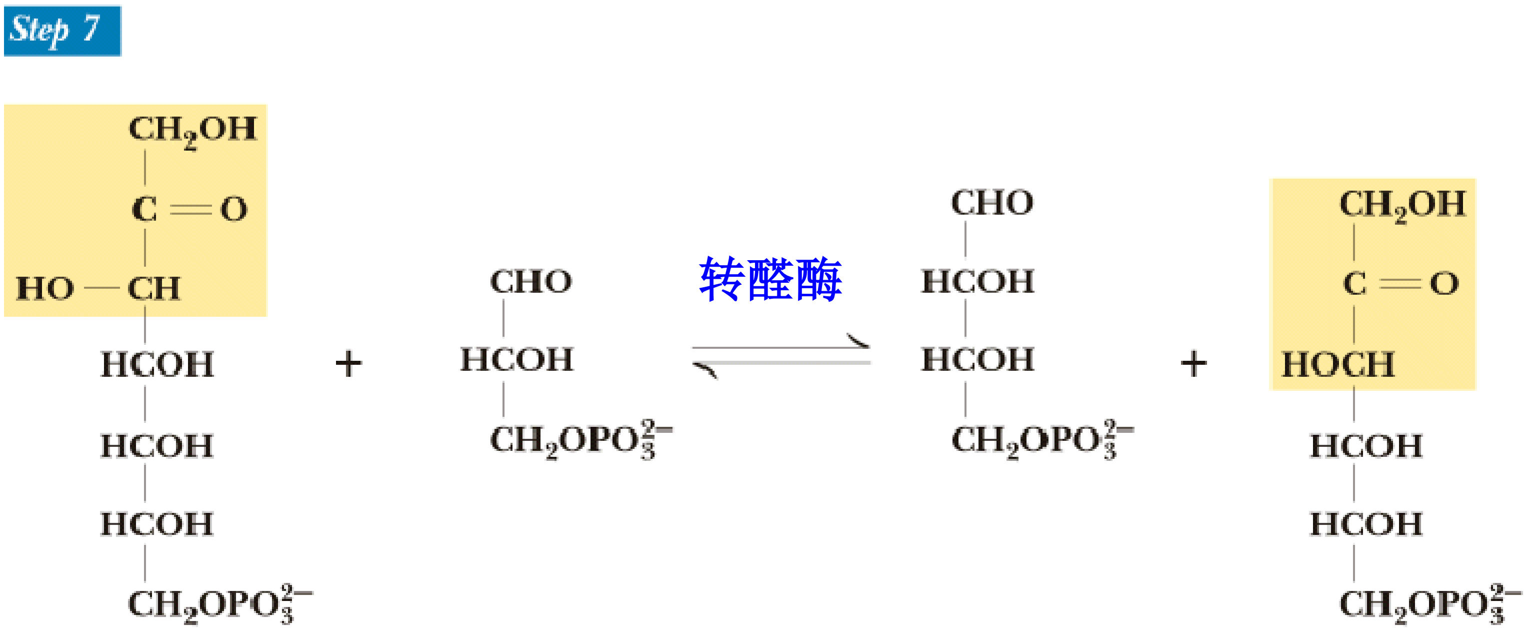
The transketolase reaction



Xylulose-5-P　　Ribose-5-P　　Glyceraldehyde-3-P　　Sedoheptulose-7-P

木酮糖**-5-P**　　核糖**-5-P**　　甘油醛**-3-P**　　景天庚酮糖**-7-P**

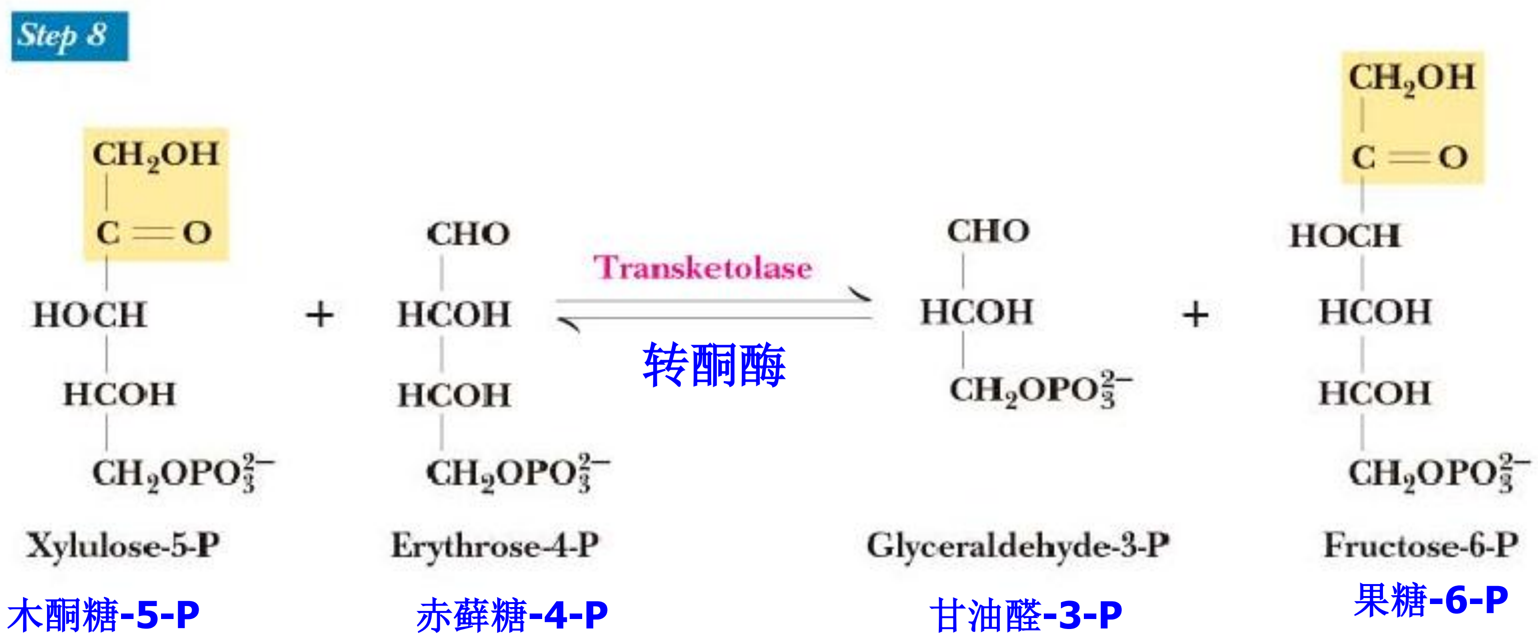
The transaldolase reaction

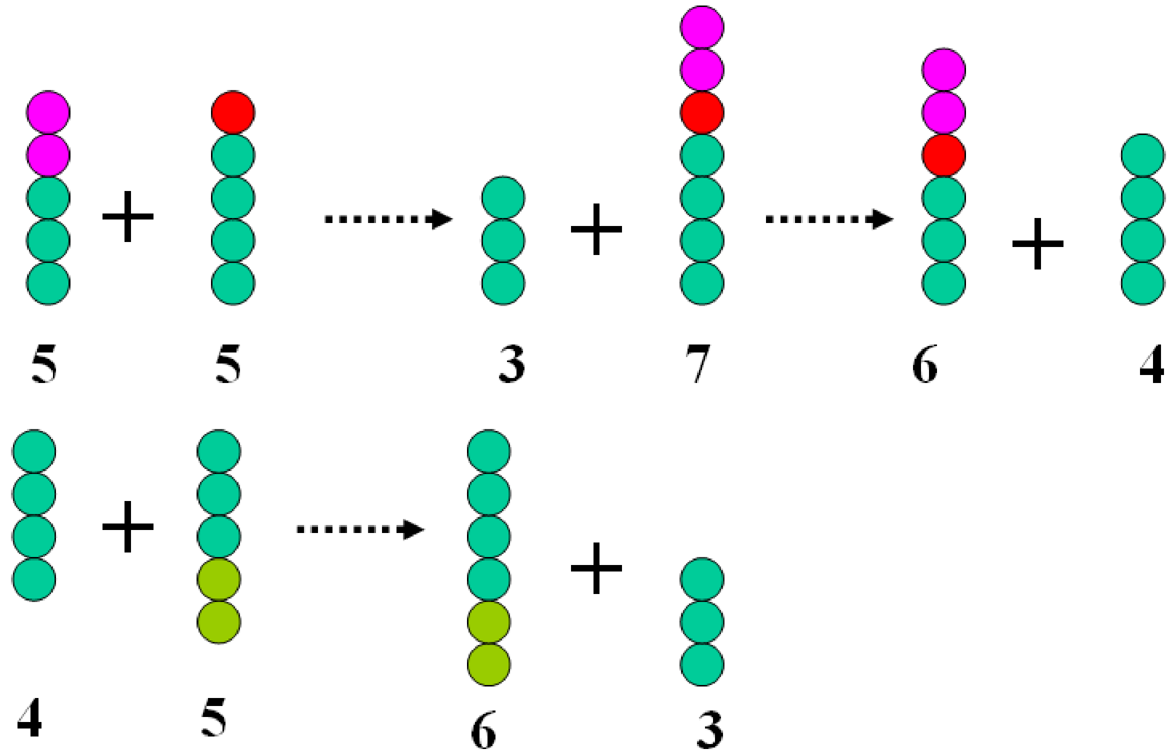


Sedoheptulose-7-P | Glyceraldehyde-3-P | Erythrose-4-P | Fructose-6-P

景天庚酮糖-7-P | **甘油醛-3-P** | **赤藓糖-4-P** | **果糖-6-P**

The transketolase reaction of step 8 in the pentose phosphate pathway





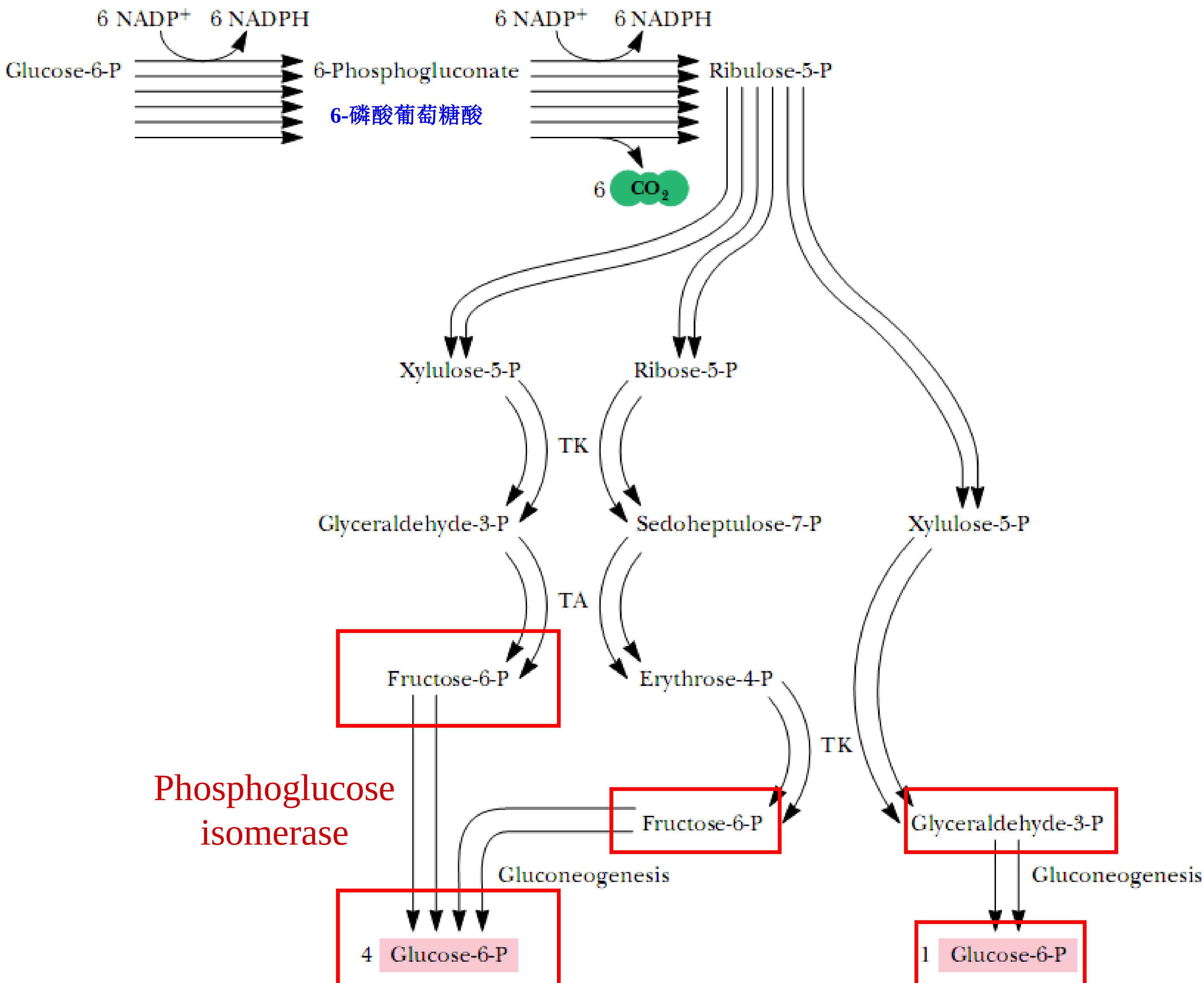
C5 + C5 --> C7 + C3

C7 + C3 --> C4 + C6

C5 + C4 --> C6 + C3

Sum:

