Metabolism

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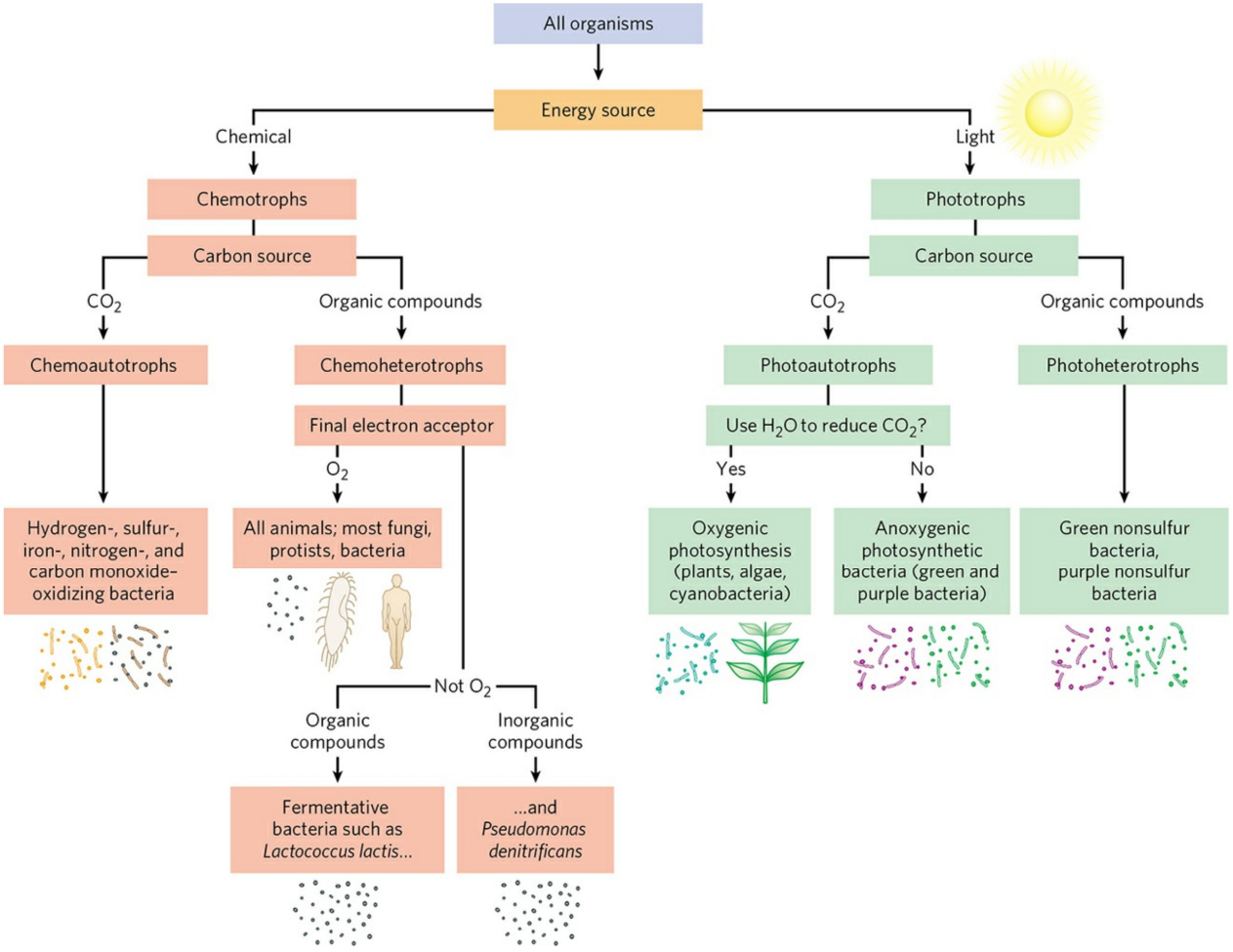
Outline

- Concept of metabolism in living organisms
- Mammalian metabolism: integration and regulation
  - Carbohydrate
  - Lipid
  - Protein
  - Nucleotide

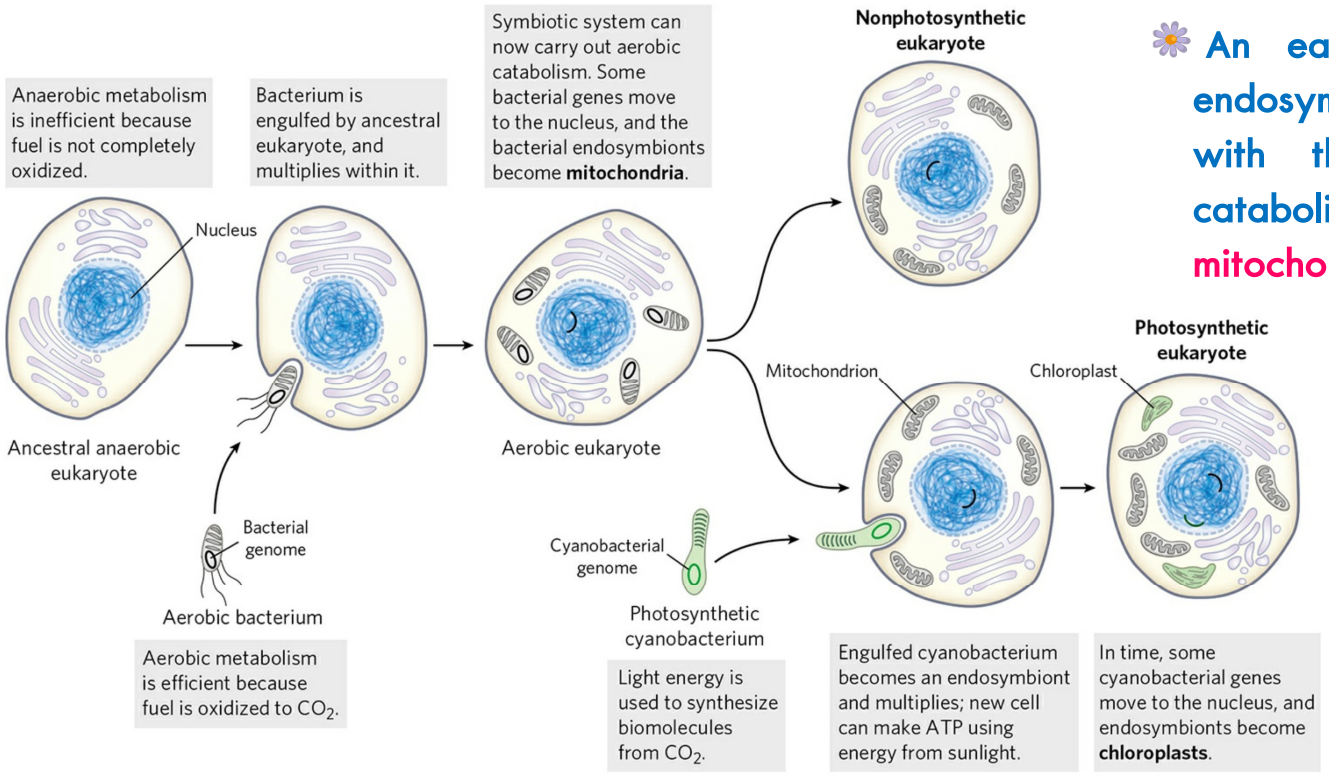


Organism classification

Organisms are classified by

- Energy sources
  - + Chemotrophs
  - + Phototrophs
- Carbon sources
  - + CO_2
  - + Organic compounds

Evolution of eukaryotes (photosynthesis vs. non-photosynthesis) through endosymbiosis

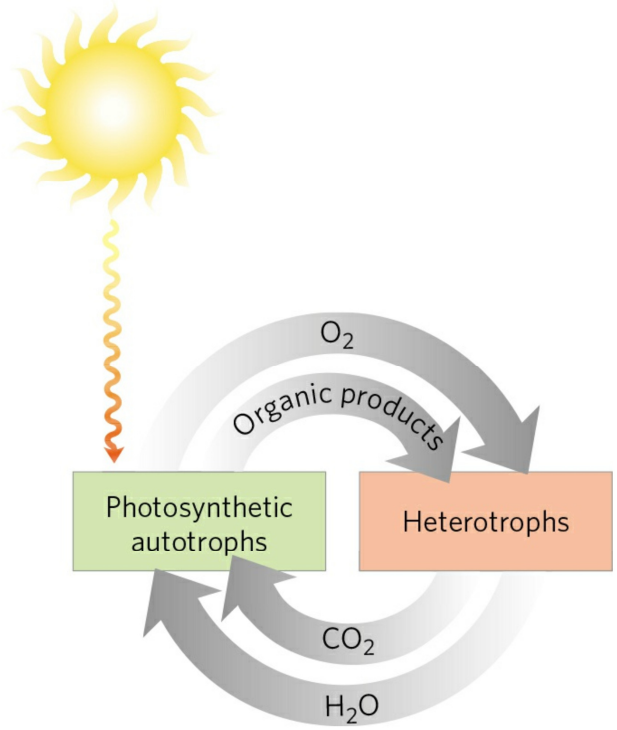


- An early anaerobic eukaryote acquired endosymbiotic purple bacteria, which carried with them their capacity for aerobic catabolism and became, over time, mitochondria.

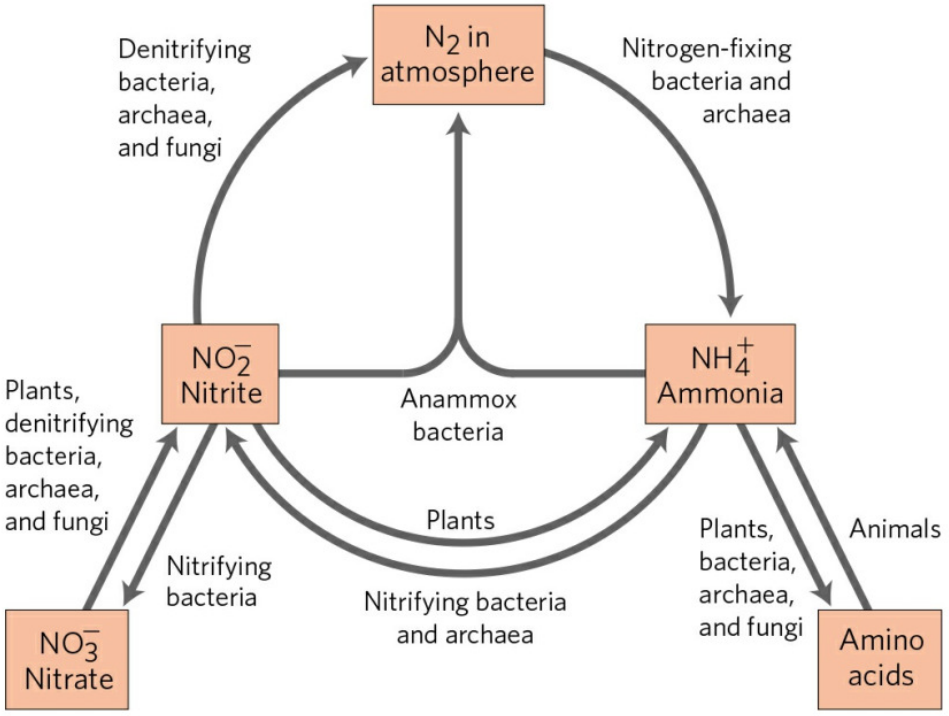
- An aerobic eukaryote acquires endosymbiotic photosynthetic cyanobacteria (green) and later becomes the photosynthetic precursors (chloroplast) of modern green algae and plants.

Energy conversions in biosphere

The cycling of carbon, oxygen, and nitrogen, which ultimately involves all species, depends on a proper balance between the activities of the producers (autotrophs) and consumers (heterotrophs) in the biosphere.



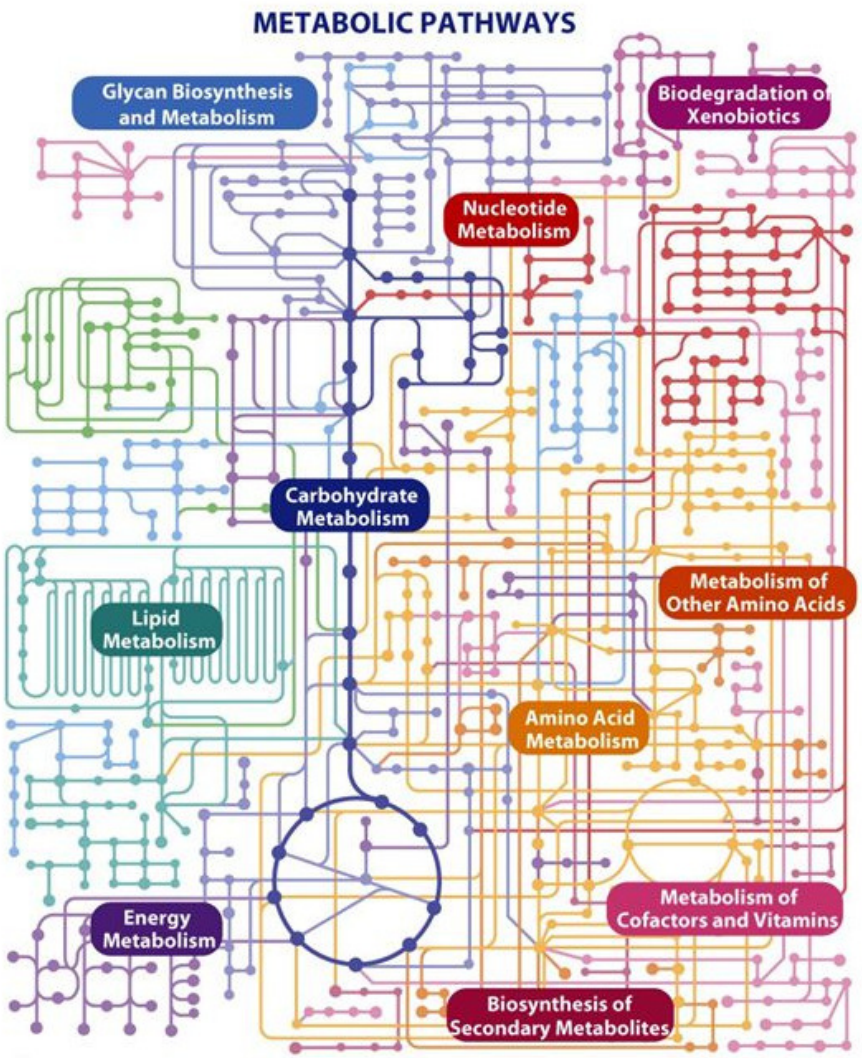
Cycling of CO_2 and O_2



Cycling of nitrogen

Energy conversions in biosphere

- Living organisms is having the systems for extracting, transforming, and using energy from the environment to be able to survive and multiply themselves.
- Metabolism is a highly coordinated cellular activity in which many multienzyme systems (metabolic pathways) cooperate to
  - (1) Obtain chemical energy by capturing solar energy or degrading energy-rich nutrients from the environment
  - (2) Convert nutrient molecules into the cell's own characteristic molecules
  - (3) Polymerize monomeric precursors into macromolecules
  - (4) Synthesize and degrade biomolecules required for specialized cellular functions, such as membrane lipids, intracellular messengers, and pigments.