3C5 --> 2C6 + C3



6 NADP+
6 NADPH
Glucose-6-P
6-Phosphogluconate
6-磷酸葡萄糖酸
6 NADP+
6 NADPH
Ribulose-5-P
6 CO2
Xylulose-5-P
Ribose-5-P
TK
Glyceraldehyde-3-P
Sedoheptulose-7-P
Xylulose-5-P
TA
Fructose-6-P
Erythrose-4-P
TK
Phosphoglucose isomerase
Fructose-6-P
Glyceraldehyde-3-P
Gluconeogenesis
Gluconeogenesis
4 Glucose-6-P
1 Glucose-6-P

outline

$\boxed{\mathbf{6\ G6P} + 6H_2O + 12NADP^+}$

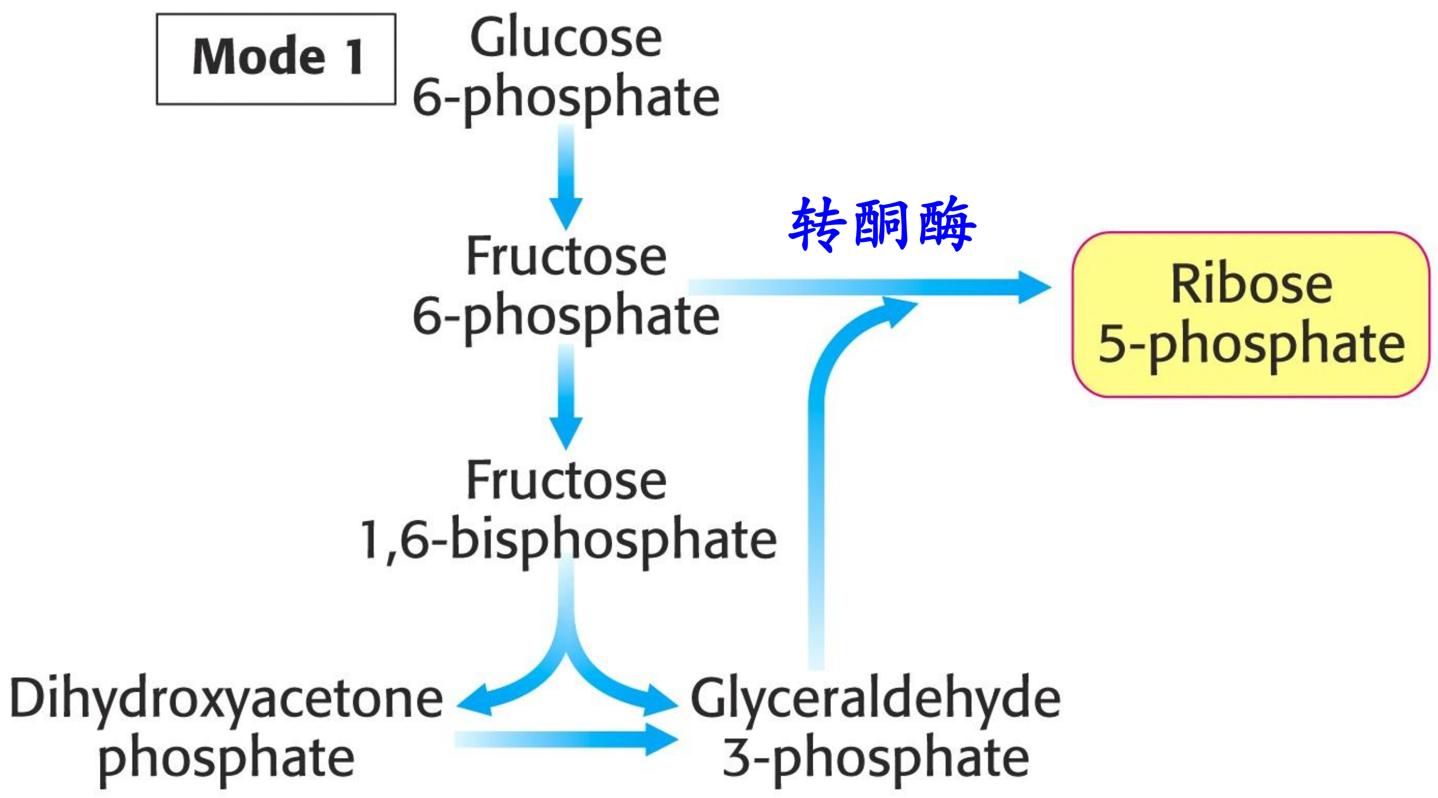
$$\Big\downarrow$$

$\boxed{\mathbf{5\ G6P} + \mathbf{6CO_2} + 12NADPH + 12H^+ + Pi}$

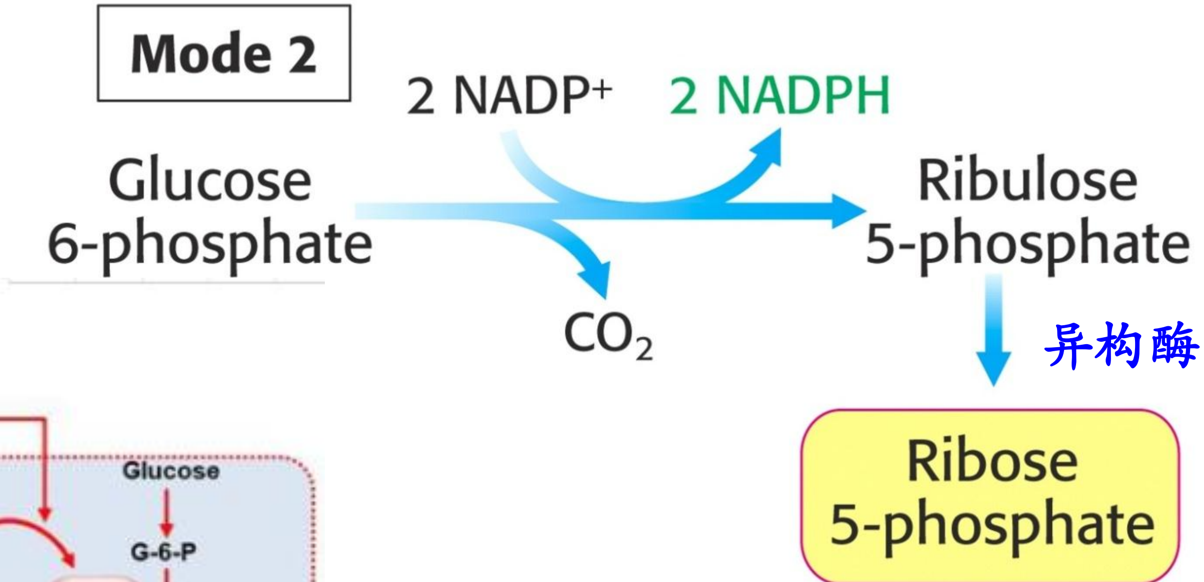
1.3 Variations on the PPP

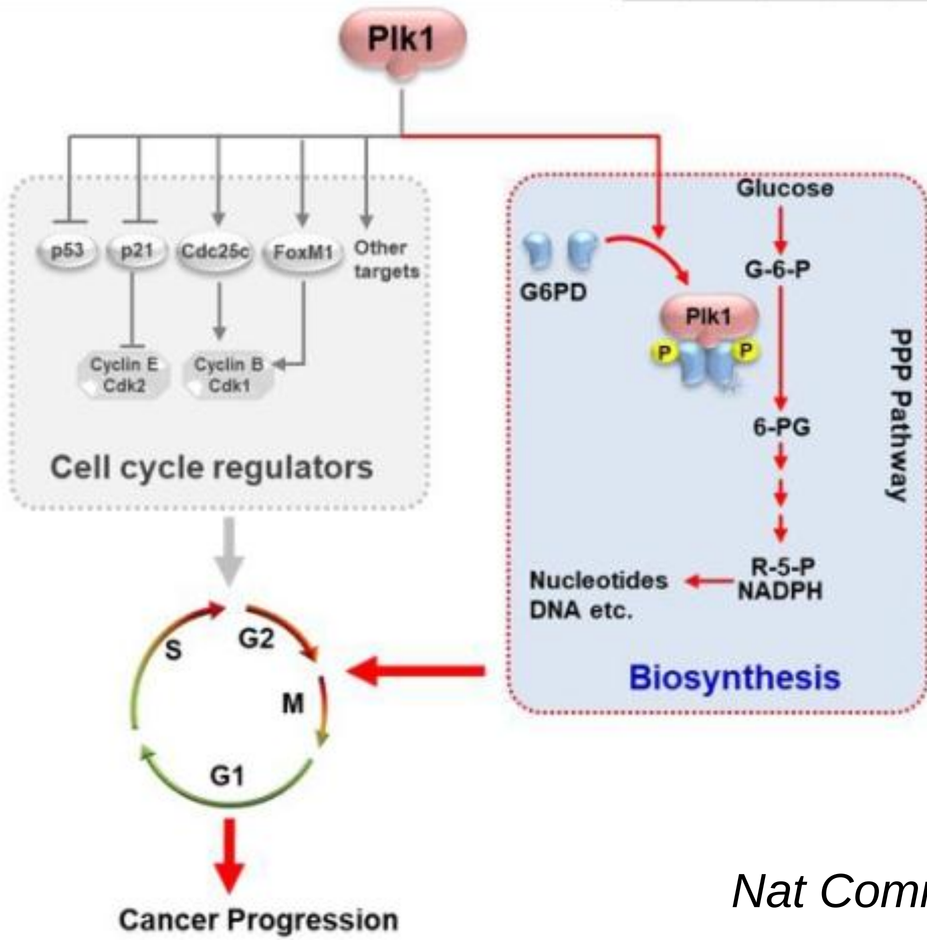
- More ribose-5-P than NADPH is needed
- Both ribose-5-P and NADPH are needed
- More NADPH than ribose-5-P is needed
- NADPH and ATP are needed, but ribose-5-P is not

Rapidly dividing cells require more ribose 5- phosphate than NADPH



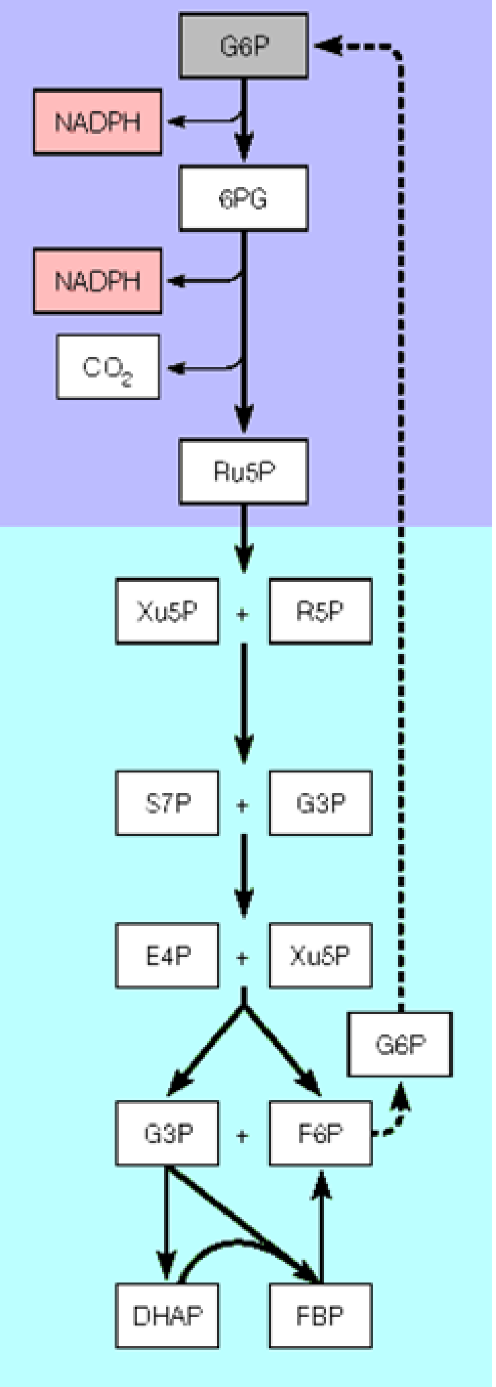
The need for NADPH and ribose 5-phosphate is balanced