Integrating metabolic pathways

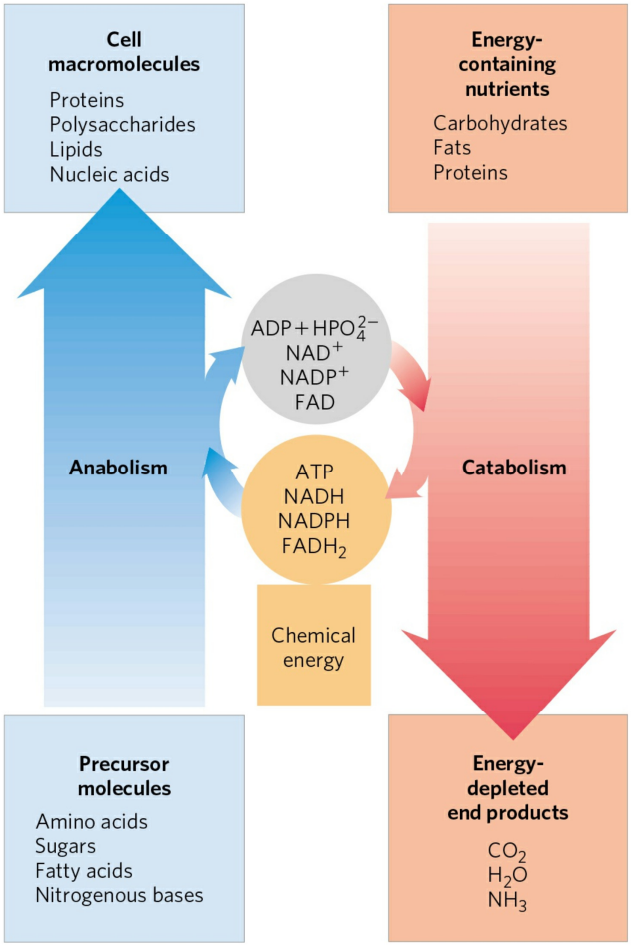
In the eukaryotic cell, a protein or an enzyme is working or catalyzing in more than one pathway.

- Metabolism is the sum of all chemical transformations in a cell or organism, occurs through a series of enzyme-catalyzed reactions.
- Each of the consecutive steps in a metabolic pathway brings about a specific, small chemical change, usually the removal, transfer, or addition of a particular atom or functional group.
- The precursor is converted into a product through a series of metabolic intermediates called metabolites.

Relationship between catabolic and anabolic pathways

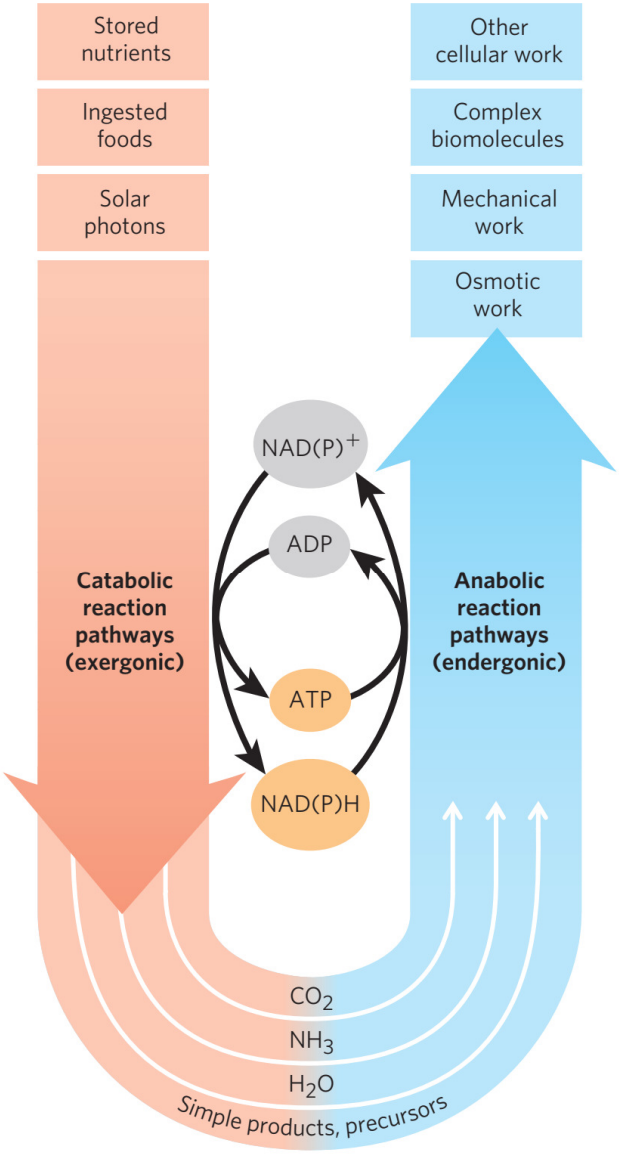
Anabolism (Biosynthesis)

- The small, simple precursors are built up into larger and more complex molecules, including lipids, polysaccharides, proteins, and nucleic acids.
- Anabolic reactions require an input of energy, generally in the form of the phosphoryl group transfer potential of ATP and the reducing power of NADH, NADPH, and $FADH_2$.



Catabolism

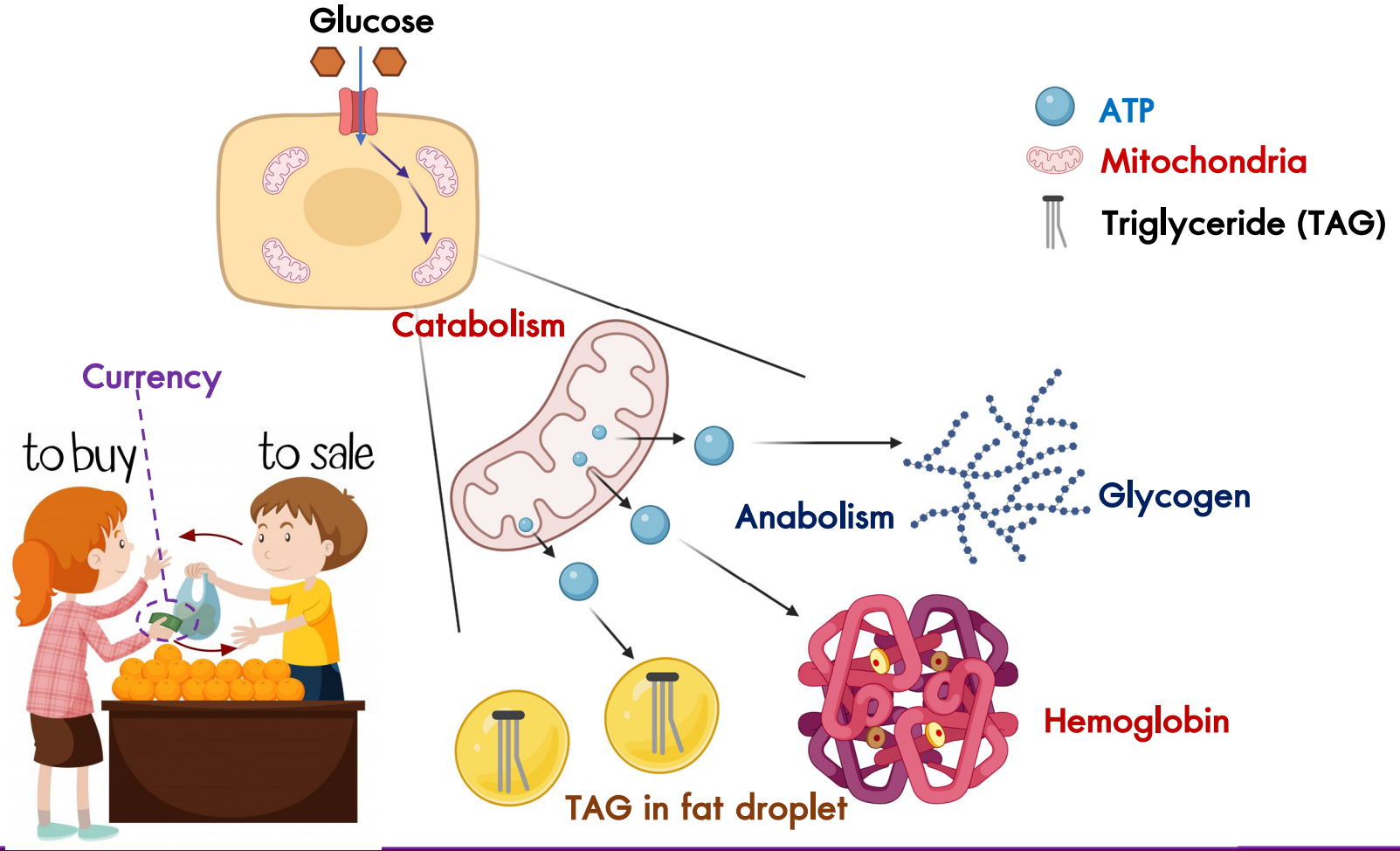
- The degradative phase of metabolism in which organic nutrient molecules (carbohydrates, fats, and proteins) are converted into smaller, simpler end products (such as lactic acid, CO_2, and NH_3).
- Catabolic pathways release energy, some of which is conserved in the formation of ATP and reduced electron carriers (NADH, NADPH, and $FADH_2$); the rest is lost as heat.



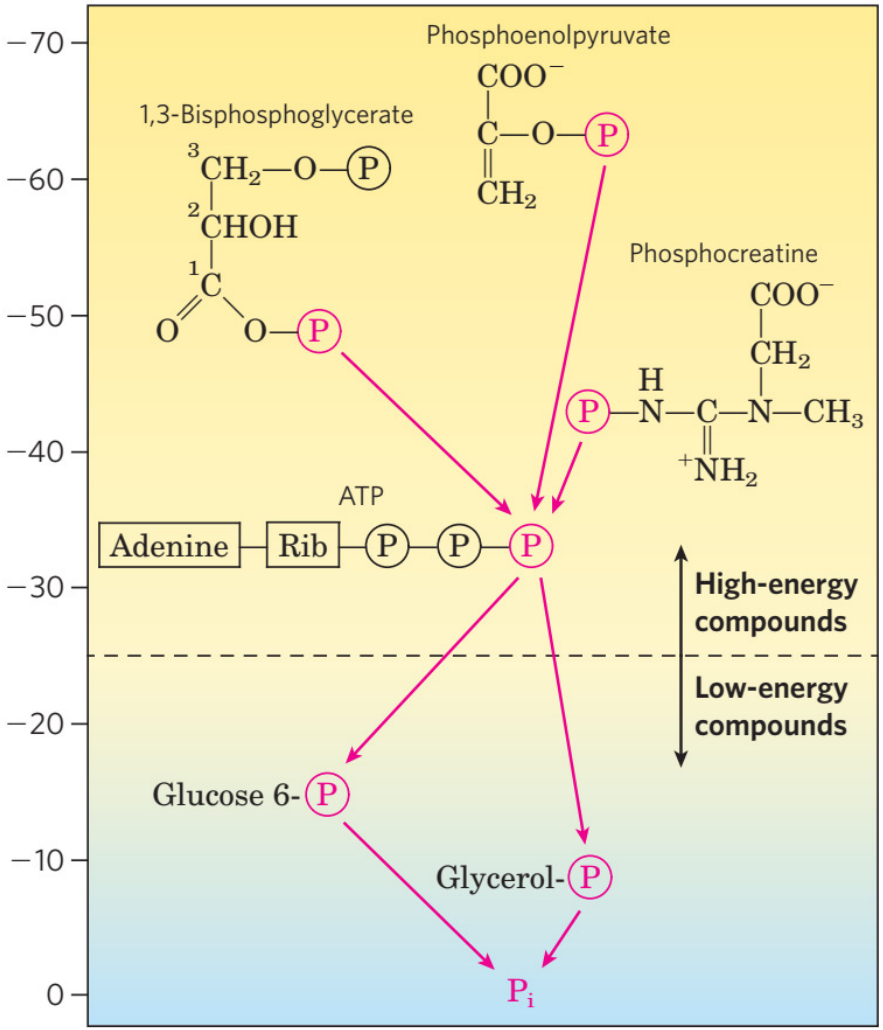
Roles of ATP and NAD(P)H in metabolism

- ATP is a shared intermediate linking energy-releasing and energy-consuming processes.
- ATP role in the cell is analogous to that of money in an economy.
- ATP is "produced" in exergonic reaction and "consumed" in endergonic reaction.
- NAD(P)H (nicotinamide adenine dinucleotide (phosphate)) is an electron-carrying cofactor that collects electrons from oxidative reactions and then donates to the reduction reactions in biosynthesis.
- NAD(P)H presents in relatively low concentrations, these cofactors essential to anabolic reactions must be constantly regenerated by catabolic reactions.

ATP is an energy currency in living cells



High energy compounds



High energy compound

$\Delta G^{\circ'}$ of hydrolysis < -25 kJ/mol

Low energy compound

$\Delta G^{\circ'}$ of hydrolysis > -25 kJ/mol

Types of metabolic pathways

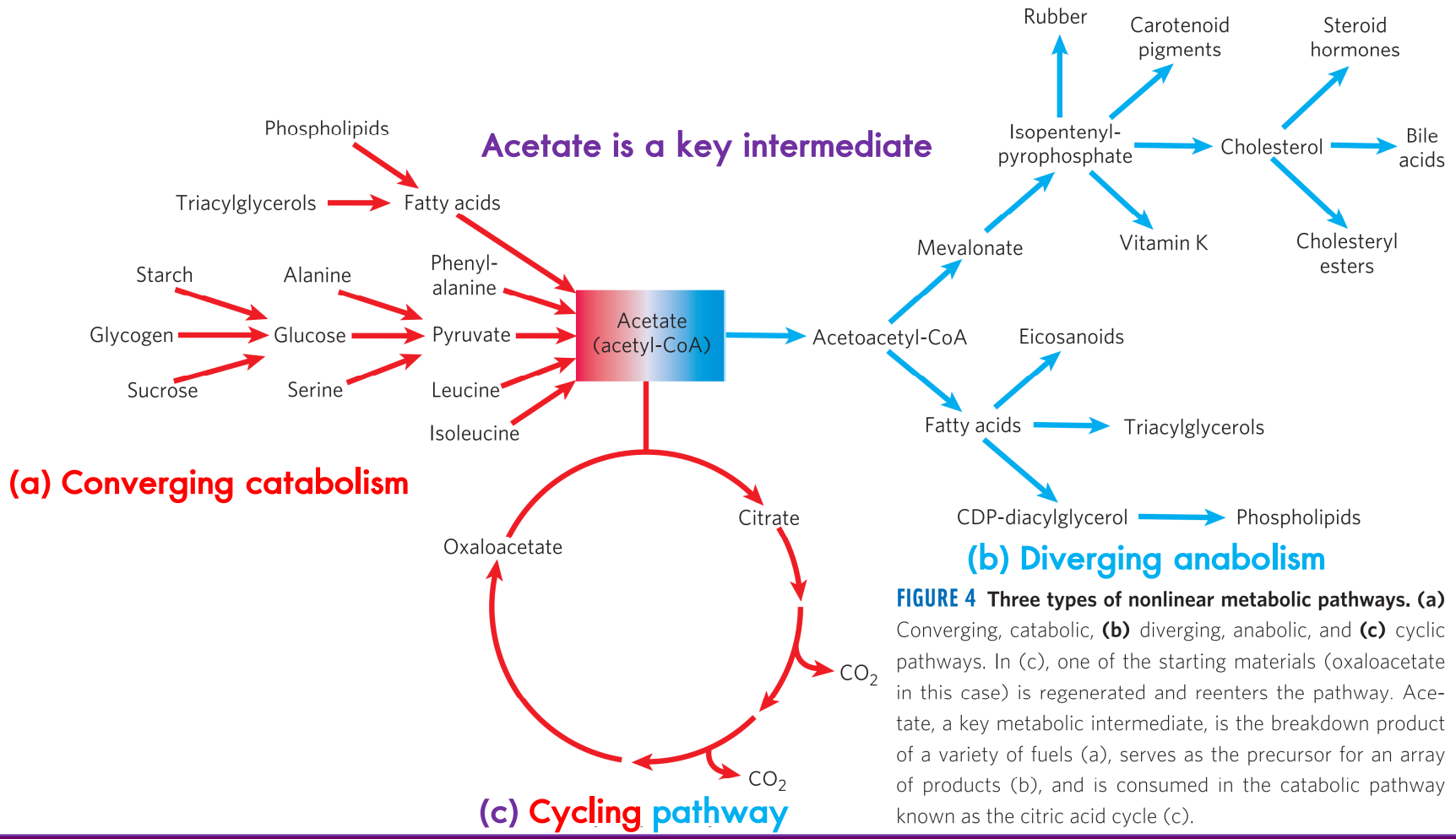
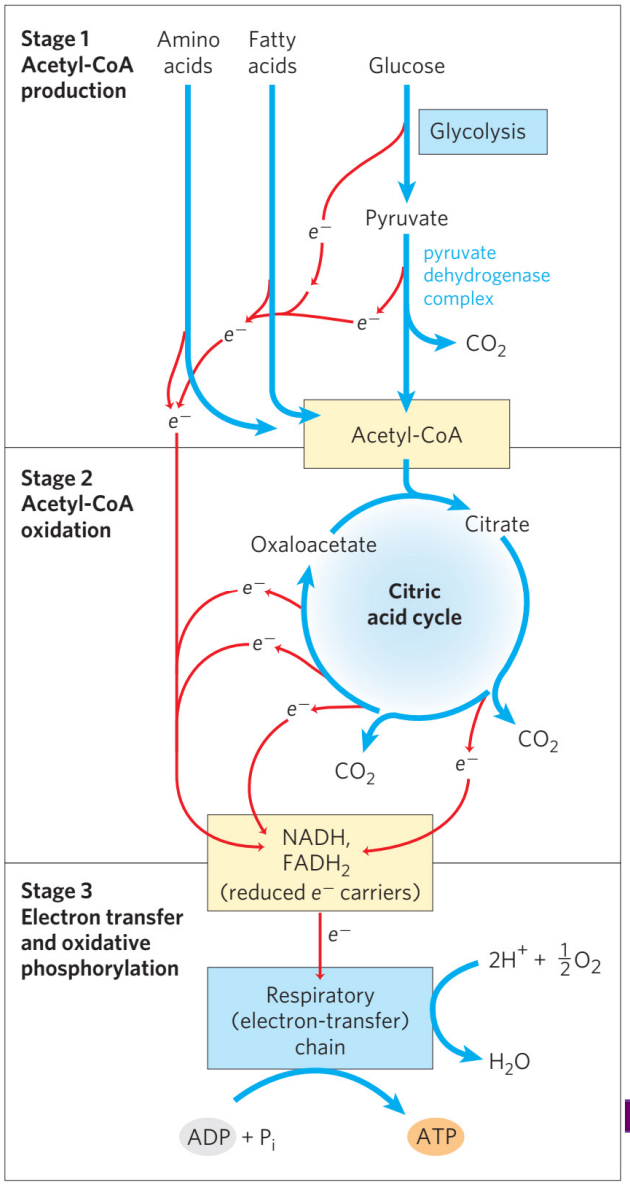


FIGURE 4 **Three types of nonlinear metabolic pathways. (a)** Converging, catabolic, **(b)** diverging, anabolic, and **(c)** cyclic pathways. In (c), one of the starting materials (oxaloacetate in this case) is regenerated and reenters the pathway. Acetate, a key metabolic intermediate, is the breakdown product of a variety of fuels (a), serves as the precursor for an array of products (b), and is consumed in the catabolic pathway known as the citric acid cycle (c).



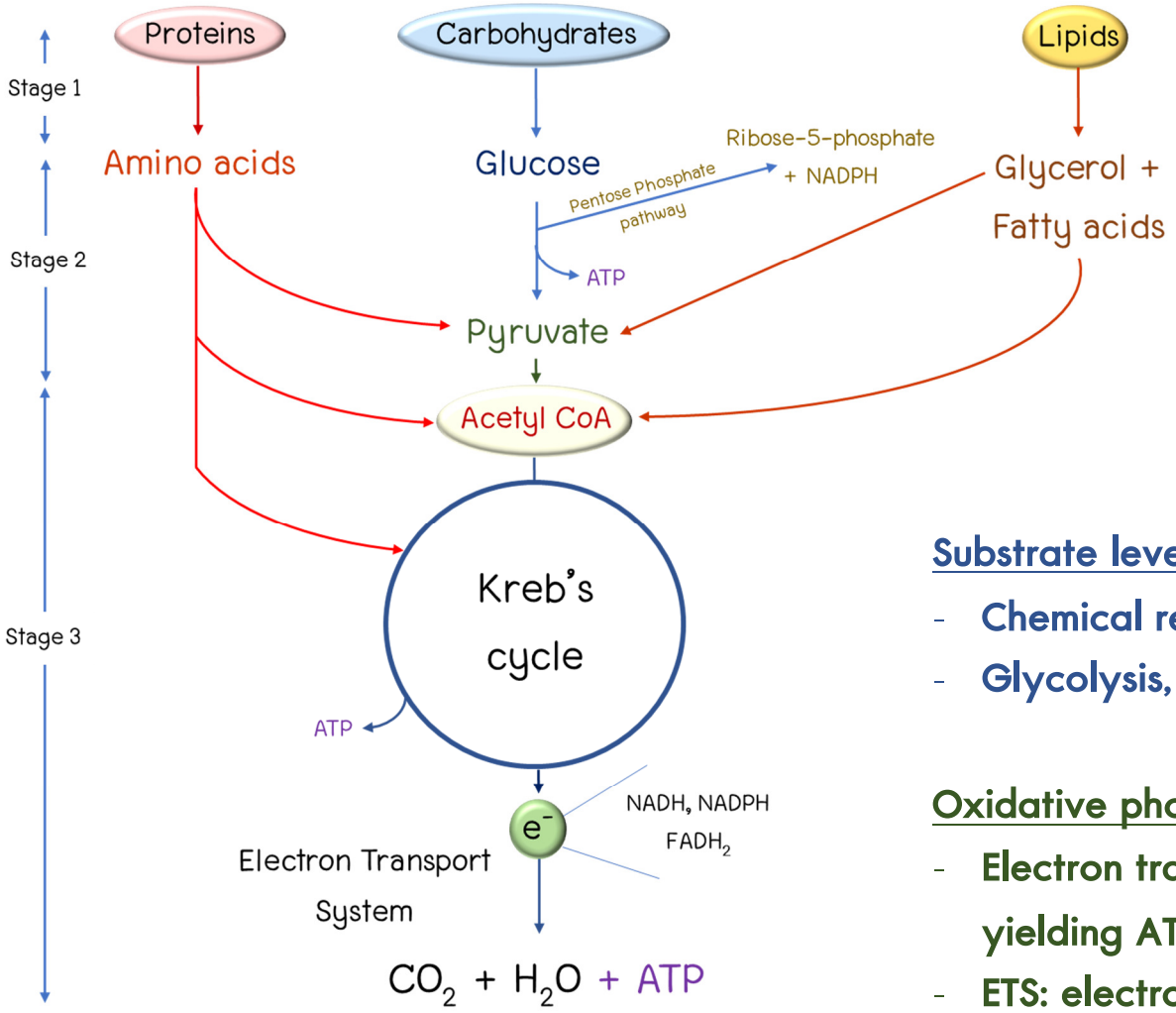
3 stages of catabolism

Stage 1: oxidation of fatty acids, glucose, and some amino acids yields acetyl-CoA.

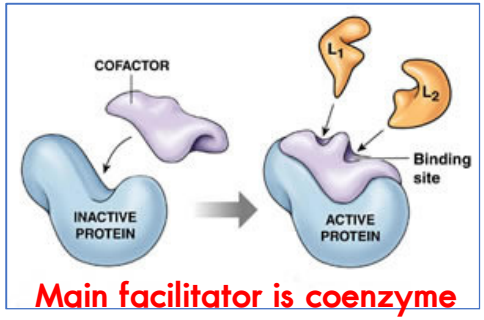
Stage 2: oxidation of acetyl groups in the citric acid cycle and electrons are abstracted.

Stage 3: electrons carried by NADH and $FADH_2$ are funneled into a chain of mitochondrial (or, in bacteria, plasma membrane–bound) electron carriers—the respiratory chain—ultimately reducing O_2 to H_2O. This electron flow drives the production of ATP.

Stages of catabolism



Key player is an enzyme



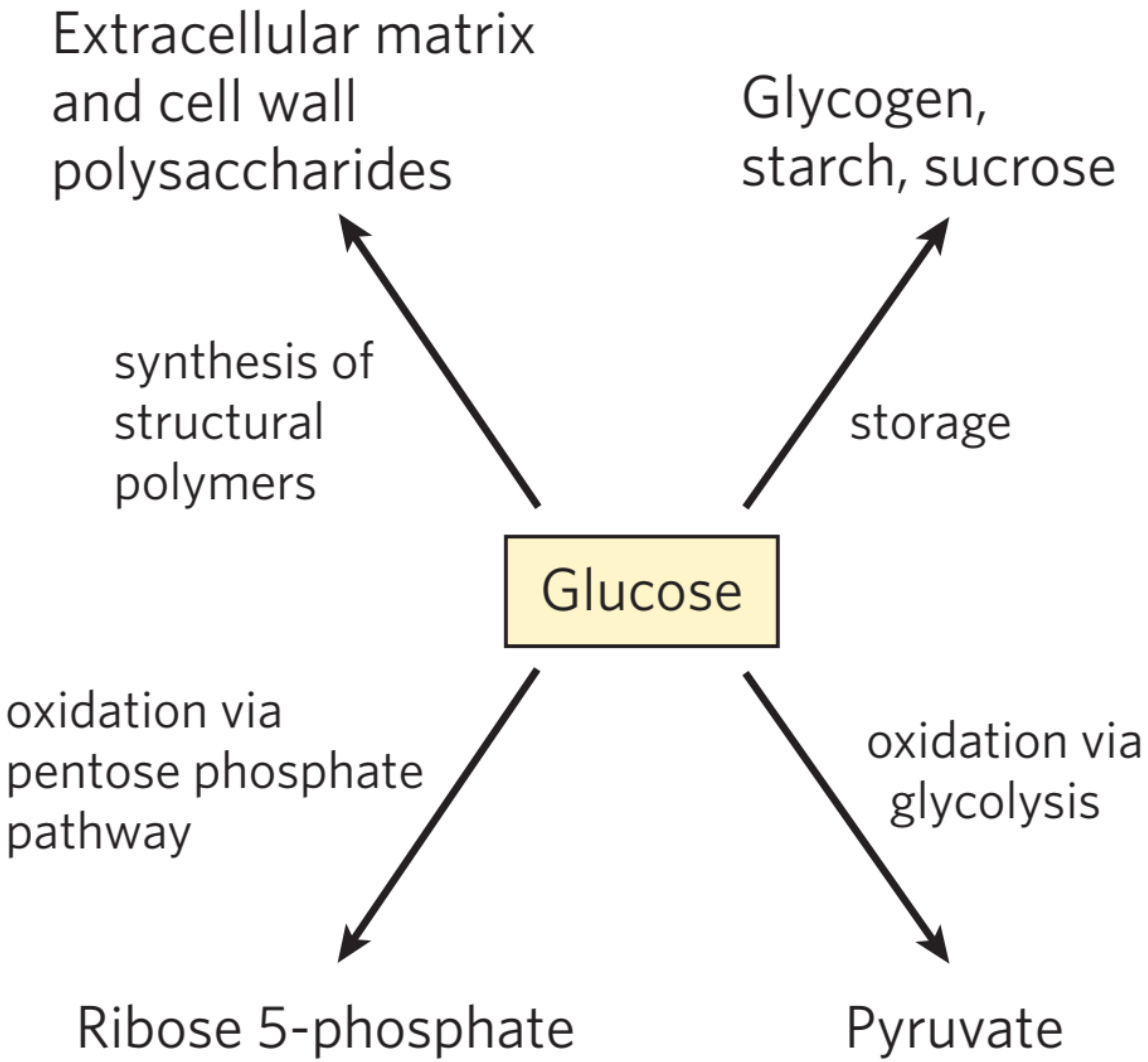
Main facilitator is coenzyme

Substrate level phosphorylation

- Chemical reaction coupled with ATP synthesis (~10% ATP)
- Glycolysis, Kreb's cycle

Oxidative phosphorylation

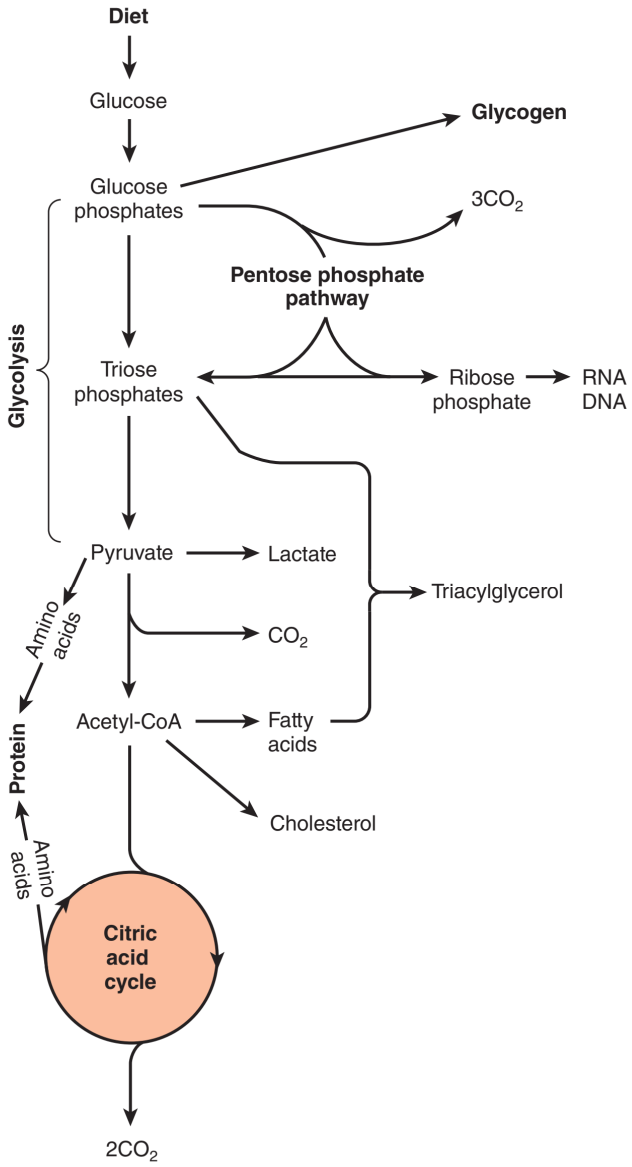
- Electron transport in the chain to O_2 in mitochondria yielding ATP (~90% ATP)
- ETS: electron transport system



Glucose utilization

Glucose

- **Excellent fuel**
- **Versatile precursor supplying a metabolic intermediates for biosynthetic reactions**



1. Carbohydrate metabolism

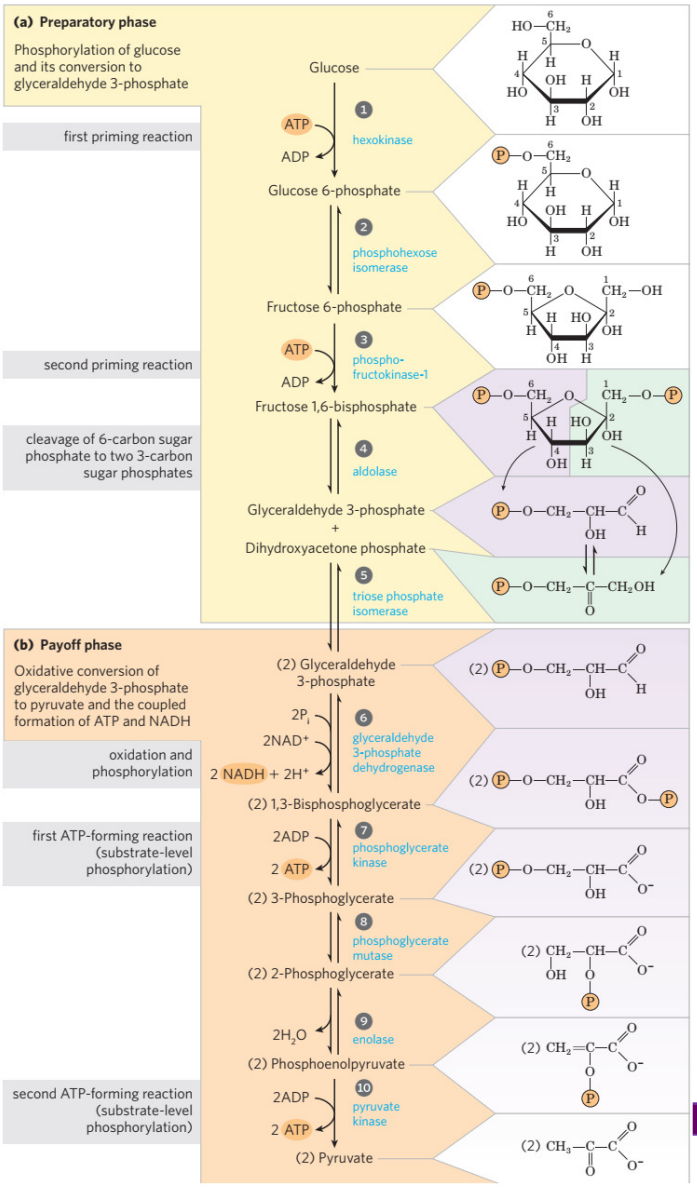
- Carbohydrate metabolism is centered on the provision & fate of glucose