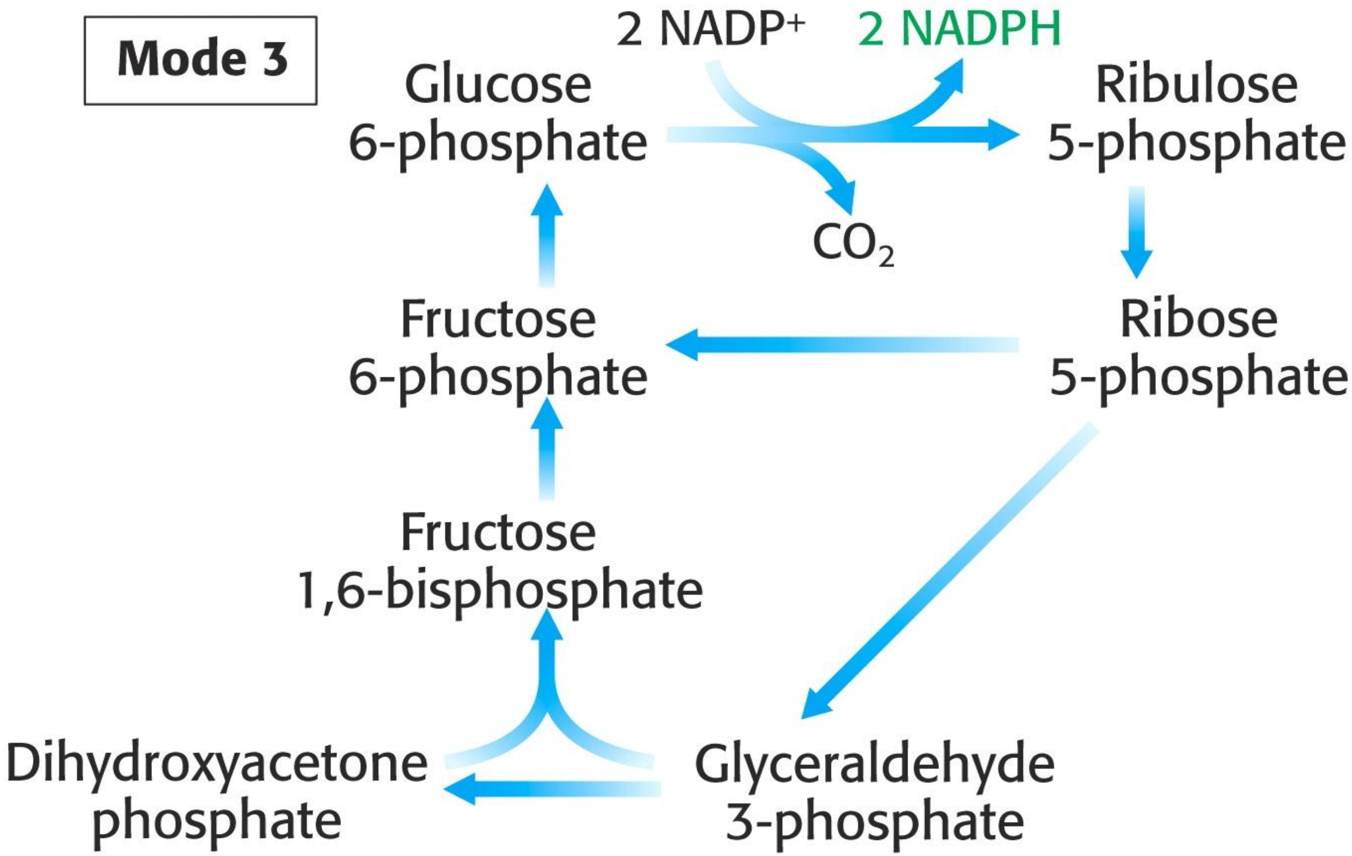


Nat Commun. 2017 Nov 15;8(1):1506

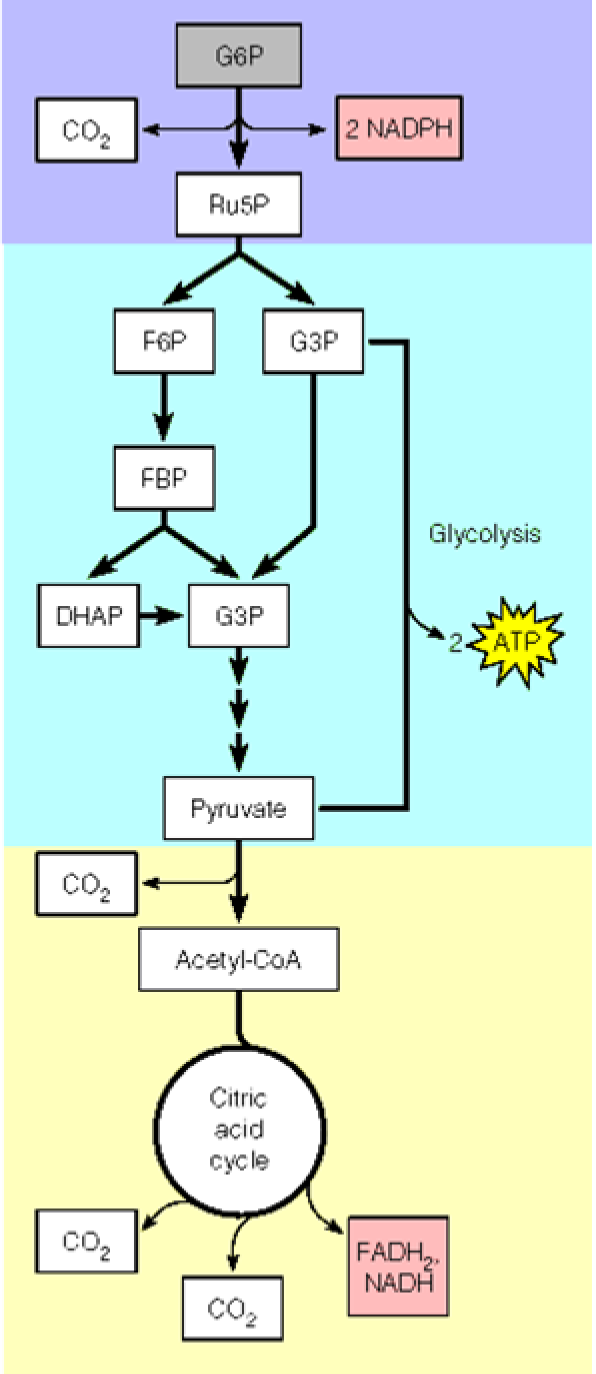
More NADPH is needed than ribose 5-P; Fatty acid synthesis in adipose cells



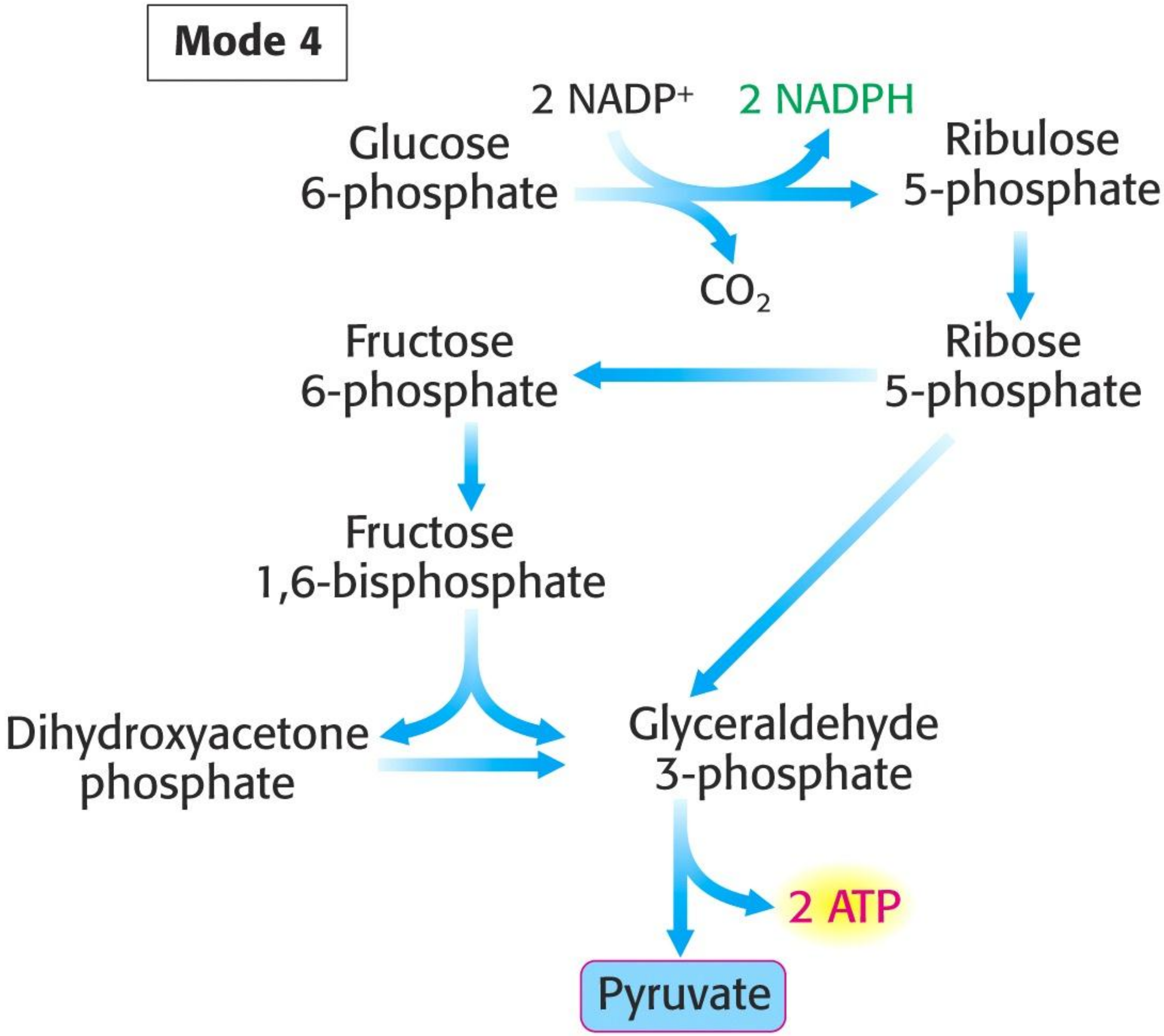
(b) NADPH synthesis



The cell needs both NADPH and ATP



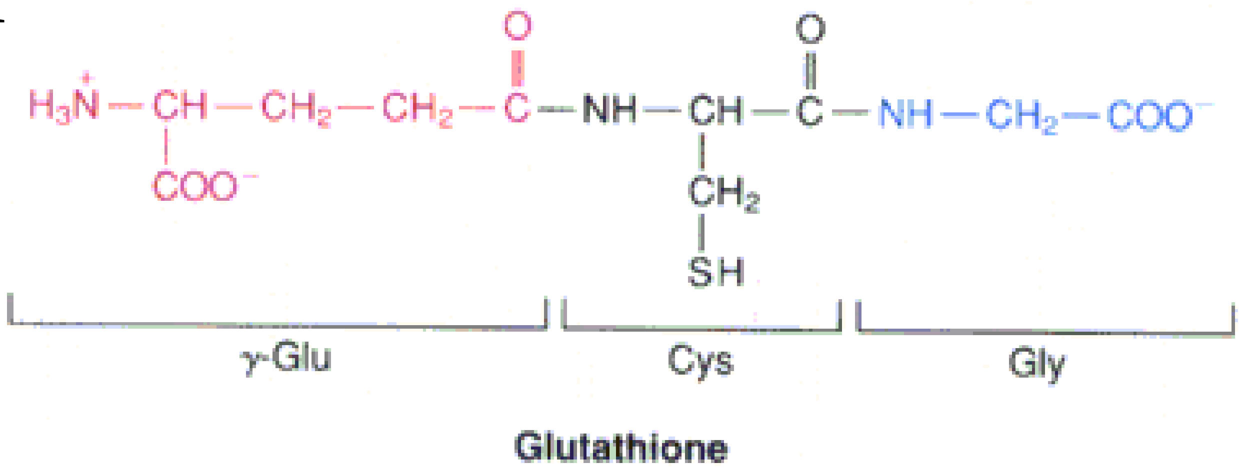
(c) Energy generation



- **Human Genetic Disorders Involving HMP Enzymes**

- **G6PDH** （Glucose-6-phosphate dehydrogenase）

- **Red cell----GSH**



$$GSSG + NADPH + H^+ \rightarrow 2\ GSH + NADP^+$$

NADPH regulates HMP

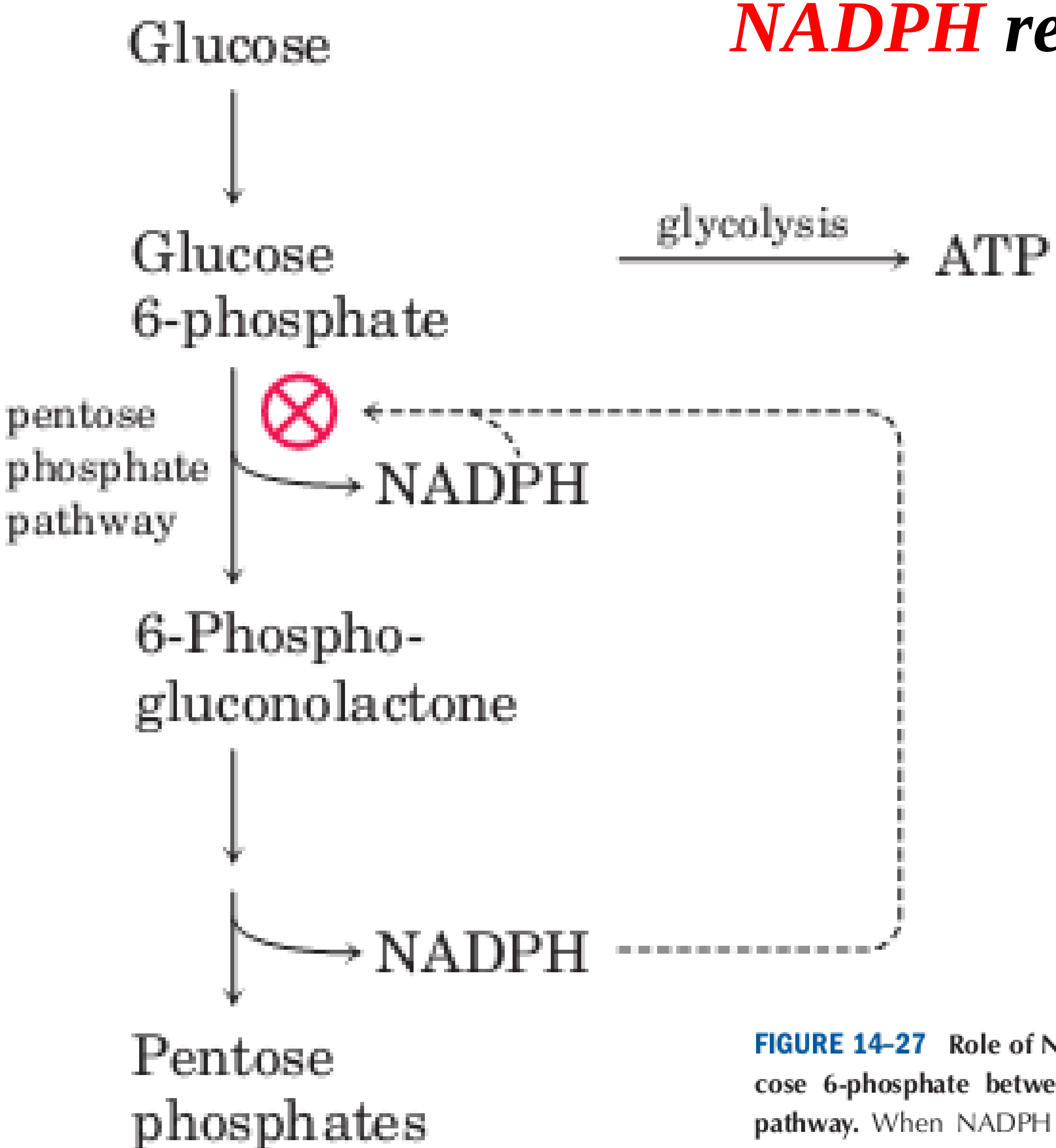


FIGURE 14–27 Role of NADPH in regulating the partitioning of glucose 6-phosphate between glycolysis and the pentose phosphate pathway. When NADPH is forming faster than it is being used for biosynthesis and glutathione reduction (see Fig. 14–20), [NADPH] rises and inhibits the first enzyme in the pentose phosphate pathway. As a result, more glucose 6-phosphate is available for glycolysis.