Catabolism

- Metabolized to Pyruvate → "Glycolysis"
- In an aerobic condition
  - Pyruvate → Acetyl CoA → CO_2 + H_2O
    "Oxidative phosphorylation"
- In an anaerobic condition
  - Pyruvate → Lactate
    "Anaerobic glycolysis"

Anabolism

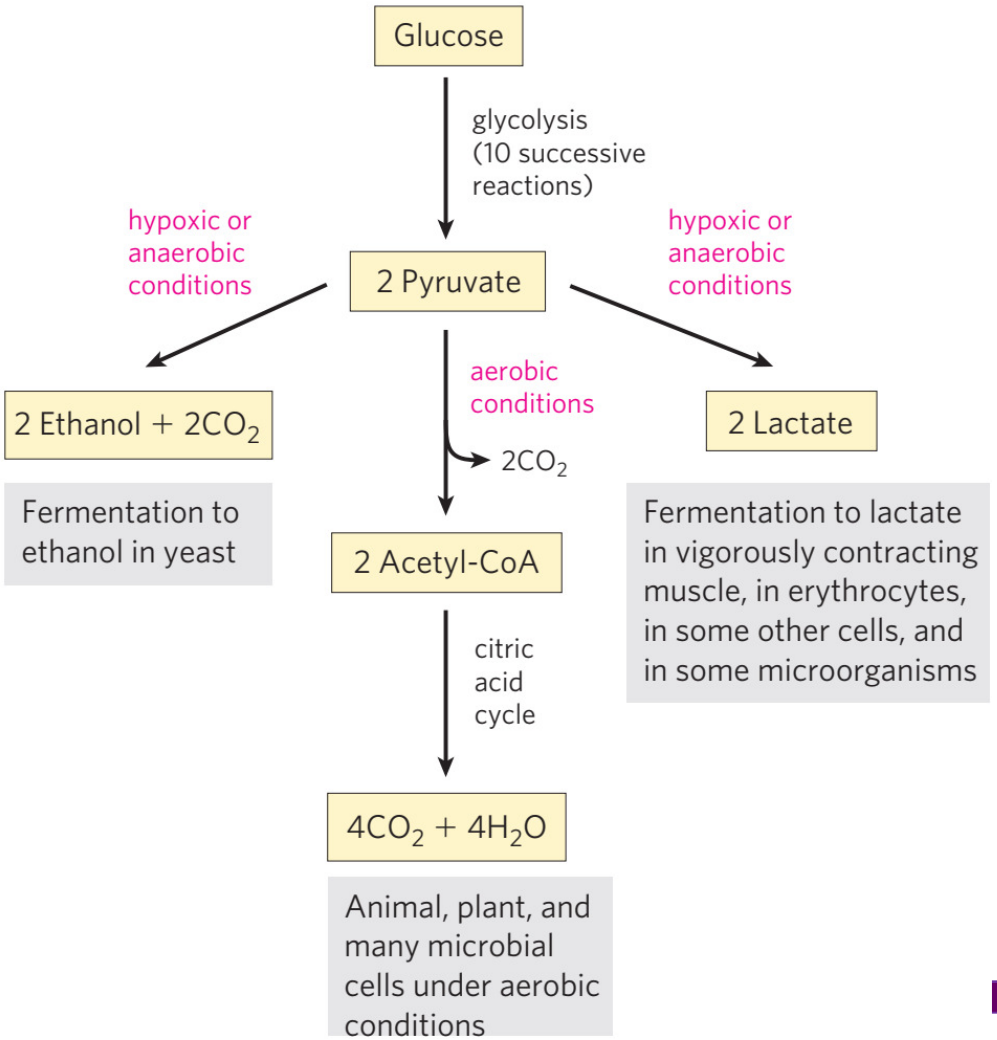
- Glucose → Glycogen (skeletal muscle & liver), "Glycogenesis"
- Glucose → Ribose-5-phosphate, "Pentose phosphate pathway"
- Glucose → Triose phosphate → Triacylglycerol
- Amino acids, fatty acids, and cholesterol



1. Carbohydrate metabolism, glycolysis

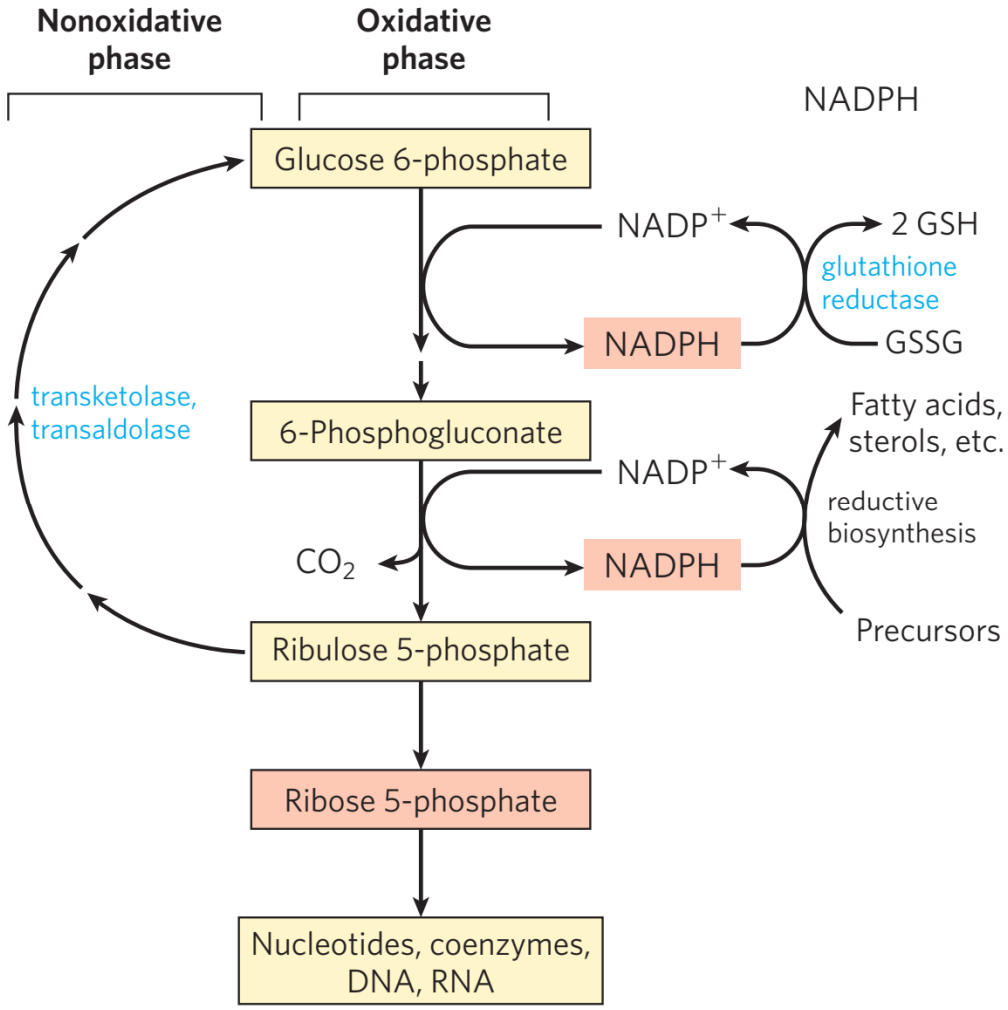
- Glucose breakdown process
- Occur in the cytoplasm
- Compose of 10 steps
  - Preparation & Payoff phases
    - Preparation phase
      - Phosphorylation of glucose → Glyceraldehyde 3-phosphate
    - Payoff phase
      - Oxidative conversion of Glyceraldehyde 3-phosphate to pyruvate coupled with ATP and NADH formation
  - 3 irreversible steps are the rate limiting steps
    1. Glucose → Glucose-6-phosphate
    2. Fructose-6-phosphate → Fructose-1,6-bisphosphate
    3. Phosphoenolpyruvate → Pyruvate

3 phases of pyruvate



- Phases of pyruvate are depending on oxygen levels and types of cells/organisms

1. Carbohydrate metabolism, Pentose phosphate pathway (PPP)



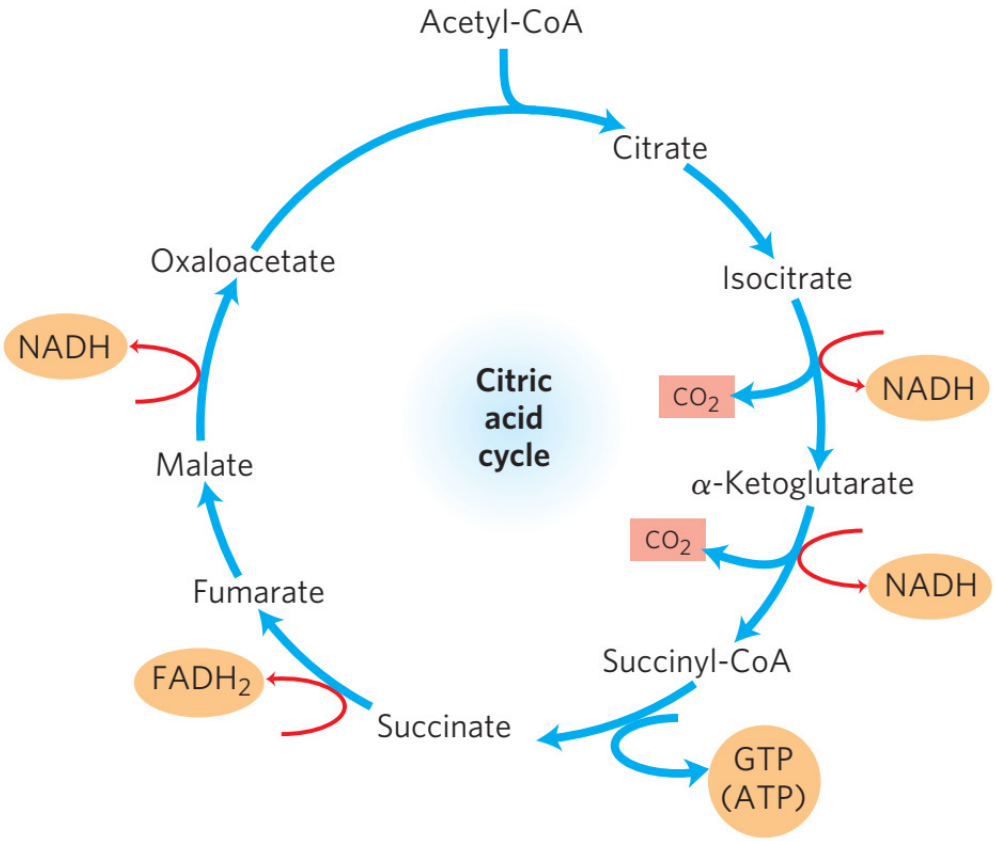
Oxidative phase

- **NADPH** is used to reduce glutathione, GSSG and to support reductive biosynthesis.
- **Ribose 5-phosphate (R-5-P)** is a precursor for nucleotides, coenzymes, and nucleic acids.

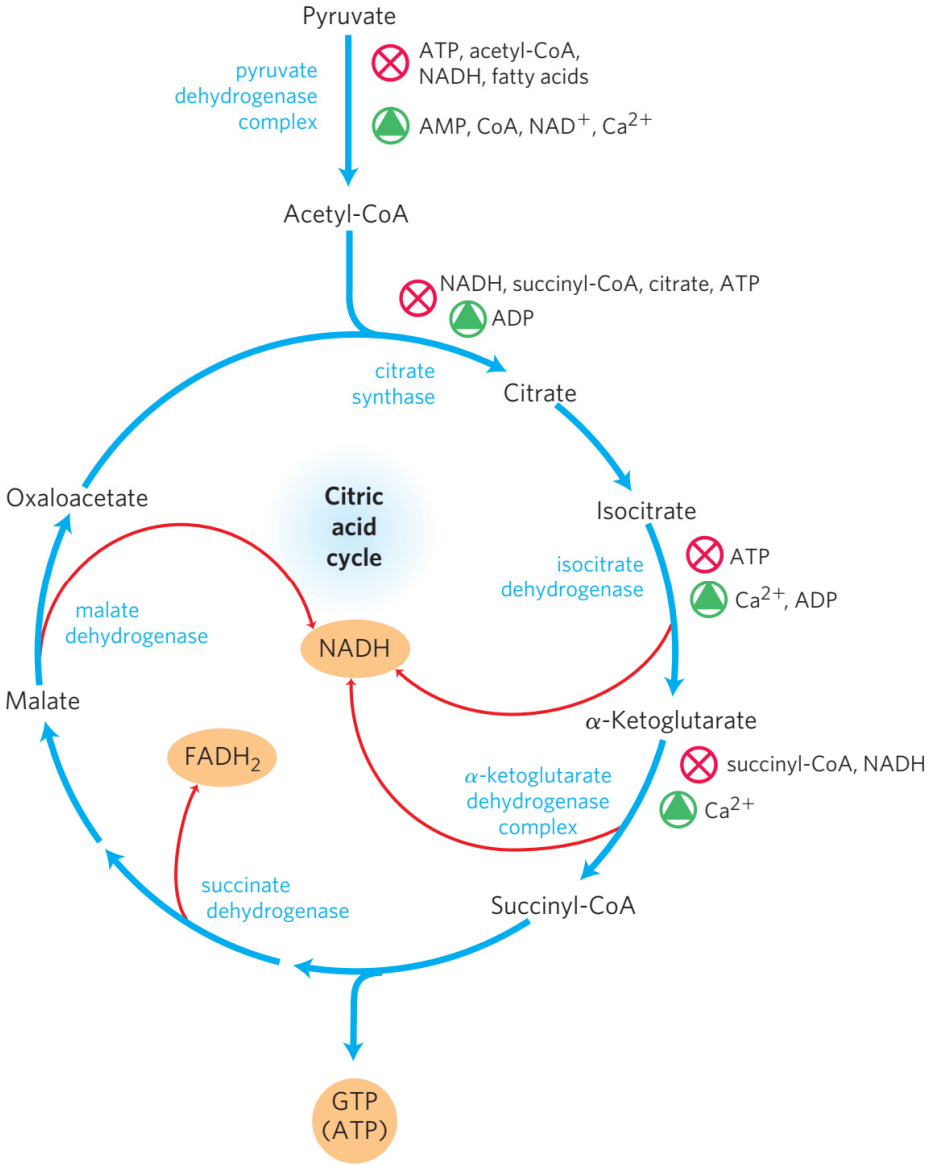
Nonoxidative phase

- In cells that are not using R-5-P for biosynthesis, the recycles of R-5-P → Glucose 6-phosphate, allowing continued production of NADPH.

1. Carbohydrate metabolism, Krebs cycle [Tricarboxylic acid (TCA) cycle or Citric acid cycle]



- A cycle produces GTP (ATP), electron carriers or reducing agents (NADH and $FADH_2$), and CO_2.
- The regulation of key enzymes
  - Allosteric effectors
  - Covalent modification
- Sufficient supply of energy (ATP) inhibits TCA cycle

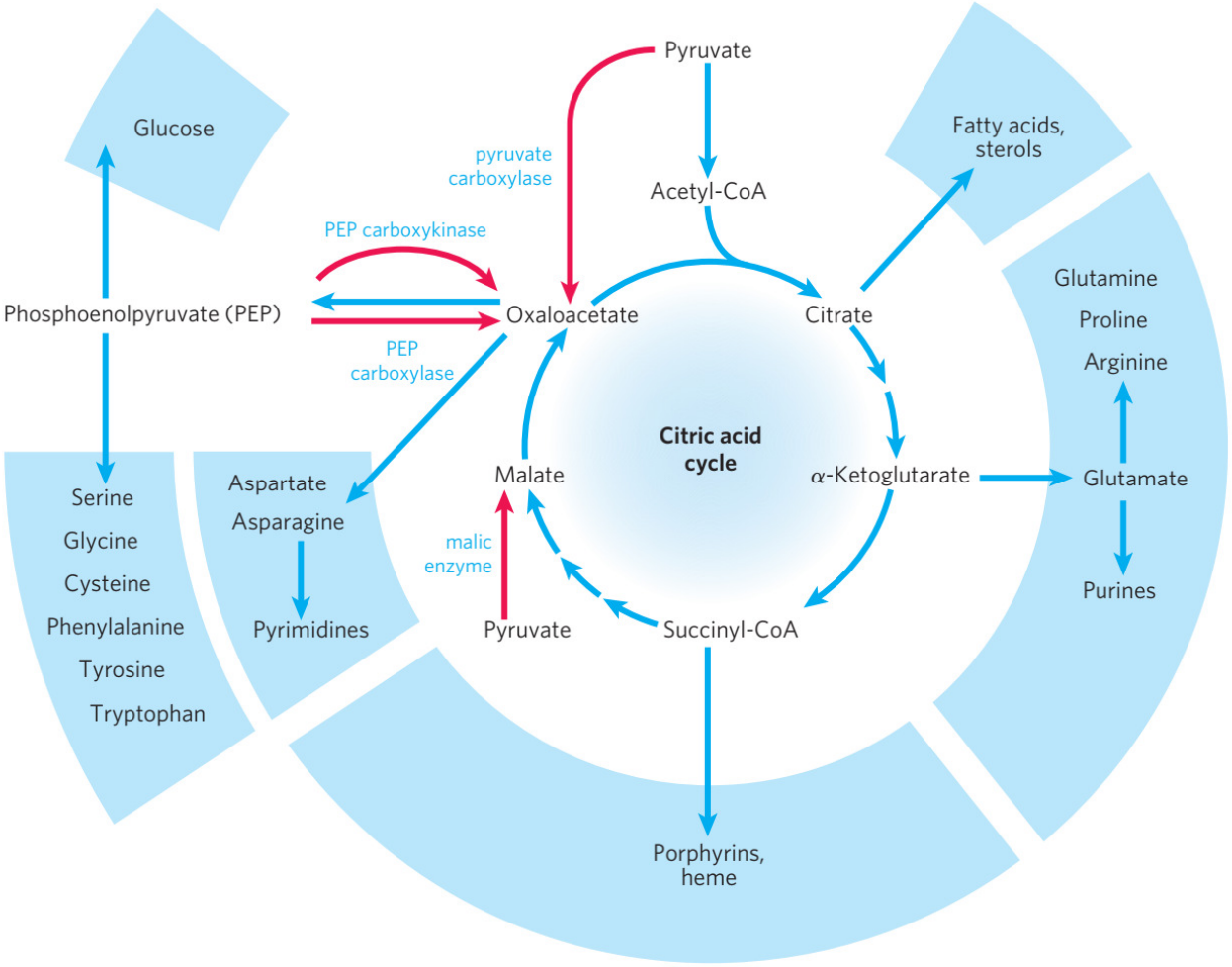


Regulations in Krebs cycle

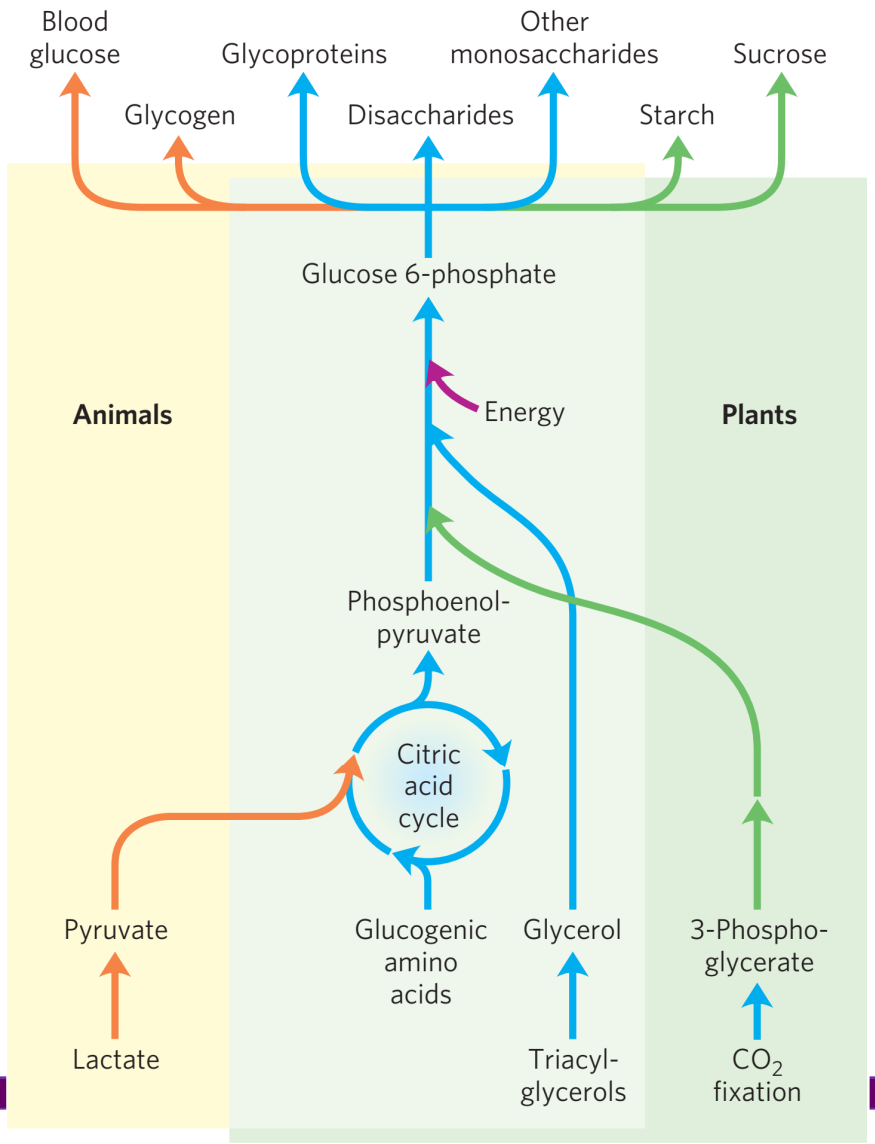
There are 4 steps that regulate TCA cycle (irreversible steps)

1. Pyruvate → Acetyl CoA
2. Entry of acetyl CoA into the cycle (citrate synthesis reaction)
3. Isocitrate → α-Ketoglutarate
4. α-ketoglutarate → Succinyl CoA

Roles of Krebs cycle in anabolism



- Intermediates of Krebs cycle are drawn off as precursors in many biosynthetic pathways.
- Red arrows are four anaplerotic reactions that replenish depleted cycle intermediates.



Glucose synthesis, "gluconeogenesis"

- Glucose is a primary fuel in all organisms
- For human brain, nervous system, erythrocytes, testes, renal medulla, and embryonic tissues, glucose from the blood is the sole or major source of fuel.
- Human brain requires approximately 120 g of glucose/day (>50% storage glycogen in liver and muscle).
- Glycogen is depleted between meals, long fasting, and after vigorous exercise
- Gluconeogenesis is the process of glucose synthesis from pyruvate, 3-C, and 4-C intermediates from glycolysis.

Glycogen synthesis, "glycogenesis"

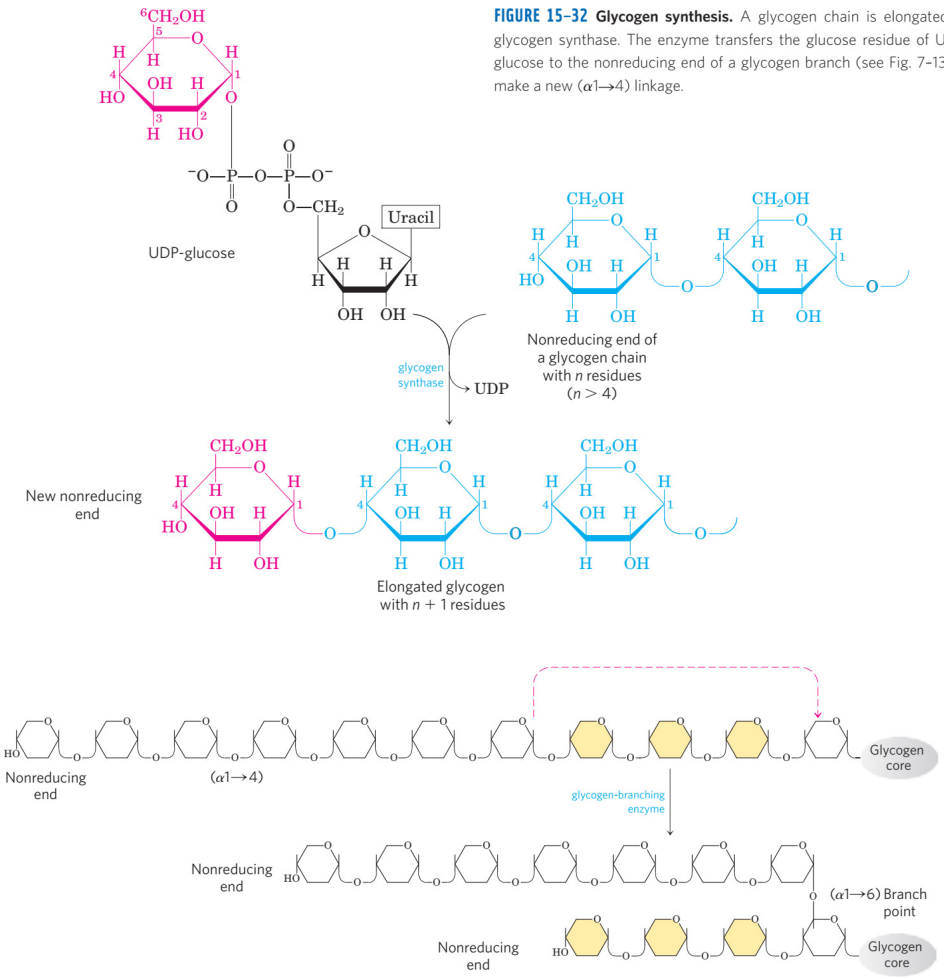


FIGURE 15–32 Glycogen synthesis. A glycogen chain is elongated by glycogen synthase. The enzyme transfers the glucose residue of UDP-glucose to the nonreducing end of a glycogen branch (see Fig. 7–13) to make a new (α1→4) linkage.

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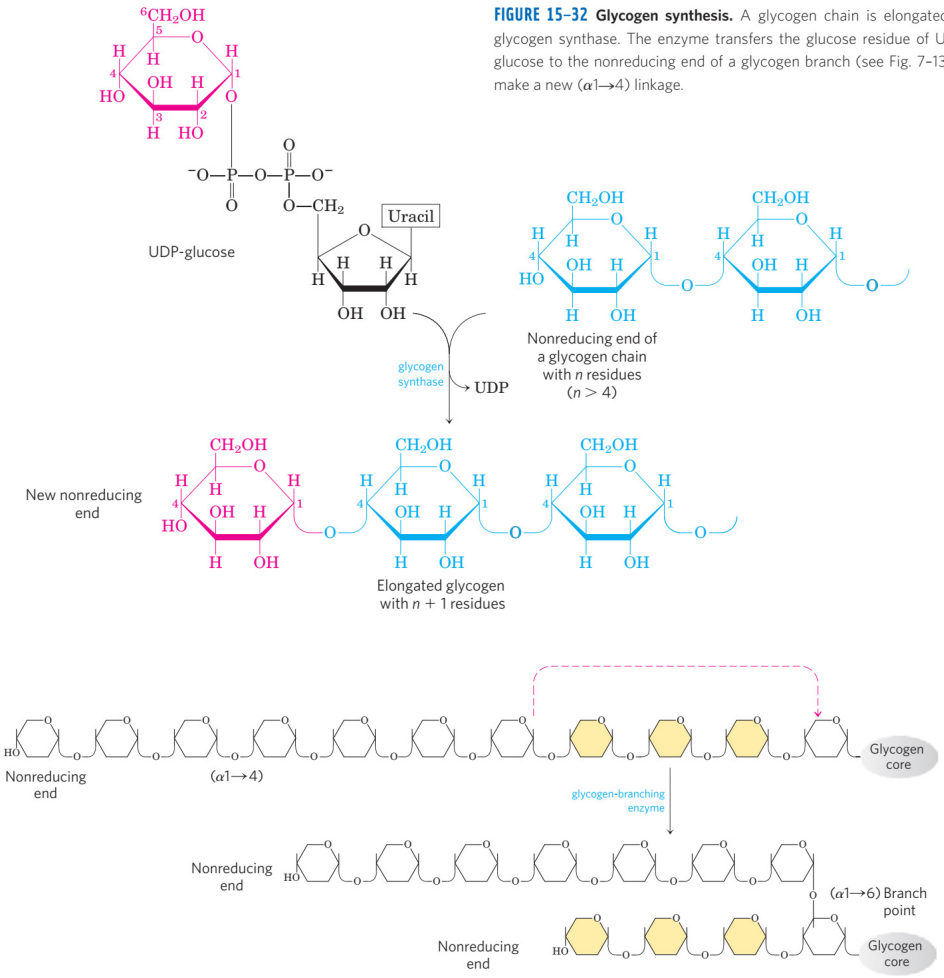
- The enzyme transfers the glucose residue of UDP-glucose to the nonreducing end of a glycogen branch to make a new (α1→4) linkage.
- Once the chain is long (n=11-12 units), the branching point is constructed by glycogen-branching enzyme, creating new (α1→6) linkage.
- Glycogen granules are stored in liver and skeletal muscle.
- Liver glycogen serves as a reservoir of glucose for other tissues when dietary glucose is not available (between meals or during a fast).