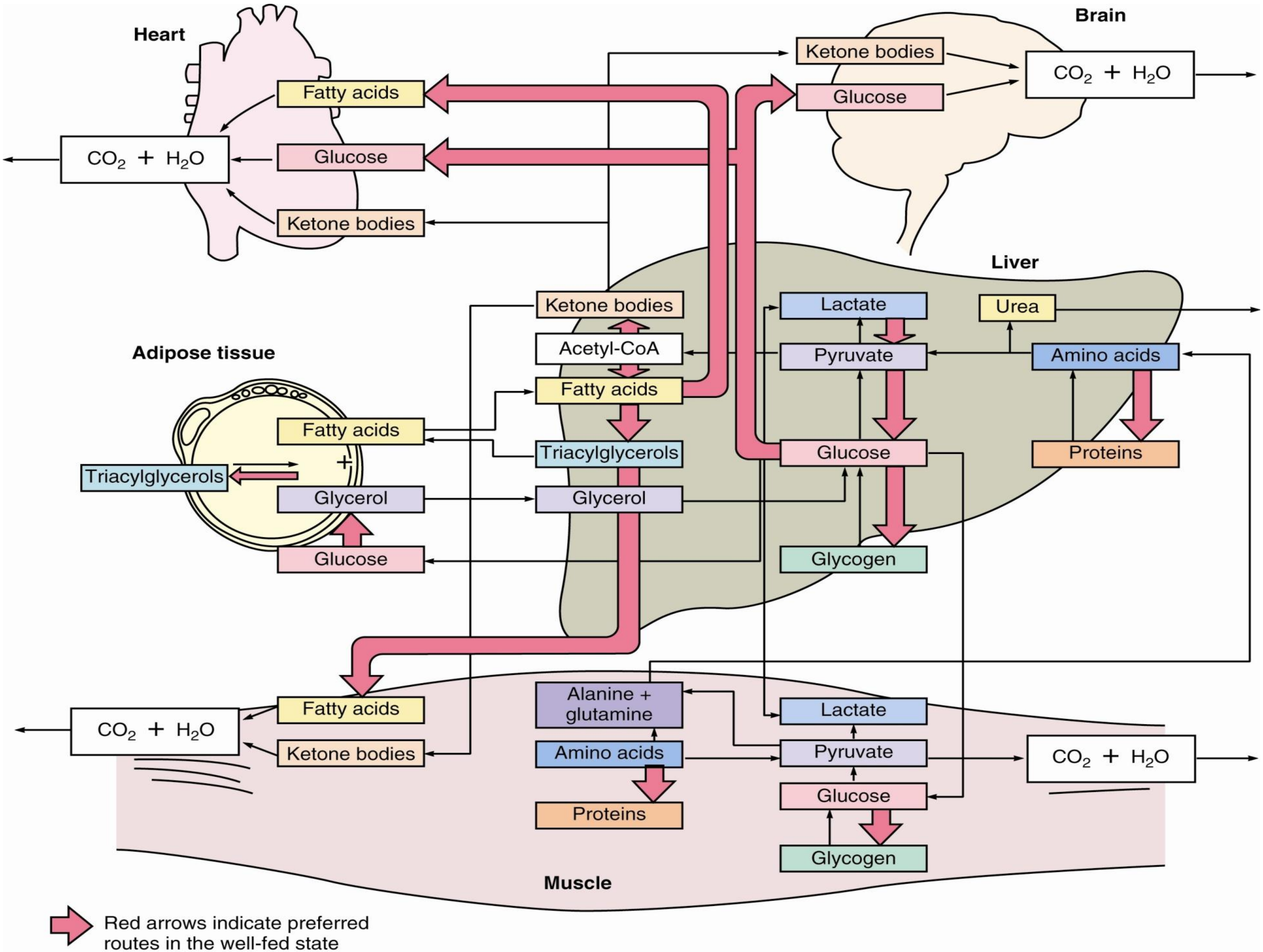
2. Gluconeogenesis
糖异生

Synthesis of "new glucose" from common metabolites

- Humans consume **160**g G /day
- 75% (120g/d) -- brain
- Body fluids contain 20g G
- Glycogen stores yield 180-200g G
- So the body must be able to make its own glucose

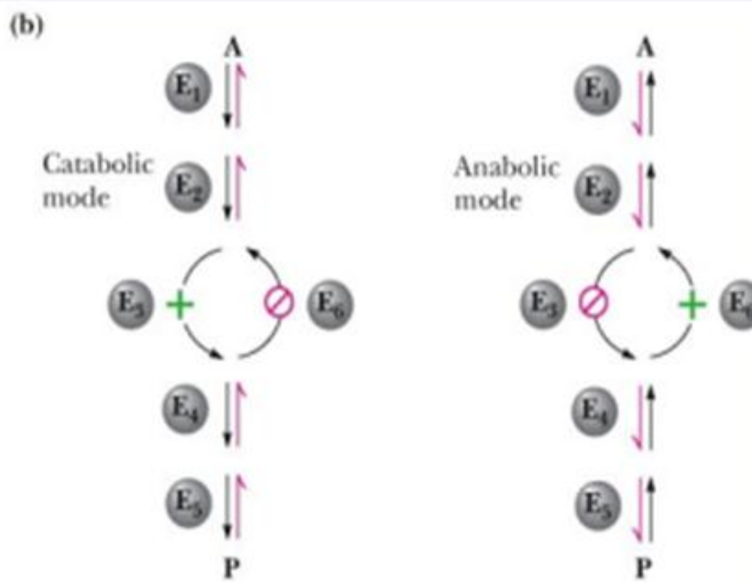
PYRUVATE → GLUCOSE

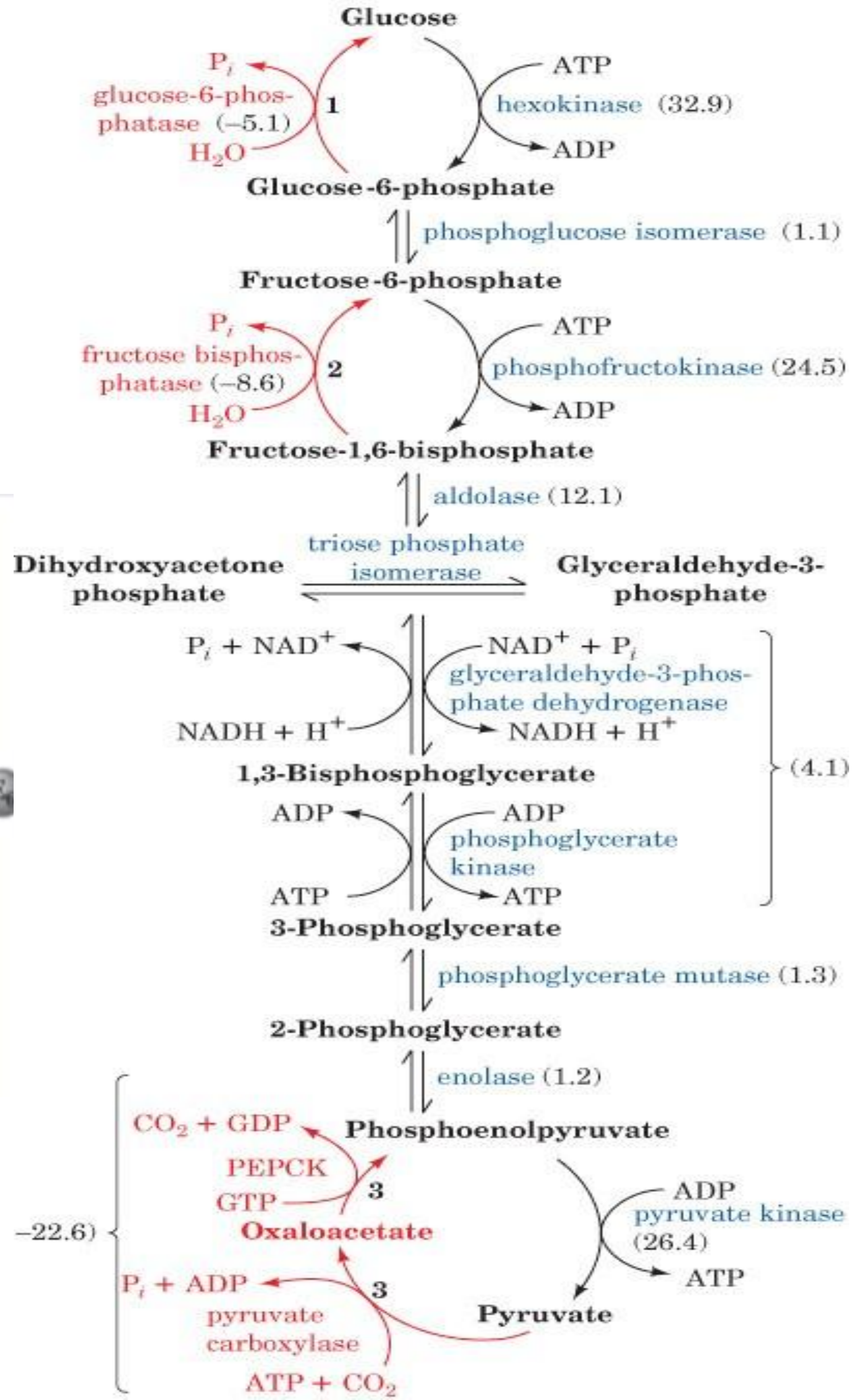
- **Occurs mainly in liver (90%) and kidney (10%)**



Heart
Brain
Fatty acids
Glucose
Ketone bodies
$CO_2 + H_2O$
Ketone bodies
Glucose
$CO_2 + H_2O$
Liver
Ketone bodies
Acetyl-CoA
Fatty acids
Triacylglycerols
Glycerol
Lactate
Pyruvate
Glucose
Glycogen
Urea
Amino acids
Proteins
Adipose tissue
Fatty acids
Triacylglycerols
Glycerol
Glucose
Fatty acids
Ketone bodies
$CO_2 + H_2O$
Alanine + glutamine
Amino acids
Proteins
Lactate
Pyruvate
Glucose
Glycogen
$CO_2 + H_2O$
Muscle
Red arrows indicate preferred routes in the well-fed state

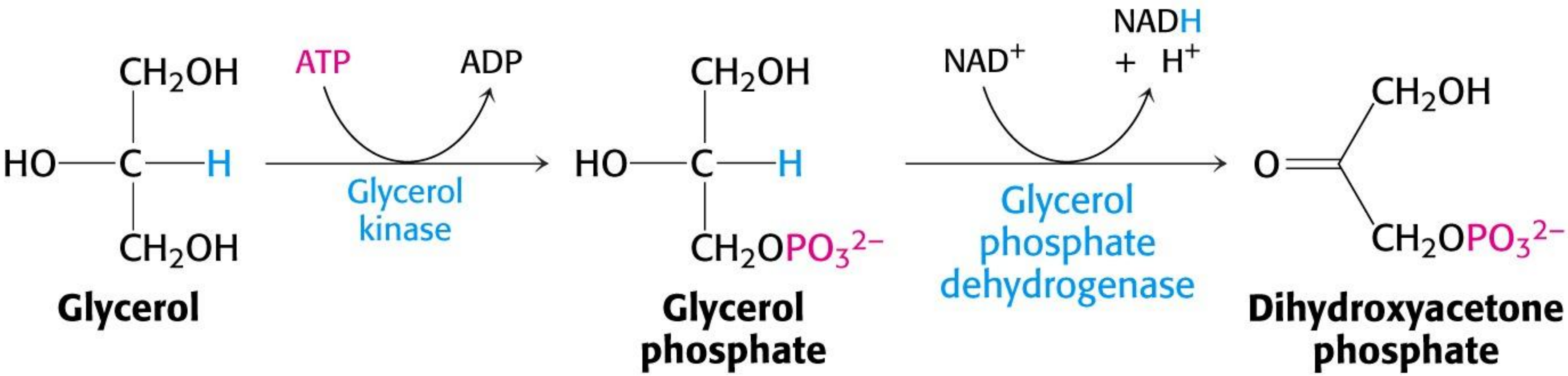
Comparison of glycolysis and gluconeogenesis



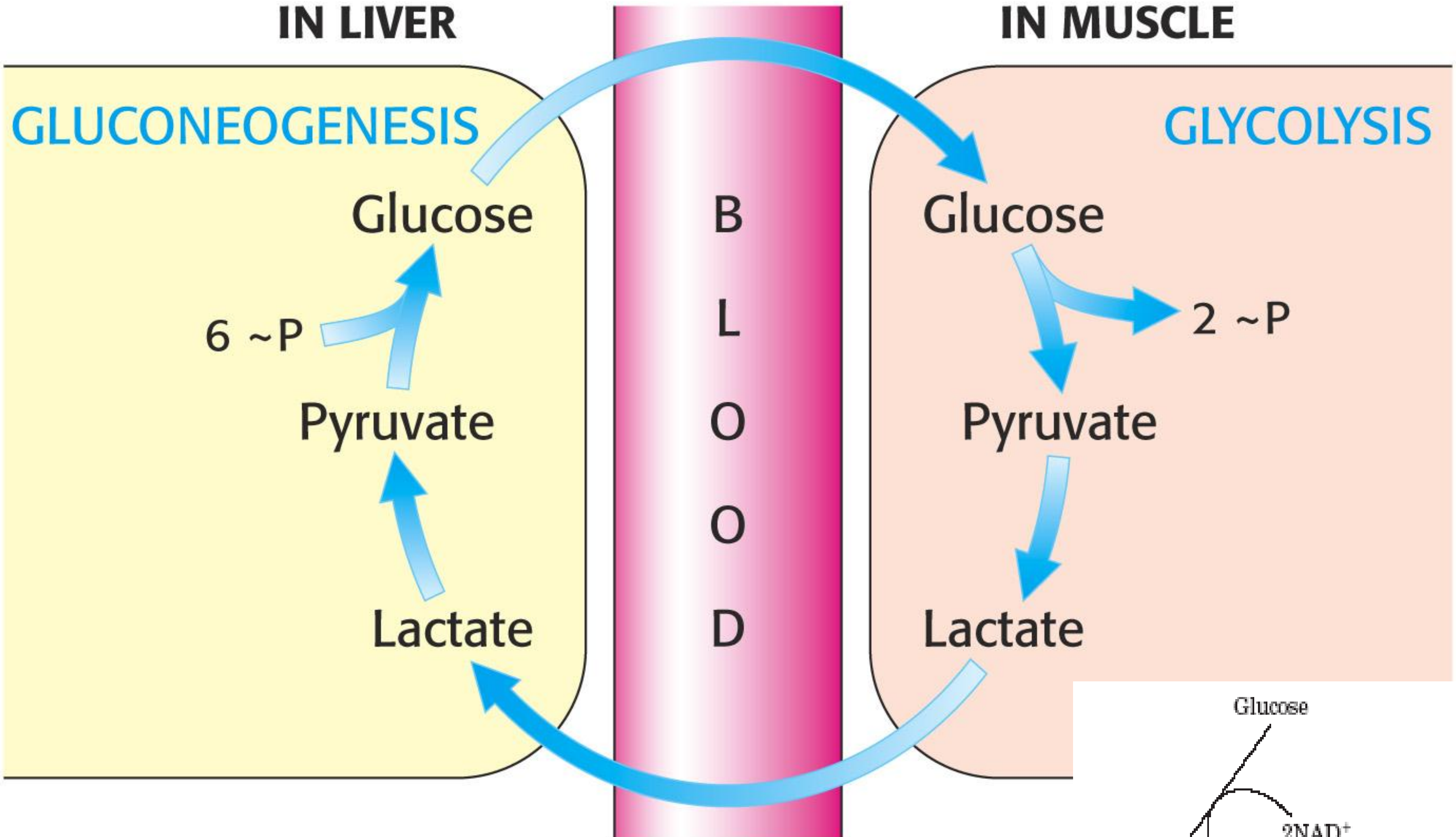


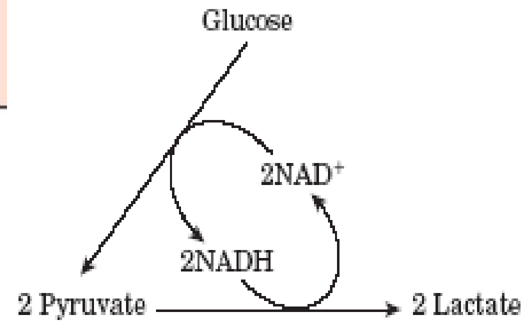
Gluconeogenesis （糖异生）

- Any molecule → **pyruvate**
- **Lactate** & **Ala**
- **Glycerol**



How your liver helps you during exercise.... The Cori Cycle





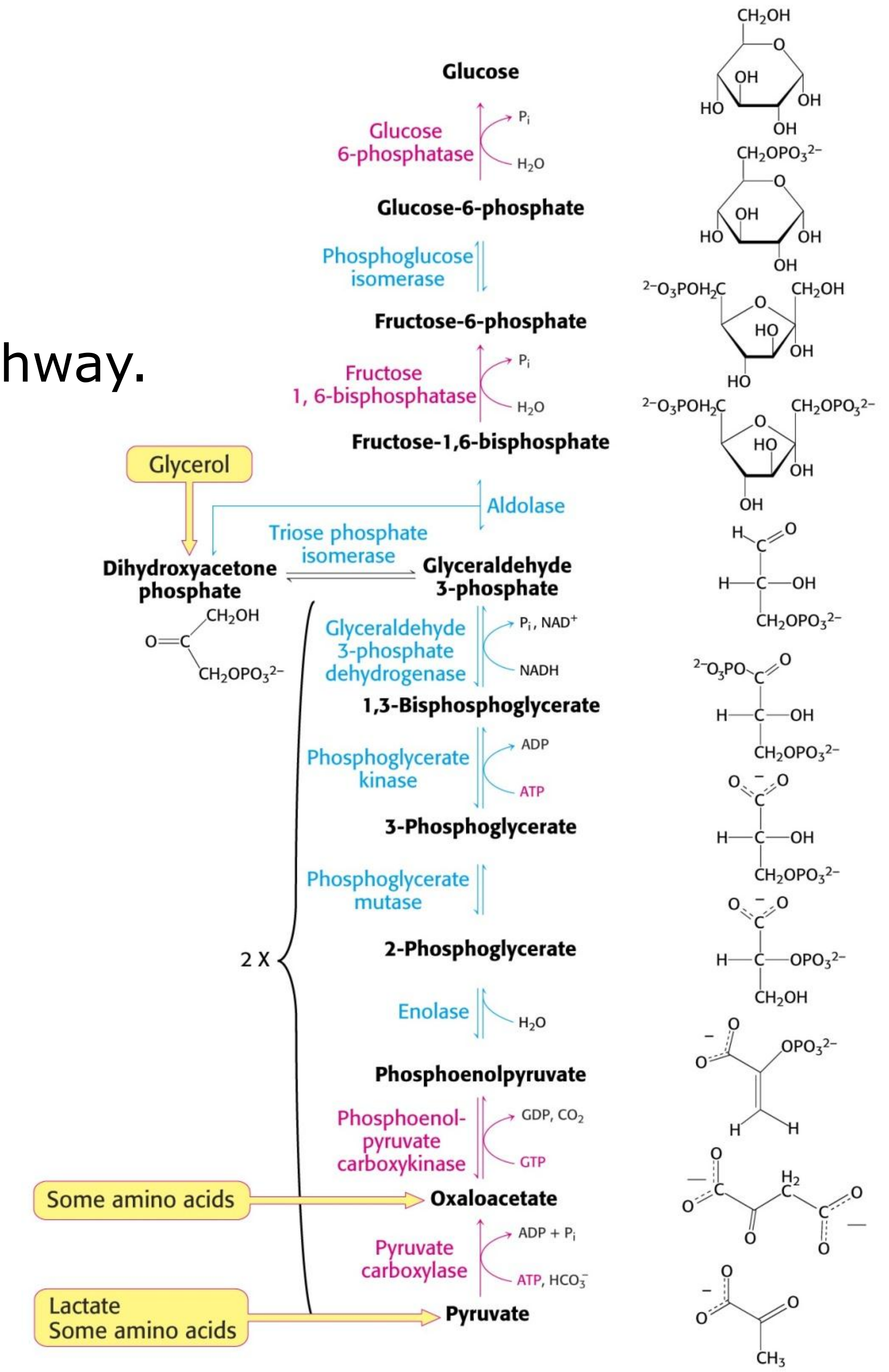
Substrates NOT for Gluconeogenesis

- **Fatty acids cannot in animals!**
  – Most fatty acids yield only acetyl-CoA
- **Acetyl-CoA $\not\rightarrow$ G in animals**
- **Acetyl-CoA $\rightarrow$ G in plants via** gloxylate cycle
- **Lysine / leucine $\not\rightarrow$ G** （Produce only acetyl-CoA upon degradation）

Gluconeogenesis

- The enzymes in **red** -- **gluconeogenic（糖异生）** pathway.

- The enzymes in **blue** – gluconeogenesis & glycolysis

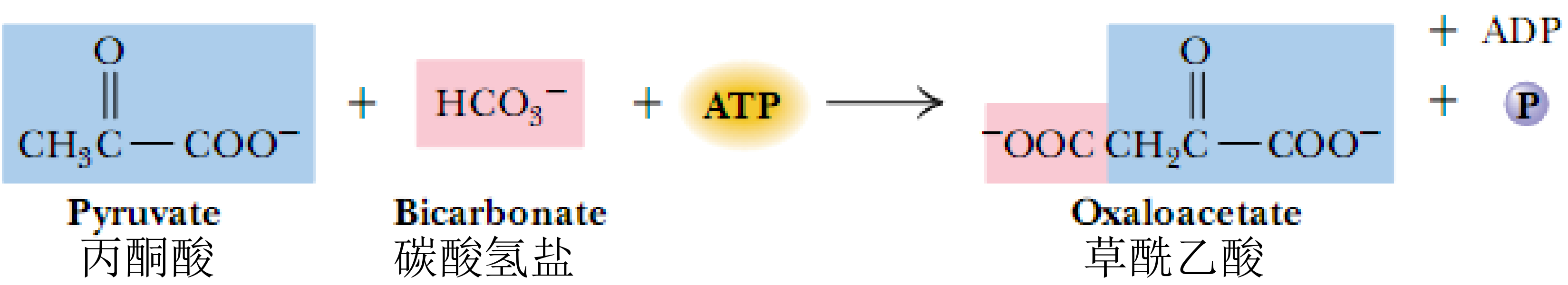


- The irreversible **glycolytic enzymes** are:
  - **hexokinase**（己糖激酶） (ΔG =-8 kcal mol^{-1})
  - **phosphofructokinase**（磷酸果糖激酶） (ΔG = -5.3 kcal mol^{-1})
  - **pyruvate kinase**（丙酮酸激酶） (ΔG = -4.0 kcal mol^{-1})

- The enzymes of **gluconeogenesis** are:
  - **pyruvate carboxylase (ATP)** 丙酮酸羧化酶
  - **phosphoenolpyruvate carboxykinase (GTP) PEP羧激酶**
  - **fructose 1,6-bisphosphatase（果糖-1，6-**二**磷酸酶）**
  - **glucose 6-phosphatase （G-6-P酶）**

2.1 Pyruvate Carboxylase

- Pyruvate + CO_2 + **ATP** + H_2O $\xrightarrow{\text{丙酮酸羧化酶}}$ oxaloacetate + ADP + P_i + 2 H^+
- Require the cofactor BIOTIN.
- **In the mitochondrial matrix**



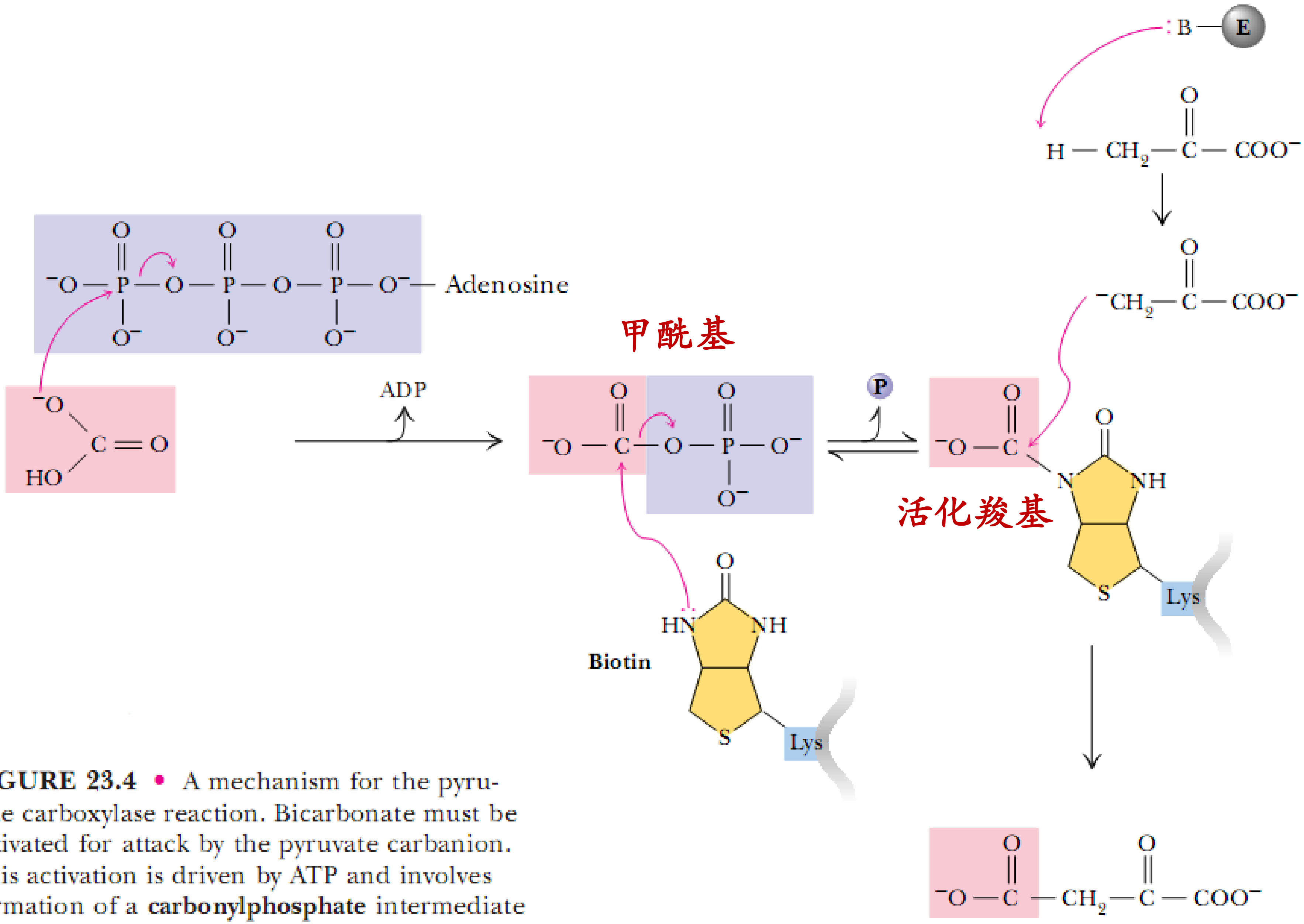
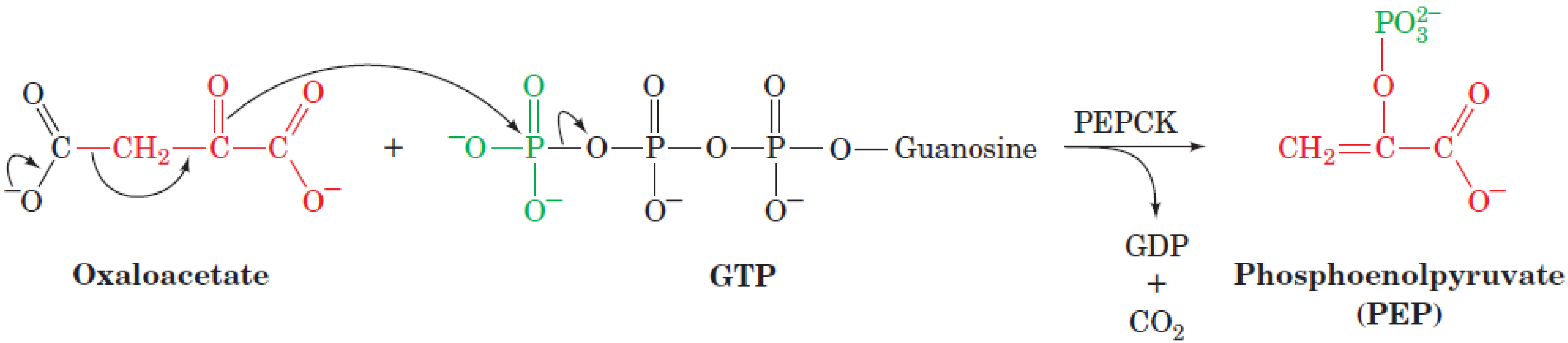


FIGURE 23.4 • A mechanism for the pyruvate carboxylase reaction. Bicarbonate must be activated for attack by the pyruvate carbanion. This activation is driven by ATP and involves formation of a **carbonylphosphate** intermediate—a mixed anhydride of carbonic and phosphoric acids. (Carbonylphosphate and carboxyphosphate are synonyms.)