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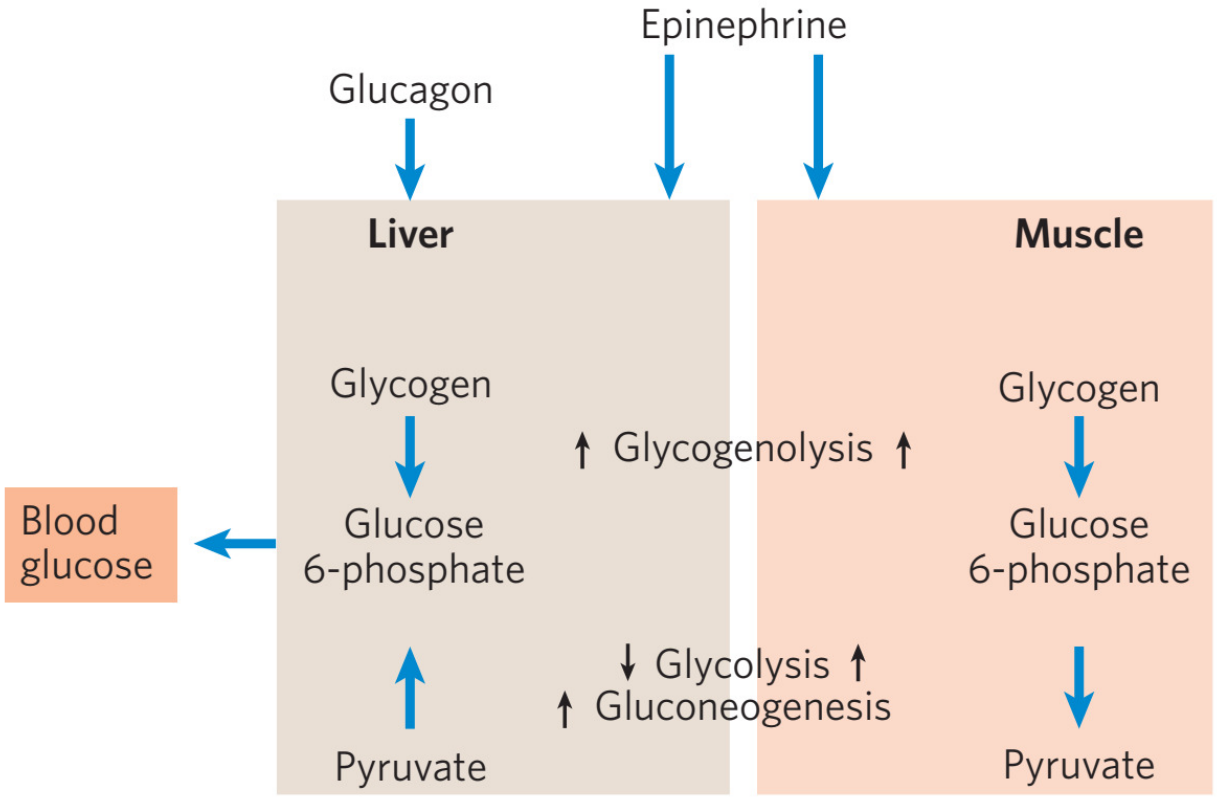
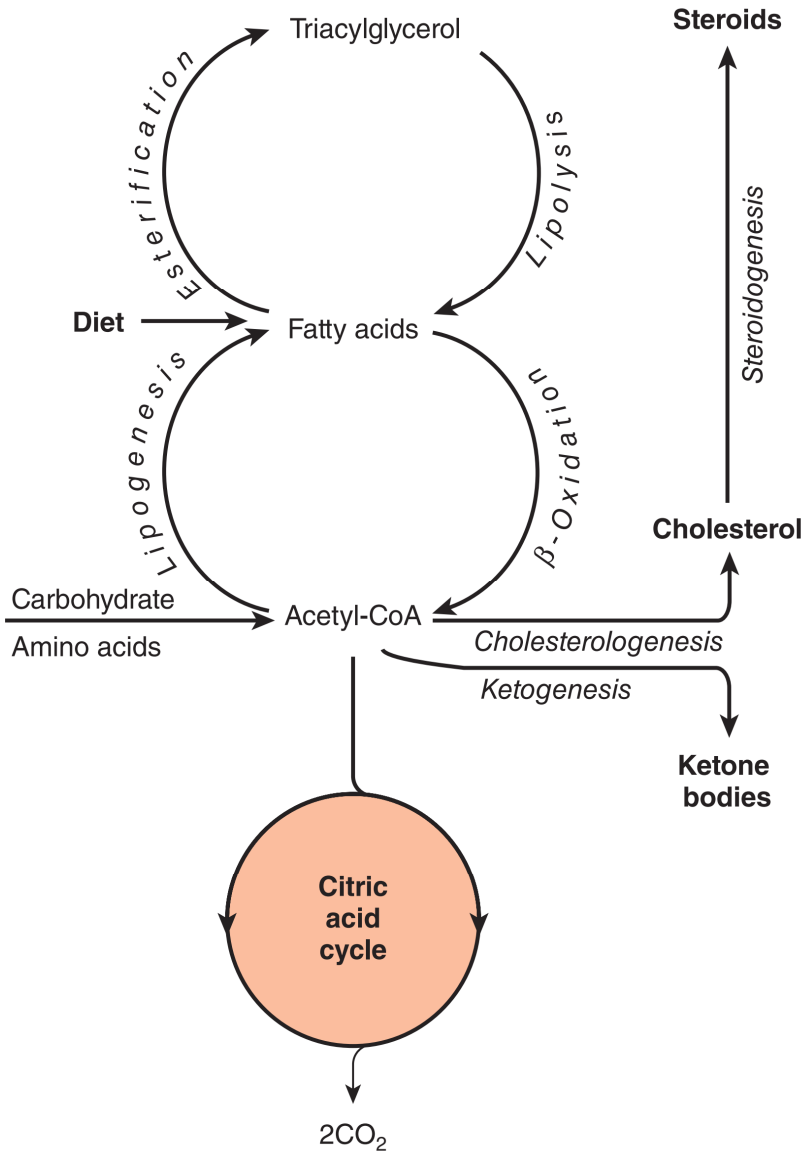
Glycogen breakdown, "glycogenolysis"

- In skeletal muscle and liver, the glucose units of glycogen is released by the actions of 3 enzymes: glycogen phosphorylase, glycogen debranching enzyme, and phosphoglucomutase.
- Glycogen phosphorylase catalyzes the reaction in which an (α1-4) glycosidic linkage between two glucose residues at a nonreducing end of glycogen undergoes attack by inorganic phosphate (Pi), removing the terminal glucose residue as α-D-glucose 1-phosphate

The regulation of carbohydrate metabolism in liver and muscle



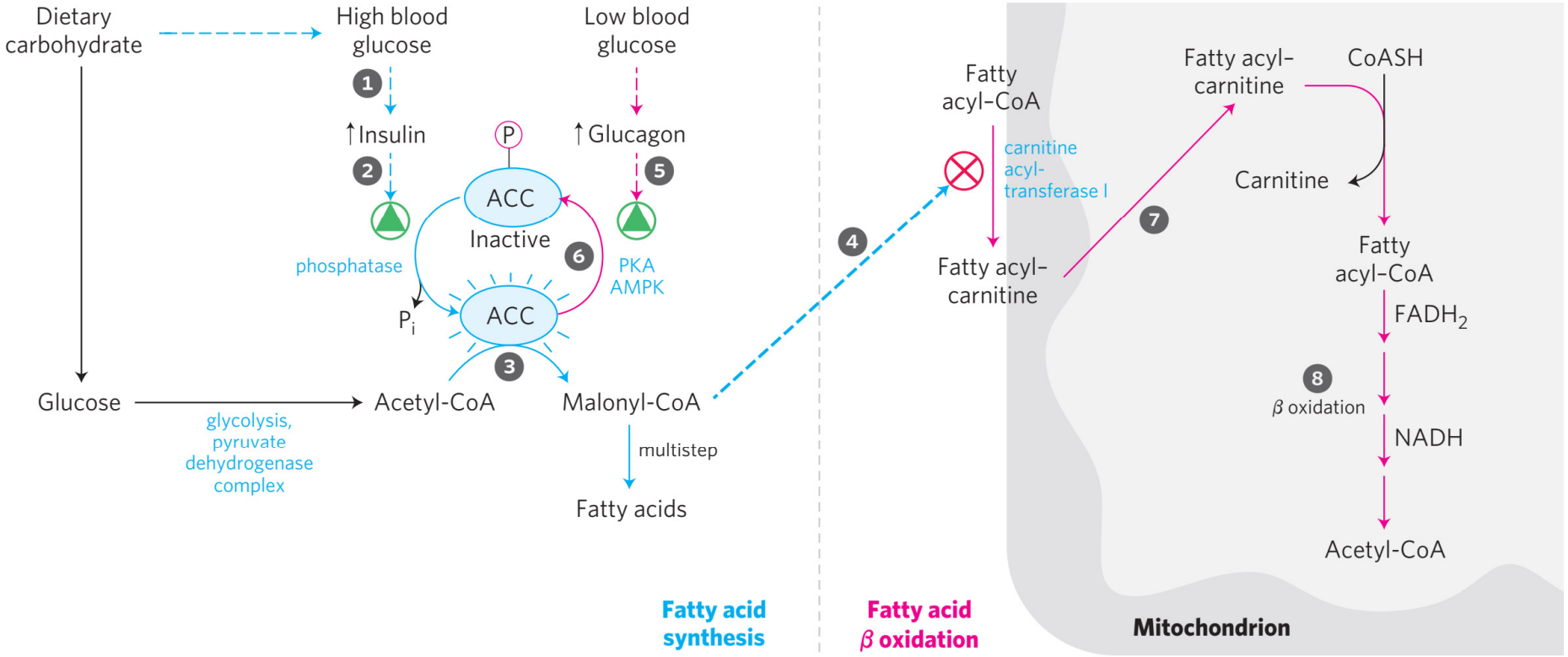
- In liver, either glucagon (indicating low blood glucose) or epinephrine (signaling the need to fight or flee) has the effect of maximizing the output of glucose into the bloodstream.
- In muscle, epinephrine increases glycogen breakdown and glycolysis, which together provide fuel to produce the ATP needed for muscle contraction.



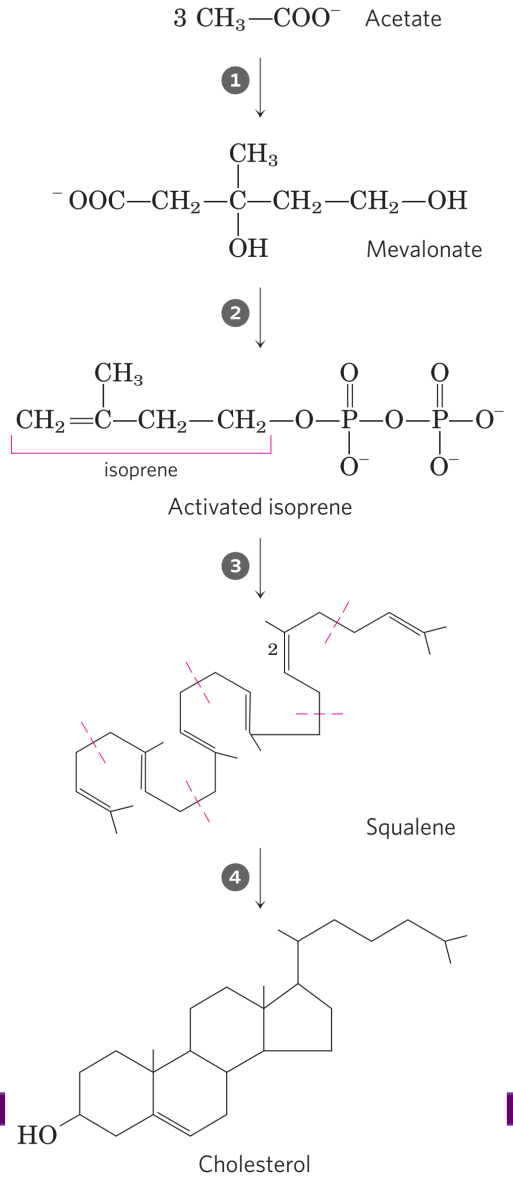
2. Lipid metabolism

- Lipid metabolism is concerned mainly with fatty acid and cholesterol
- Fatty acid synthesis → elongate the fatty acid in a repeating reaction sequence using
  - Fatty acid synthetase enzyme
  - Acetyl CoA as carbon source
  - Reducing agent (NADPH)
  - Energy from ATP
- Fatty acid oxidation → Acetyl CoA then metabolizes to
  - CO_2 and H_2O
  - Cholesterol
  - Ketone bodies

Coordinated regulation of fatty acid synthesis and breakdown



Two enzymes are key to the coordination of fatty acid metabolism: acetyl-CoA carboxylase (ACC), the first enzyme in fatty acid synthesis, and carnitine acyltransferase I, which limits the transport of fatty acids into the mitochondrial matrix for oxidation

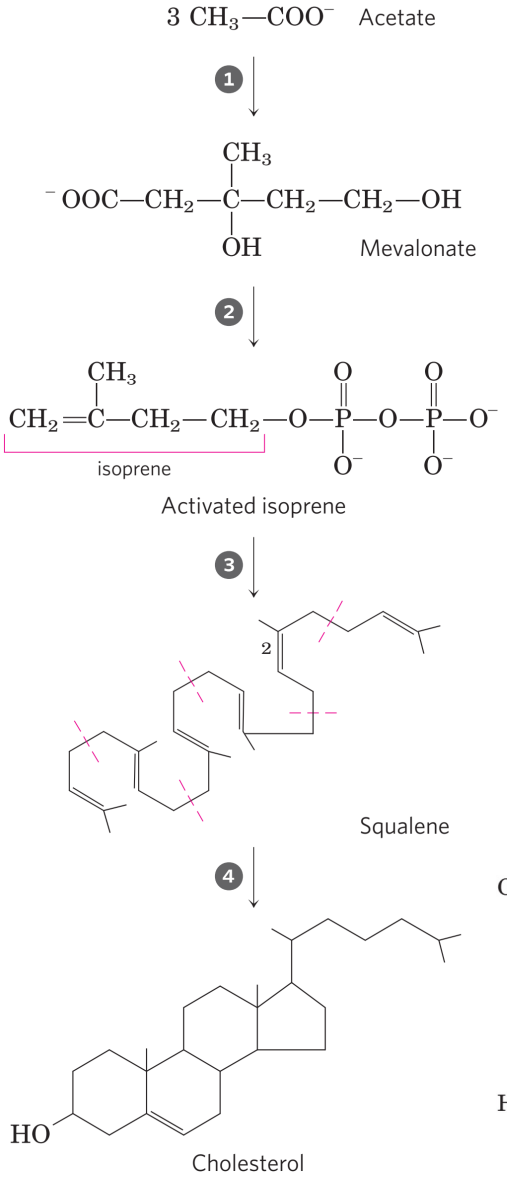


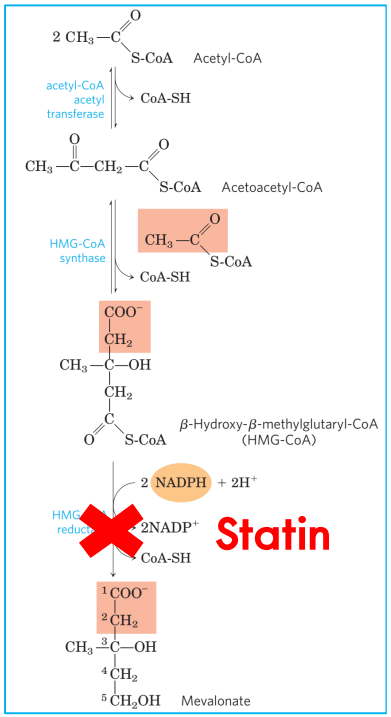
Cholesterol biosynthesis

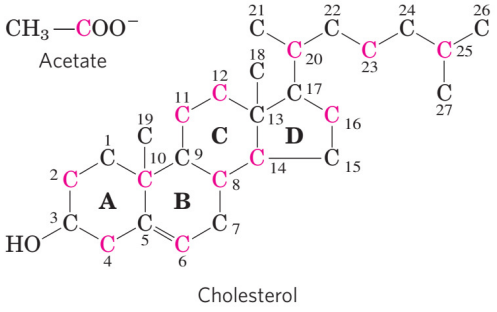
Cholesterol, like long-chain fatty acids, is made from acetyl-CoA but the synthesis of cholesterol is different from long-chain fatty acids.

Cholesterol is made from acetyl-CoA in four stages;

1. Condensation of three acetate units to form a six-carbon intermediate, mevalonate.
2. Conversion of mevalonate to activated isoprene units
3. Polymerization of six 5-carbon isoprene units to form the 30-carbon linear squalene
4. Cyclization of squalene to form the four rings of the steroid nucleus, with a further series of changes (oxidations, removal or migration of methyl groups) to produce cholesterol.