2.2 Phosphoenolpyruvate Carboxykinase

PEP羧激酶, PEPCK



- in the cytosol or mit
- the sum of the two reaction is:

Pyruvate + **ATP + GTP** + H_2O →

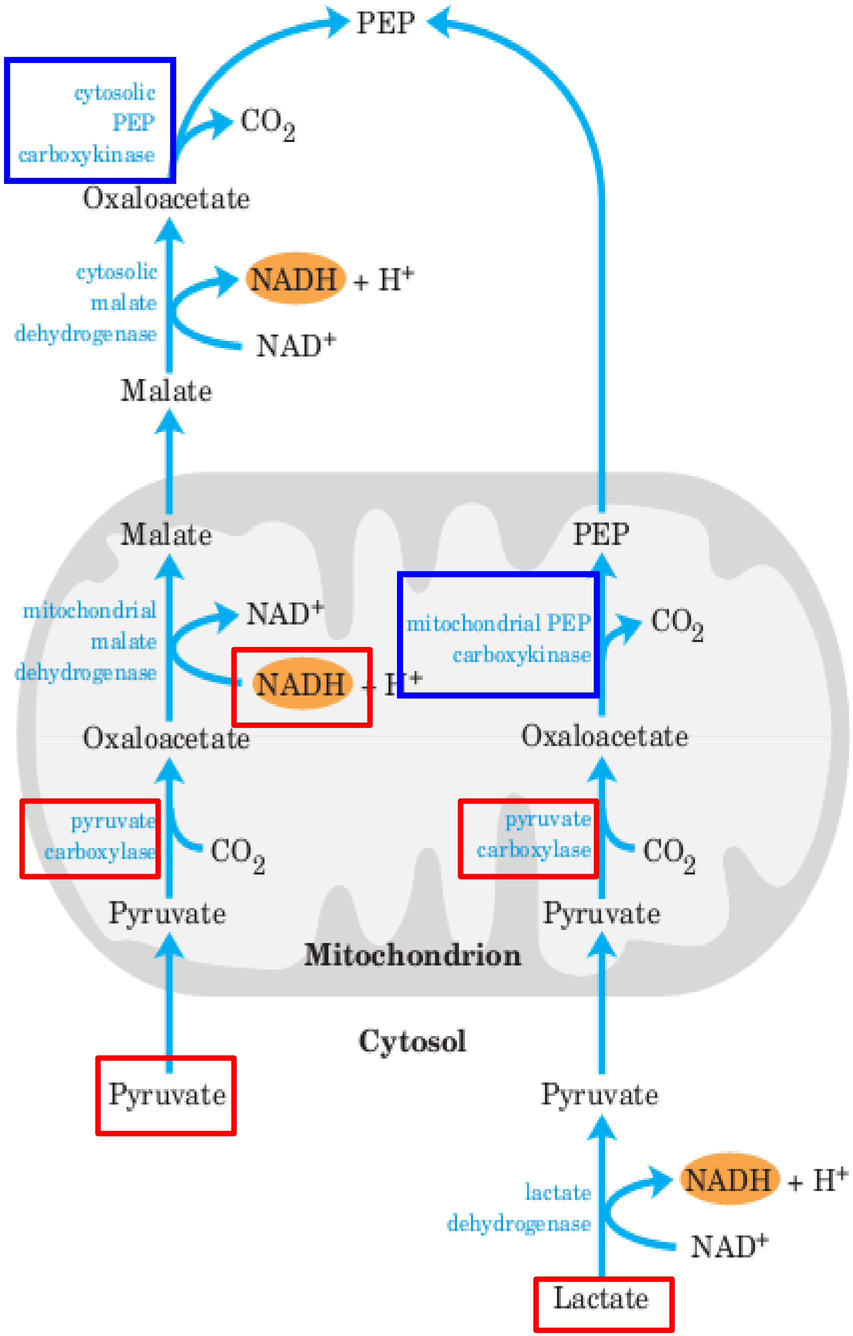
PEP + ADP + GDP + P_i + H^+

- **Pyruvate Carboxylase:**

  -in mit.

- **Phosphoenolpyruvate Carboxykinase**（羧激酶）：

  -Oxaloacetate decarboxylated and phosphorylated in the cytosol or mit.



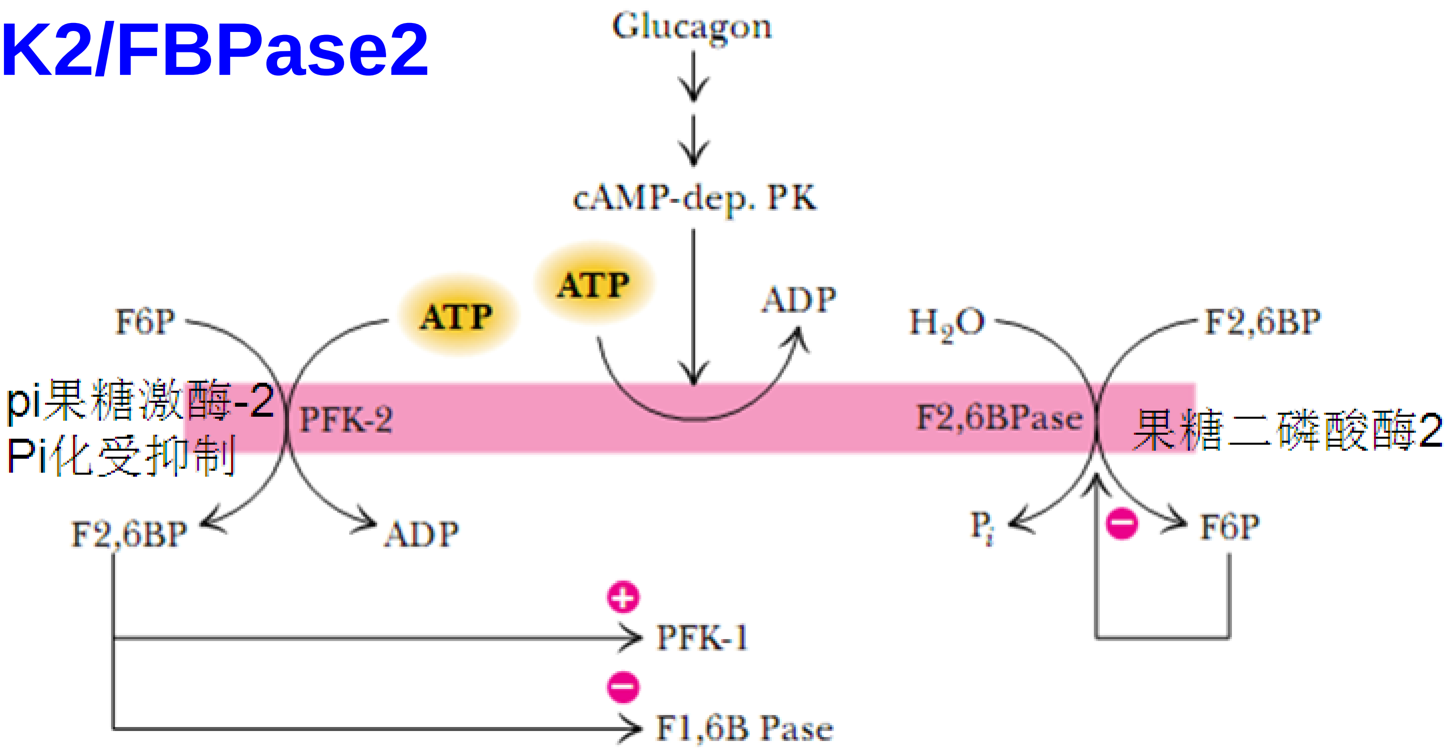
2.3 Fructose 1,6-bisphosphatase

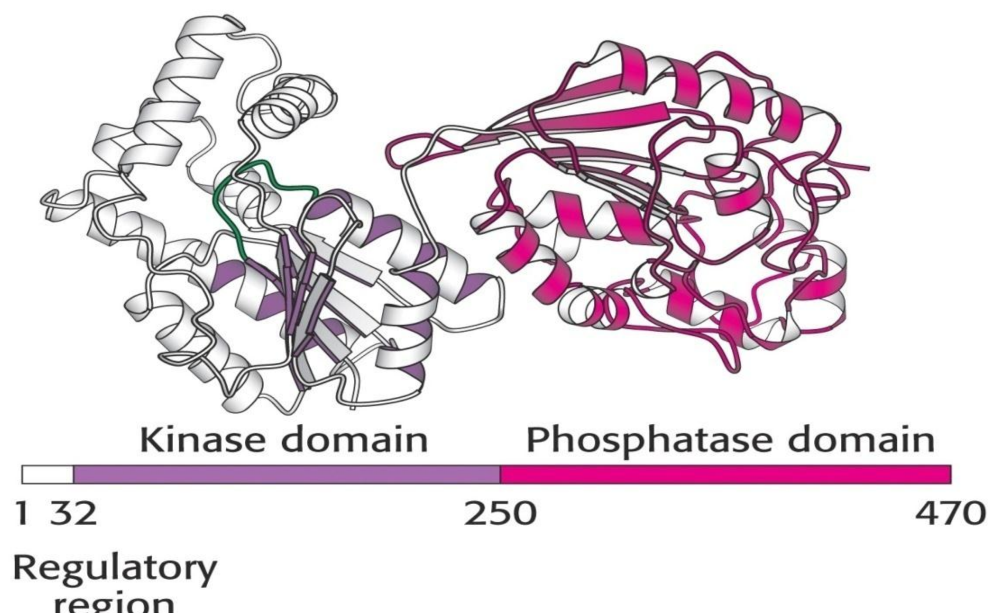
$$\text{F- 1,6-2P} + H_2O \xrightarrow{\text{果糖-1，6-二磷酸酶}} \text{6-P-F} + P_i$$

- an **allosteric** enzyme and regulates gluconeogenesis.

  - **Allosteric regulation:**
    - ATP and citrate stimulates
    - F-2,6-2P inhibits
    - AMP inhibits