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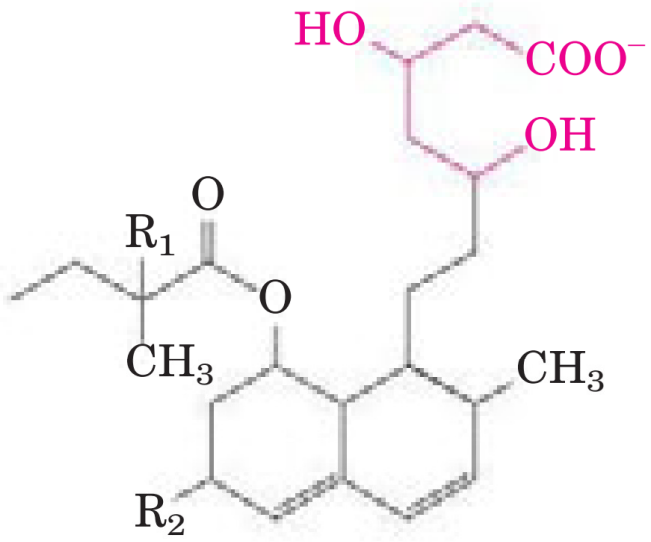
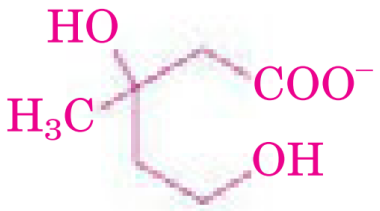
HMG CoA reductase inhibitor; Statin



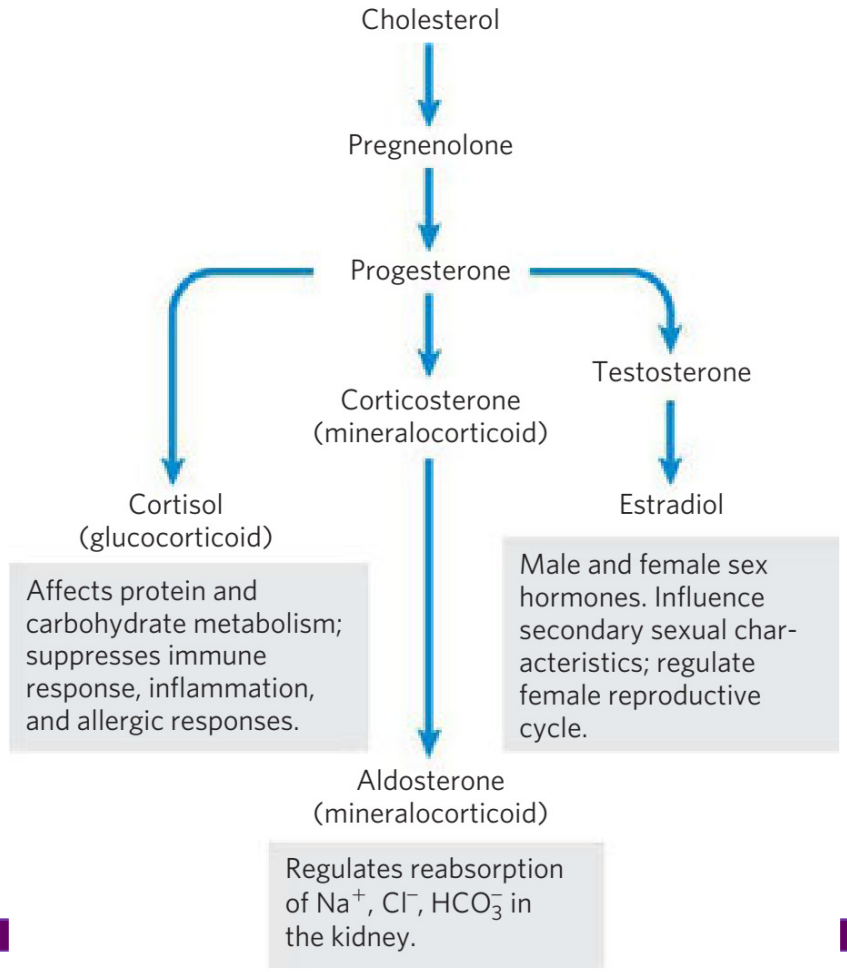


Mevalonate

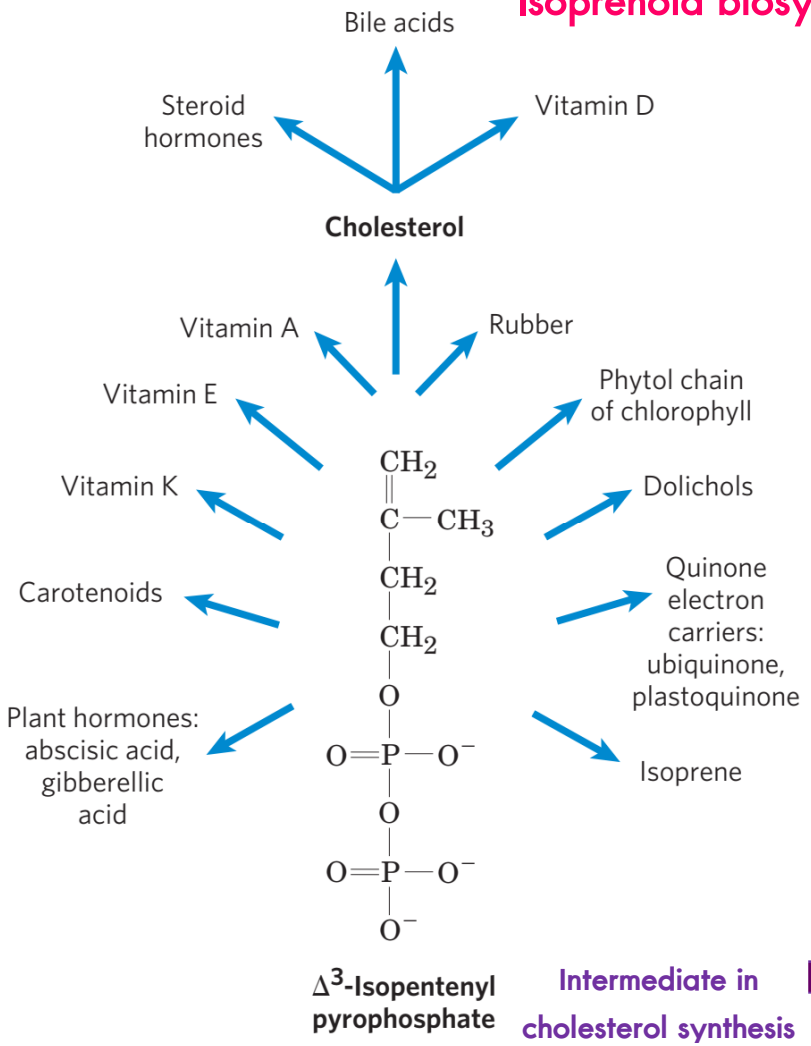
$R_1 = H$	$R_2 = H$	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
$R_1 = H$	$R_2 = OH$	Pravastatin (Pravachol)
$R_1 = H$	$R_2 = CH_3$	Lovastatin (Mevacor)

Cholesterol derivatives

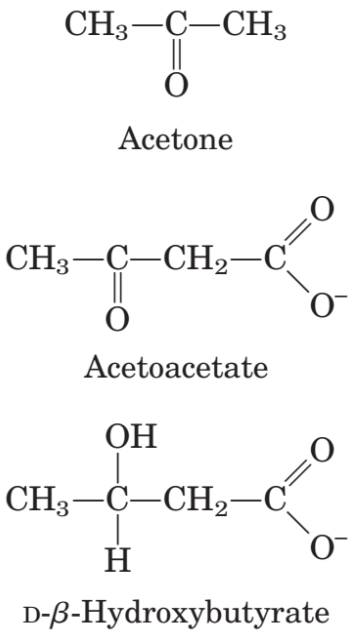
Steroid hormones



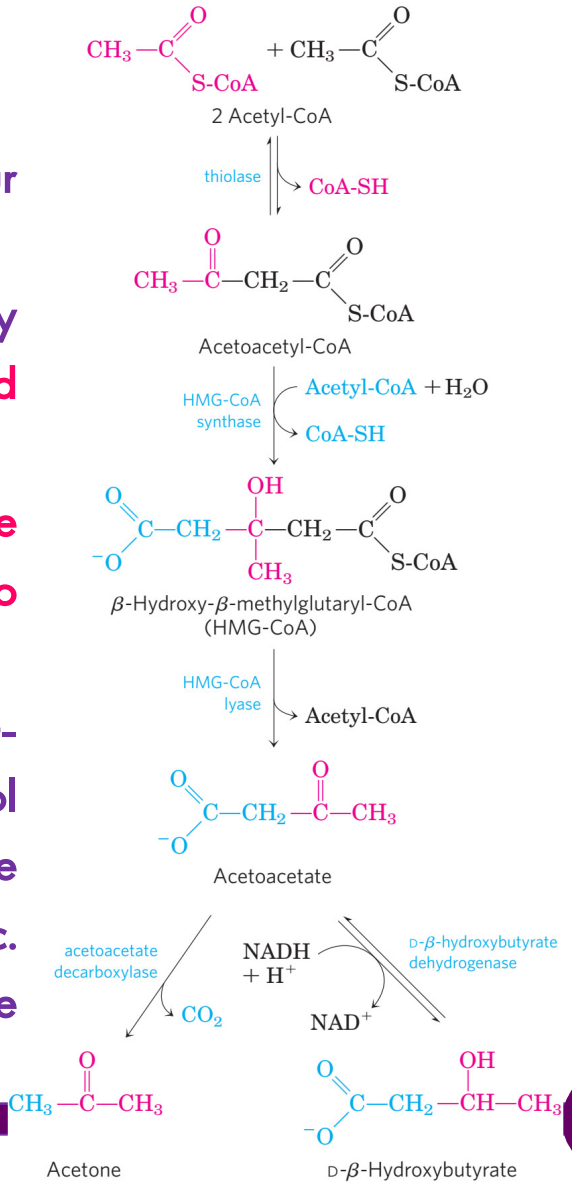
Isoprenoid biosynthesis



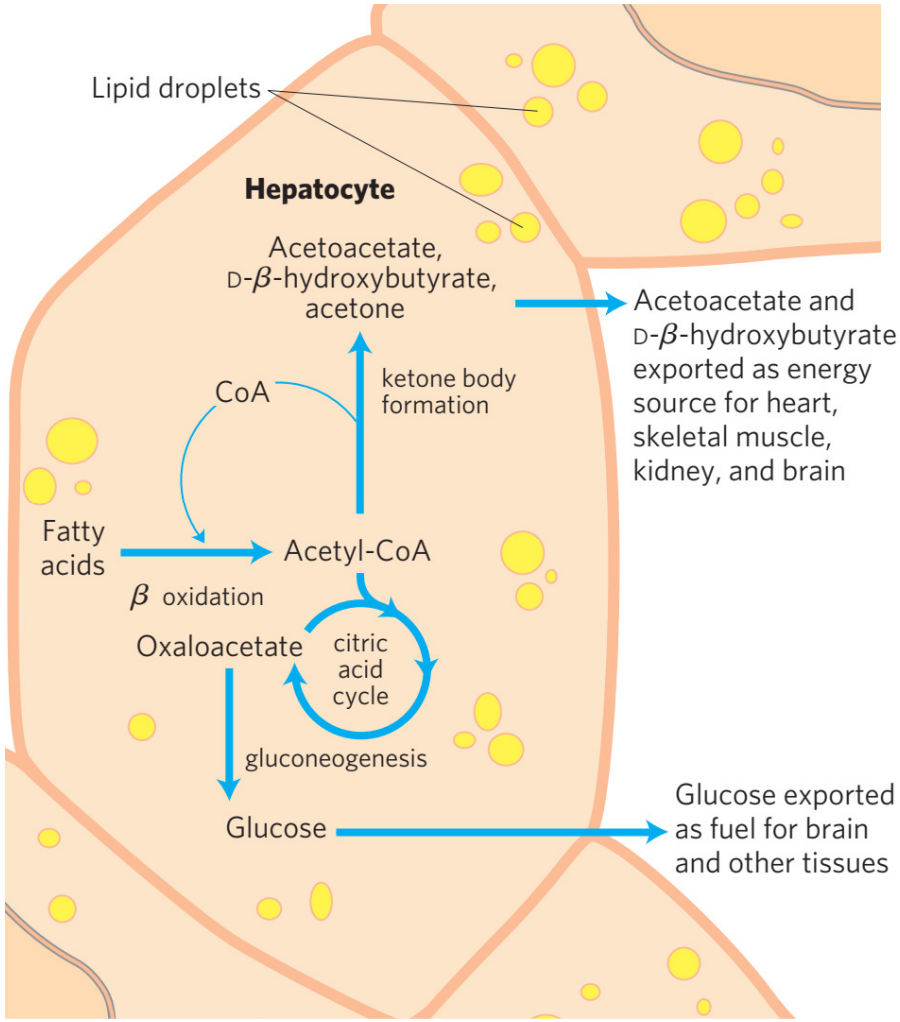
Ketone body formation



- Ketone body formation (Ketogenesis) occur in the matrix of liver mitochondria.
- Ketone bodies are produced at relatively low rate in healthy, well-nourished individual.
- In starvation or untreated DM, thiolase enzyme catalyzes the condensation of two acetyl-CoA to acetoacetyl-CoA.
- β-hydroxyl-β-methylglutaryl-CoA (HMG-CoA) is an intermediate of sterol biosynthesis and ketogenesis, but the enzyme for sterol biosynthesis is cytosolic. HMG-CoA lyase is present only in the mitochondrial matrix.



Ketone body export from the liver.



Conditions that promote gluconeogenesis (untreated diabetes, severely reduced food intake) slow the citric acid cycle (by drawing off oxaloacetate) and enhance the conversion of acetyl-CoA to acetoacetate. The released coenzyme A allows continued oxidation of fatty acids