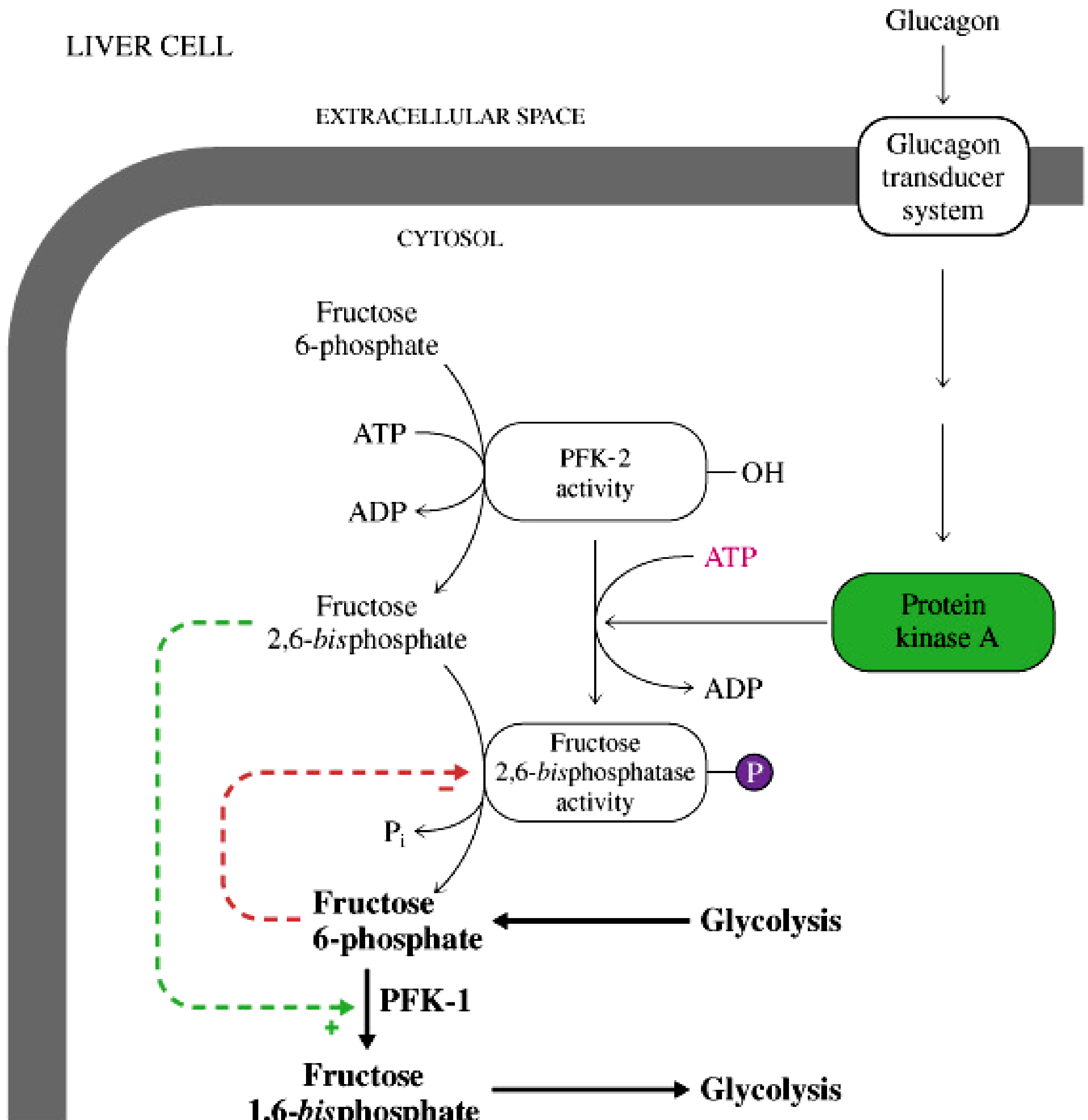
PFK2/FBPase2





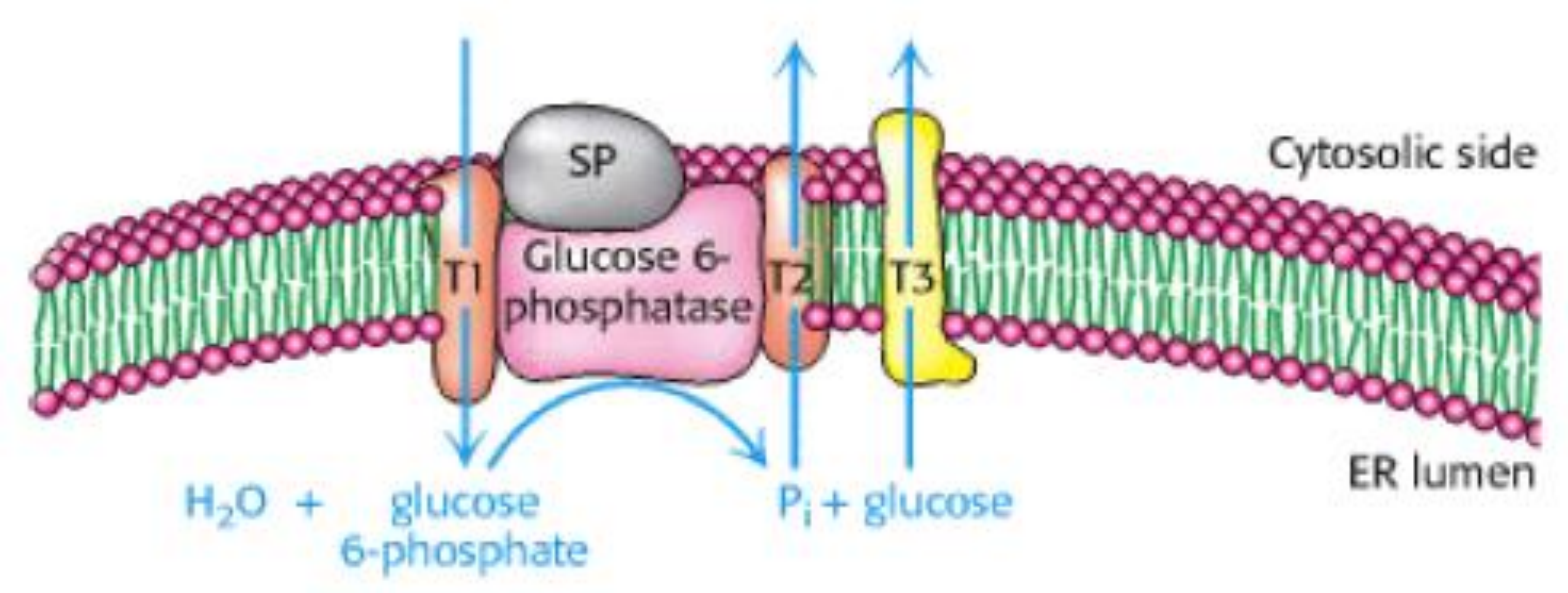
Effect of glucagon on liver glycolysis

F-2,6-BP ↓ glycolysis ↓



2.4 Glucose 6-phosphatase

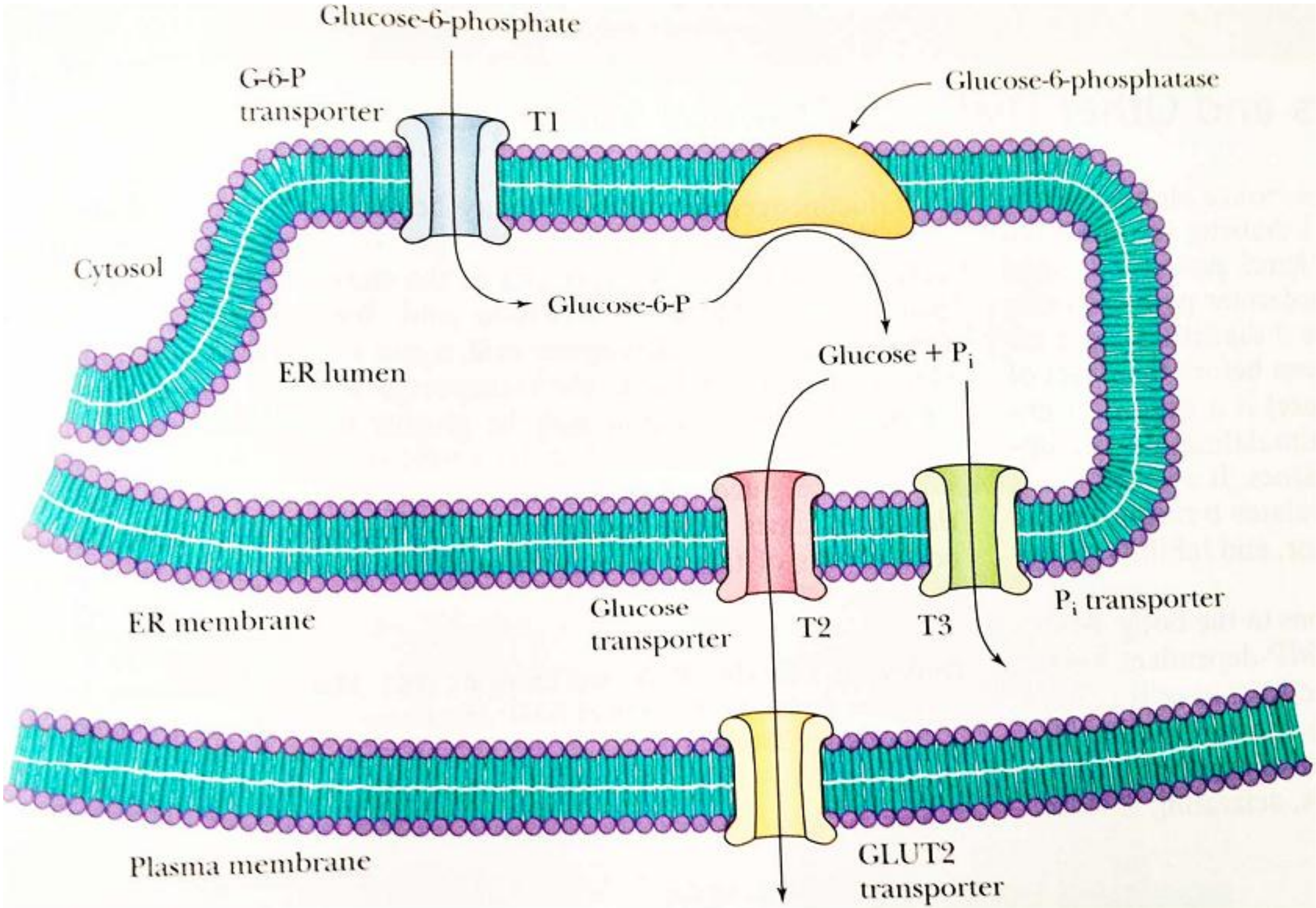
- **G-6-P** + $H_2O \xrightarrow{\text{G-6-Phosphatase (ER)}}$ **G** + P_i



- **Glucose 6-phosphatase is stabilized by a Ca^{2+}-binding protein (SP)**

GLUT2

- **G** in ER vesicles → cytosol ---------------→ blood stream



Gluconeogenesis ends at **G-6-P**

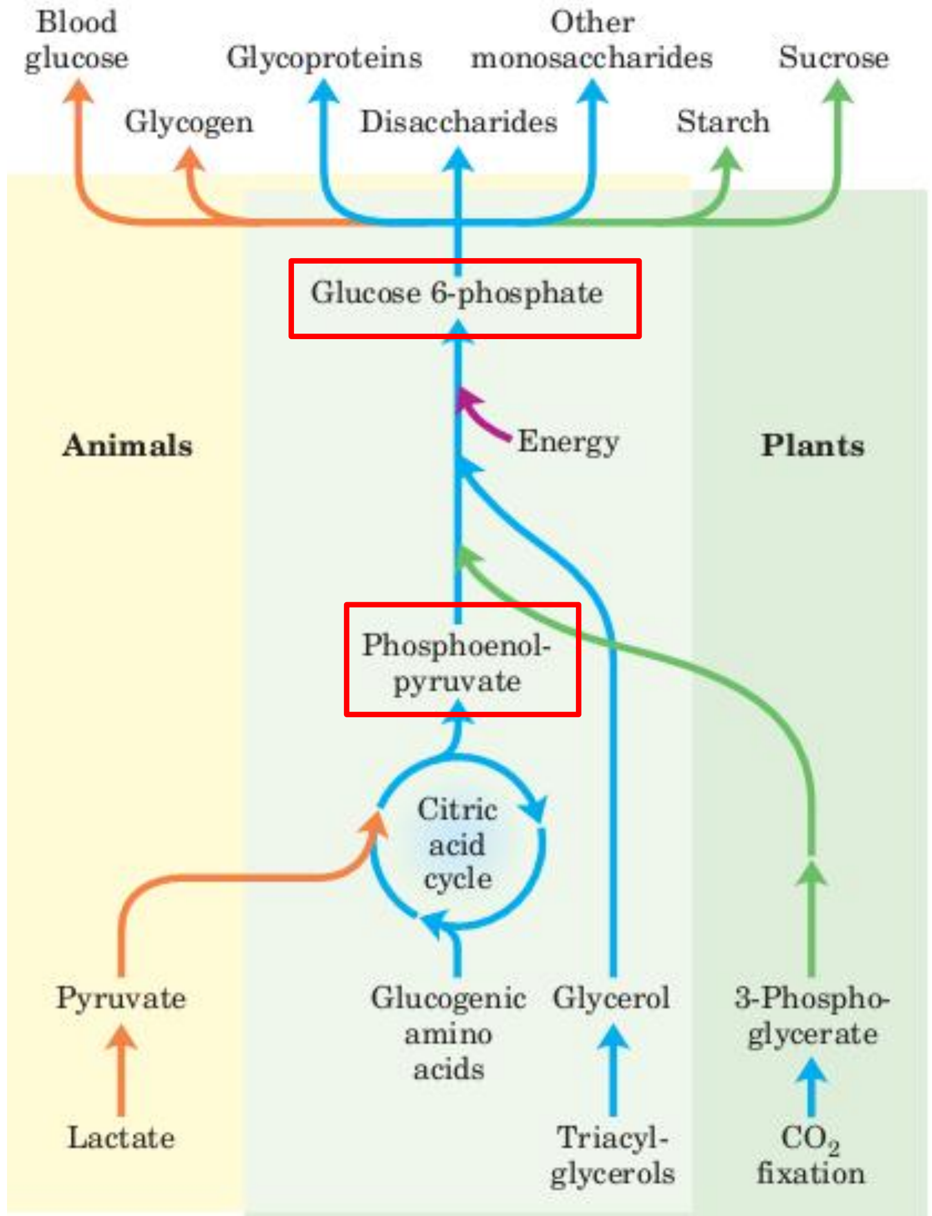
- **G-6-P** is valuable; a precursor for glycogen synthesis.
- **Glucose 6-phosphatase** is present only in tissues responsible for maintaining blood glucose levels**, liver （90%） and kidney（10%）**.
- In liver, **glucose 6-phosphatase** is highly regulated.

Gluconeogenesis Stoichiometry

- 2pyruvate $+ 4ATP + 2GTP + 2NADH + 6H_2O \rightarrow$ glucose $+ 4ADP + 2GDP + 6P_i + 2NAD^+ + 2H^+$;

  $G^{\circ}{}' = -9 kcal\ mol^{-1}$.

- It consumes **6** ATP/GTP in gluconeogenesis while only **2** ATP generated from glycolysis



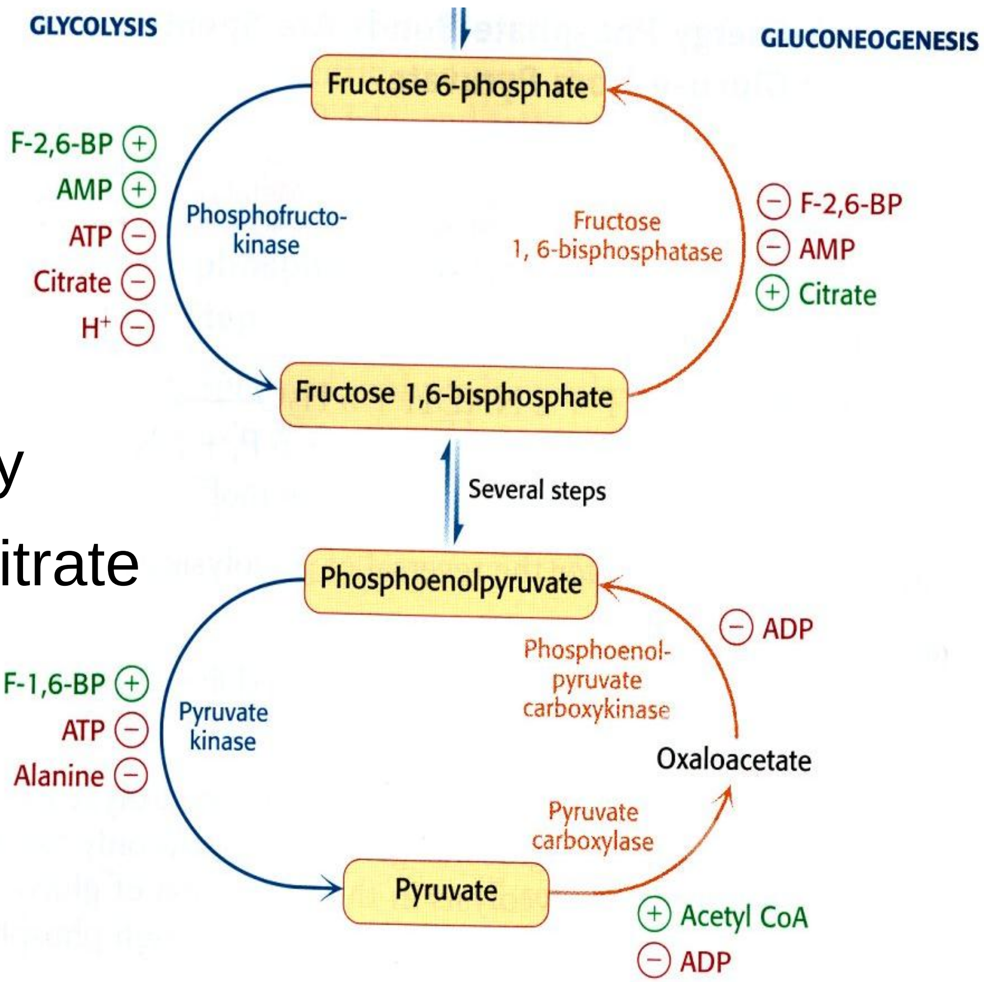
The pathway from **PEP** to **6-P-G** is common to the biosynthetic conversion of many different precursors of carbohydrates in animals and plants.

2.5 Regulation of Gluconeogenesis

Allosteric and Substrate-Level Control

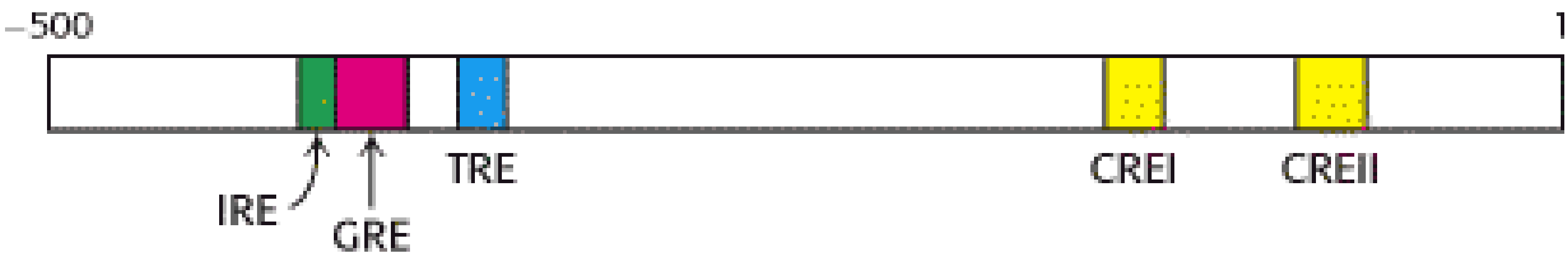
- **Glucose-6-phosphatase -** substrate-level control, not allosteric control

- **F-1,6-bisPase** is inhibited by AMP, F-2,6-2P ; activated by citrate



Hormone Control

- **Insulin** stimulates the expression of phosphofructokinase（磷酸果糖激酶）, pyruvate kinase（丙酮酸激酶）
- **Glucagon** stimulates two key **gluconeogenic** enzymes, phosphoenolpyruvate carboxykinase（PEP羧激酶）and fructose 1,6-bisphosphatase（果糖-1，6-二磷酸酶）.
- Transcriptional control in eukaryotes：hours or days



- The Promoter of the **Phosphoenolpyruvate Carboxykinase**

（PEP羧激酶）

- regulatory sequences

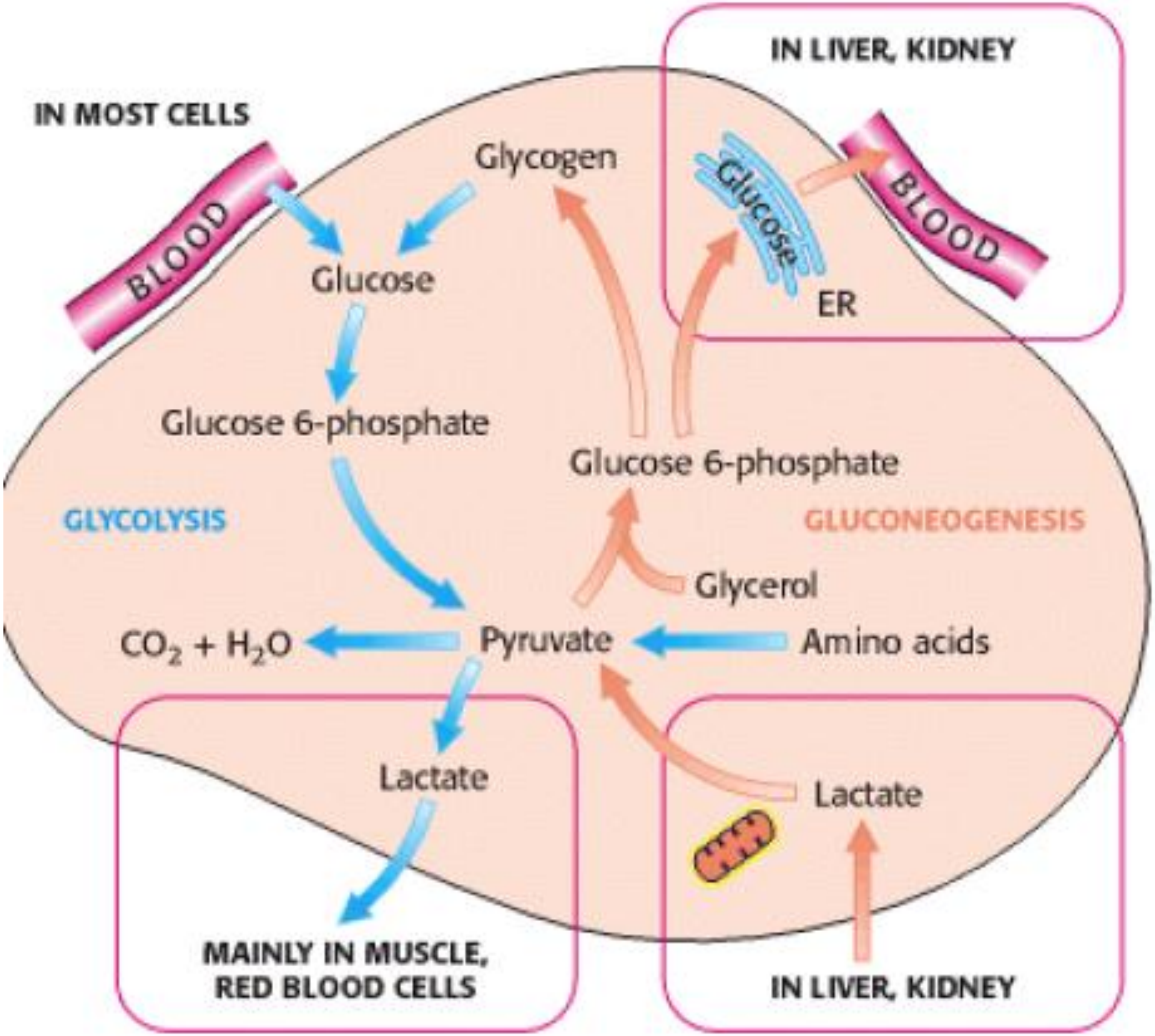
IRE：insulin response element

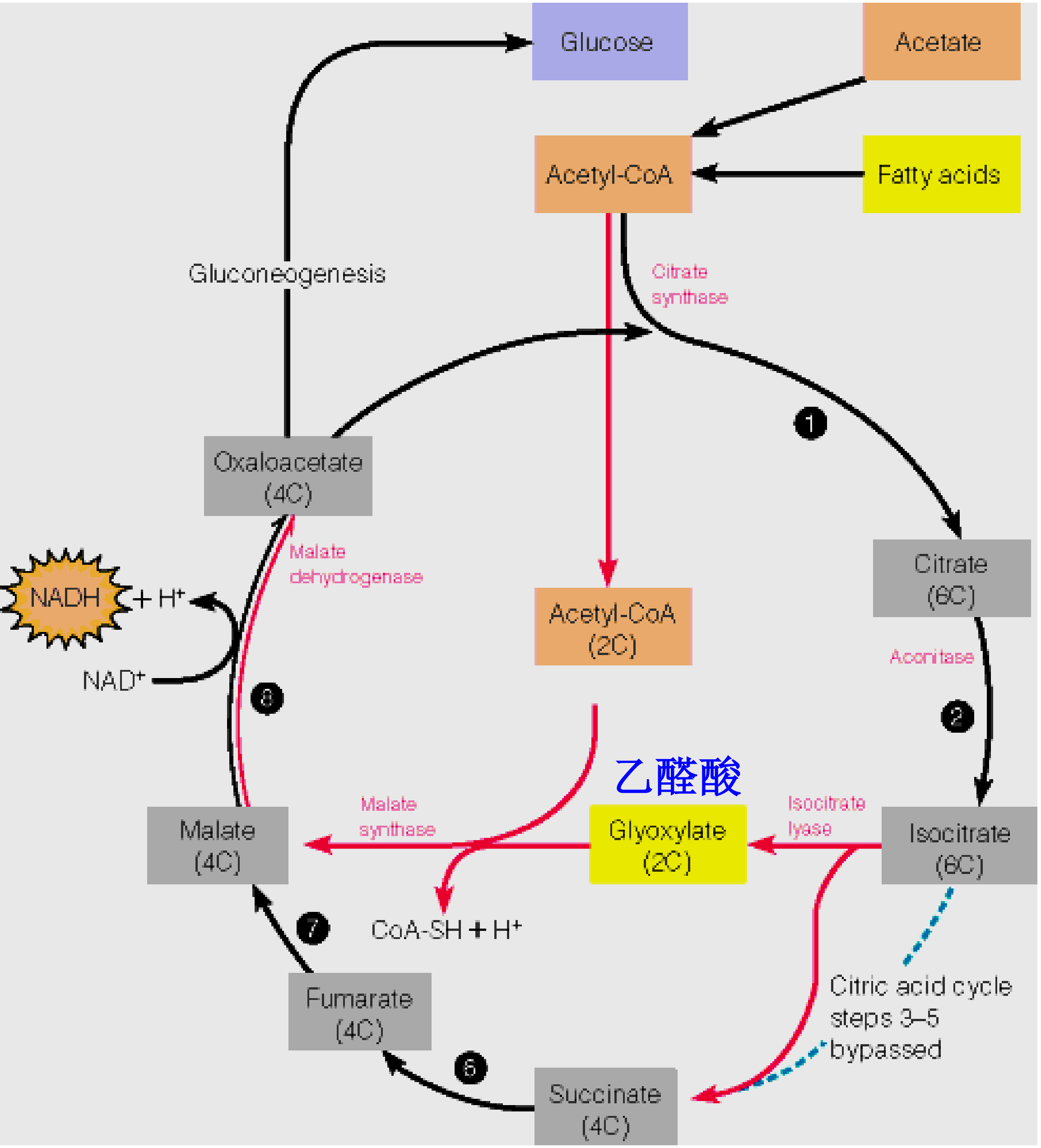
GRE：glucocorticoid糖(肾上腺)皮质激素response element

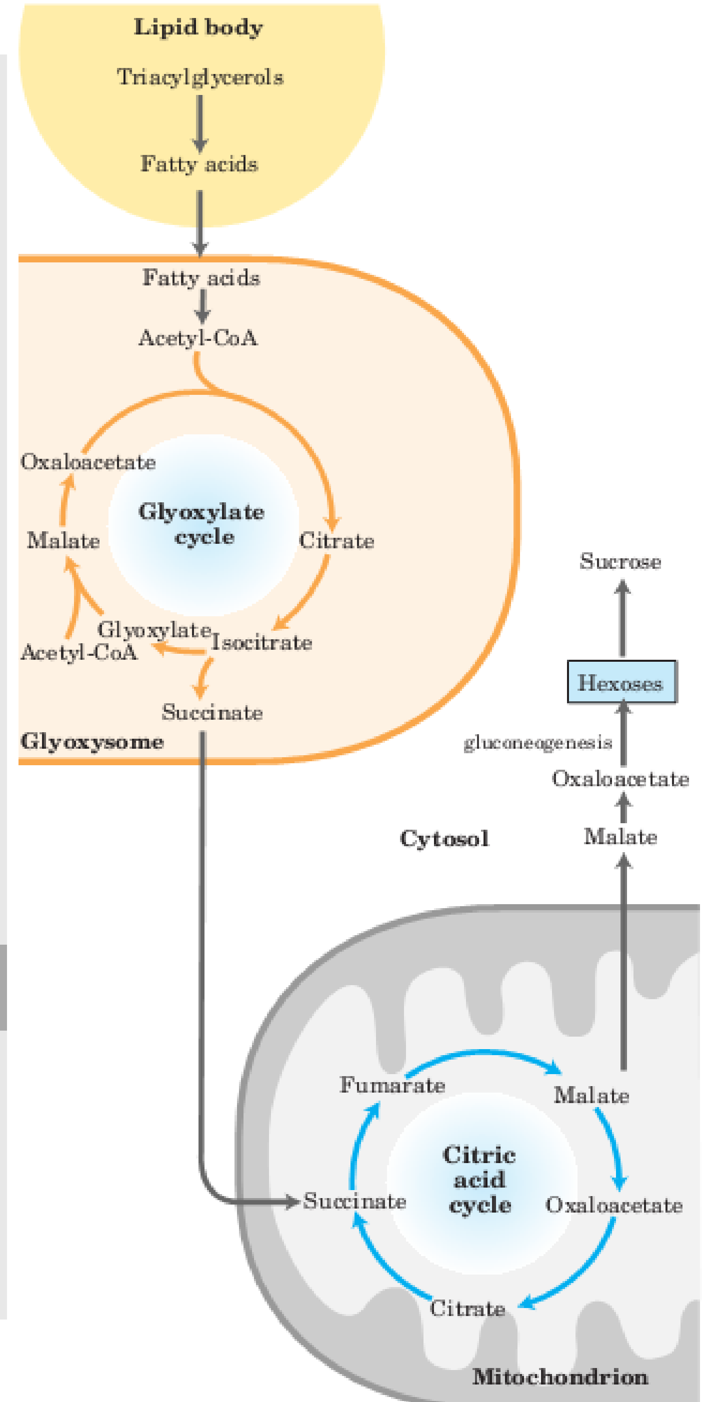
TRE： thyroid hormone甲状腺素 response element

CREI and CREII：cAMP response elements.

Cooperation between Glycolysis and Gluconeogenesis.
in a tissue-specific fashion




Glucose
Acetate
Acetyl-CoA
Fatty acids
Gluconeogenesis
Citrate synthase
1
Oxaloacetate (4C)
Malate dehydrogenase
NADH + H+
NAD+
8
Acetyl-CoA (2C)
Citrate (6C)
Aconitase
2
乙醛酸
Malate (4C)
Malate synthase
Glyoxylate (2C)
Isocitrate lyase
Isocitrate (6C)
CoA-SH + H+
7
Fumarate (4C)
Citric acid cycle steps 3–5 bypassed
6
Succinate (4C)


Lipid body
Triacylglycerols
Fatty acids
Fatty acids
Acetyl-CoA
Oxaloacetate
Glyoxylate cycle
Malate
Citrate
Glyoxylate
Isocitrate
Acetyl-CoA
Succinate
Glyoxysome
Sucrose
Hexoses
gluconeogenesis
Oxaloacetate
Cytosol
Malate
Fumarate
Malate
Citric acid cycle
Succinate
Oxaloacetate
Citrate
Mitochondrion

summary

- Pentose Phosphate Pathway

  --The Oxidative Phase - NADPH +CO_2

  --The Nonoxidative phase - three-, four-, five-, six-,seven-carbon sugars

- Gluconeogenesis（11 **RXNs** ）

- Regulation of Gluconeogenes （Allosteric or Substrate-Level Control or hormone）

思考题：

1. **什么是糖异生？详述糖异生的过程。并比较该过程与糖酵解有何差异？**
2. **What is the cost (in ATP equivalents) of transforming glucose to pyruvate via glycolysis and back again to glucose via gluconeogenesis?**
3. **2，6-二磷酸果糖如何调控糖异生和糖酵解的？**
4. **什么是HMP途径？HMP有何生理意义？**
5. **什么是Cori循环？**