2. Lipid metabolism

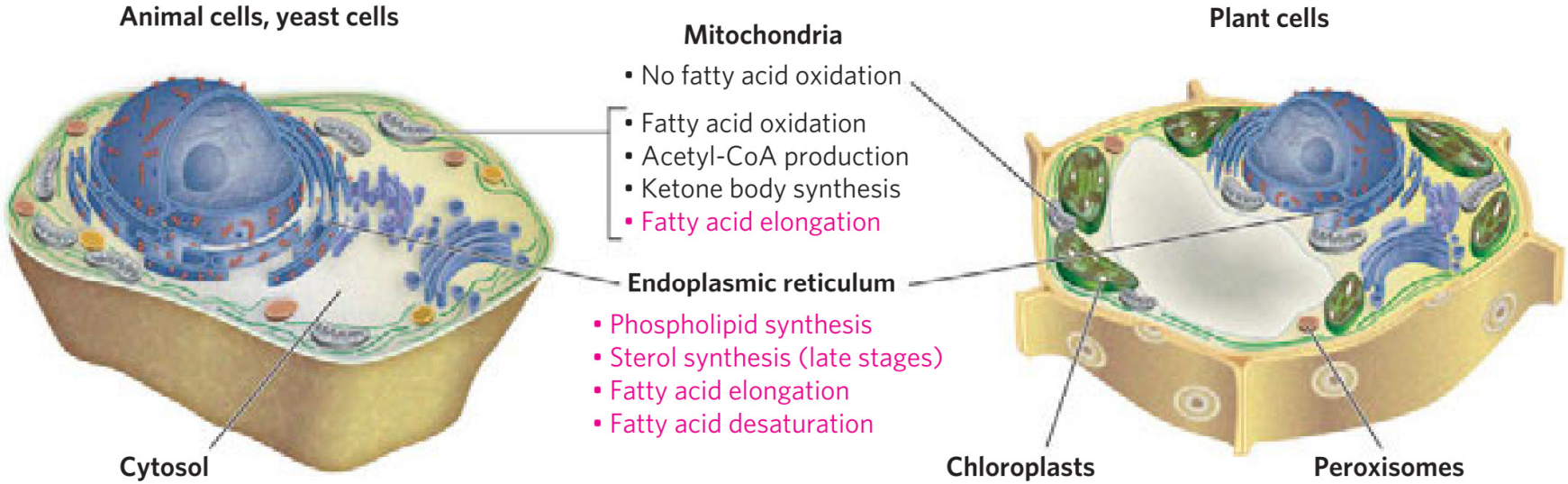
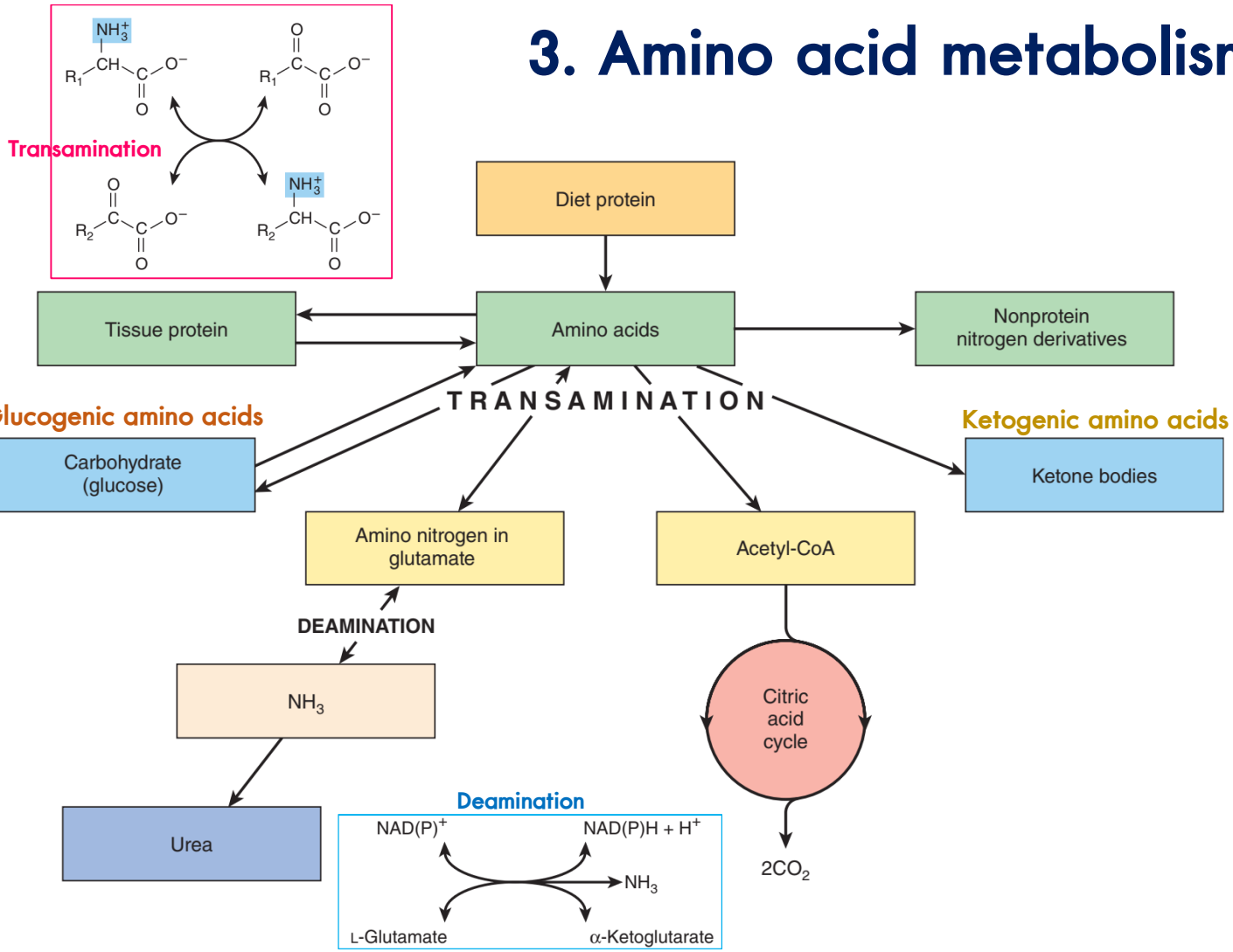


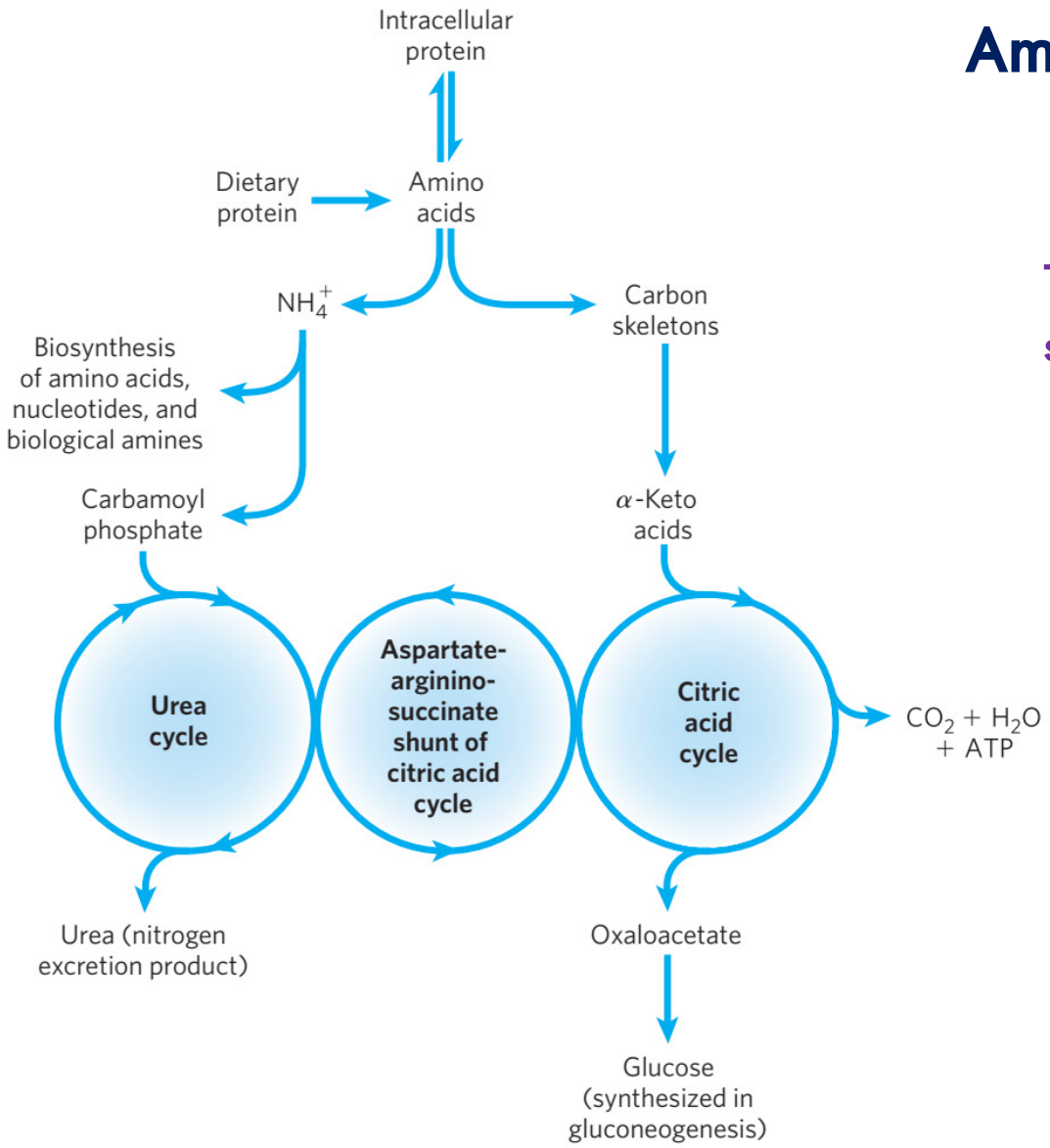
FIGURE 21–8 Subcellular localization of lipid metabolism. Yeast and vertebrate cells differ from higher plant cells in the compartmentation of lipid metabolism. Fatty acid synthesis takes place in the compartment in which NADPH is available for reductive synthesis (i.e., where the [NADPH]/[$NADP^+$] ratio is high); this is the cytosol in animals and yeast, and the chloroplast in plants. Processes in red type are covered in this chapter.

3. Amino acid metabolism



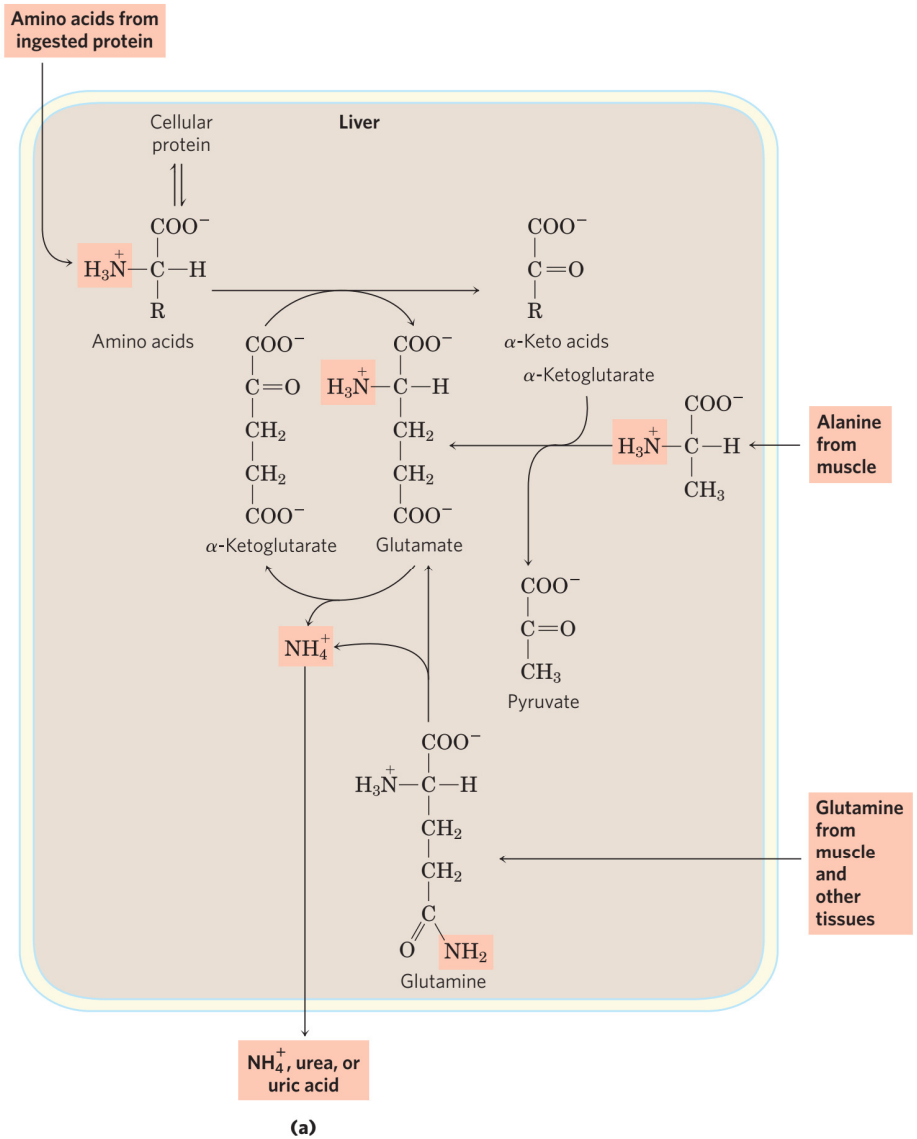
- **Transamination** = transfer amino group from one amino acid to another amino acid
- **Deamination** = remove nitrogen and excrete from the body as urea
- Carbon skeleton after nitrogen removal
  - Oxidize to CO_2 and generate energy
  - Use to synthesize glucose, "Gluconeogenesis"
  - Form acetyl CoA or ketone bodies

Amino acid catabolism in mammals



The amino groups and the carbon skeleton take separate but interconnected pathways

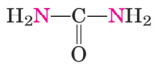
Amino group catabolism



NH_4^+

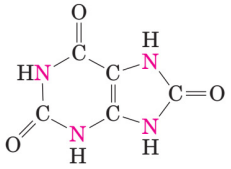
Ammonia (as ammonium ion)

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia



Urea

Ureotelic animals: many terrestrial vertebrates; also sharks



Uric acid

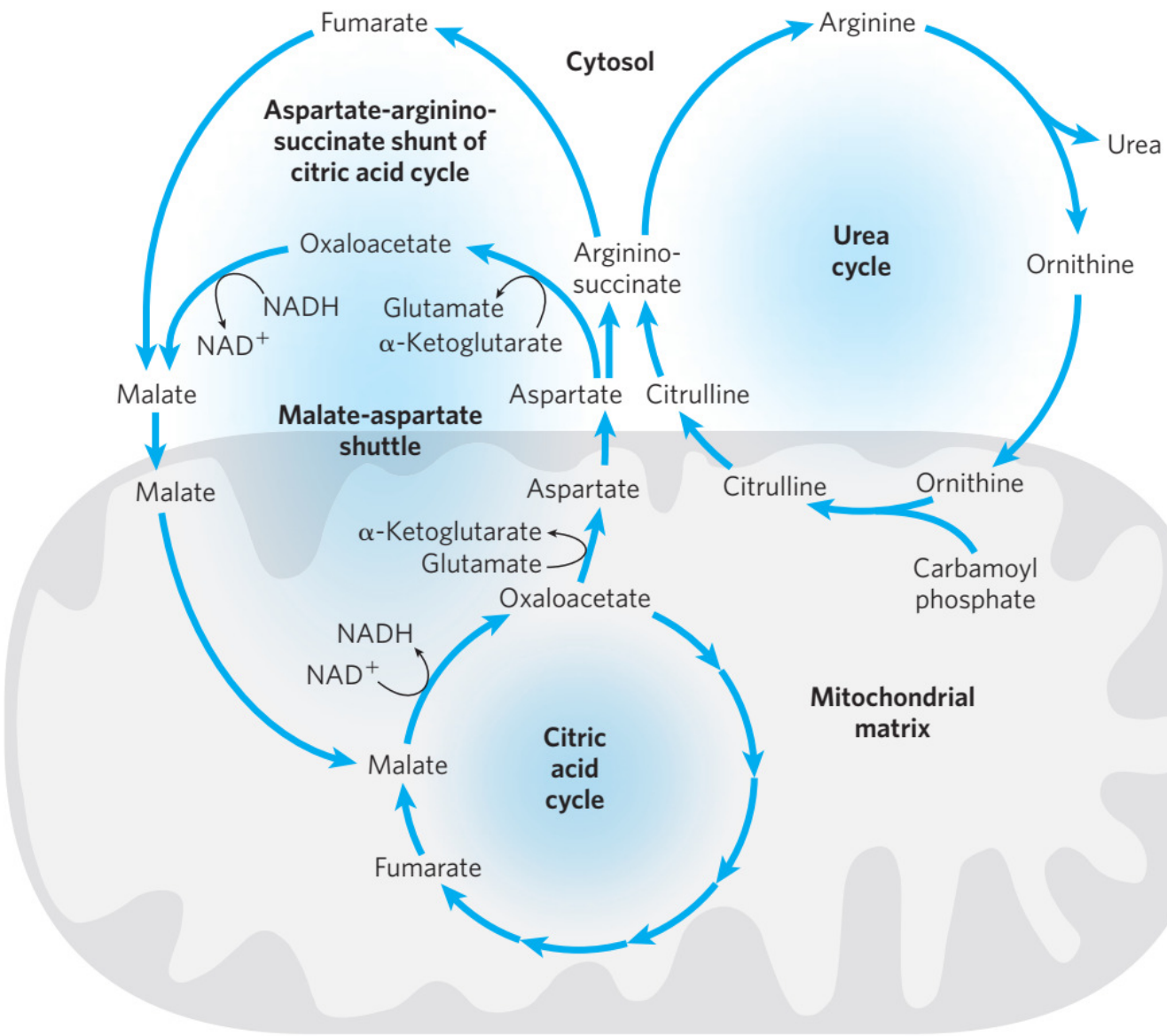
Uricotelic animals: birds, reptiles

(b)

Catabolism of amino groups (shaded) in vertebrate liver.

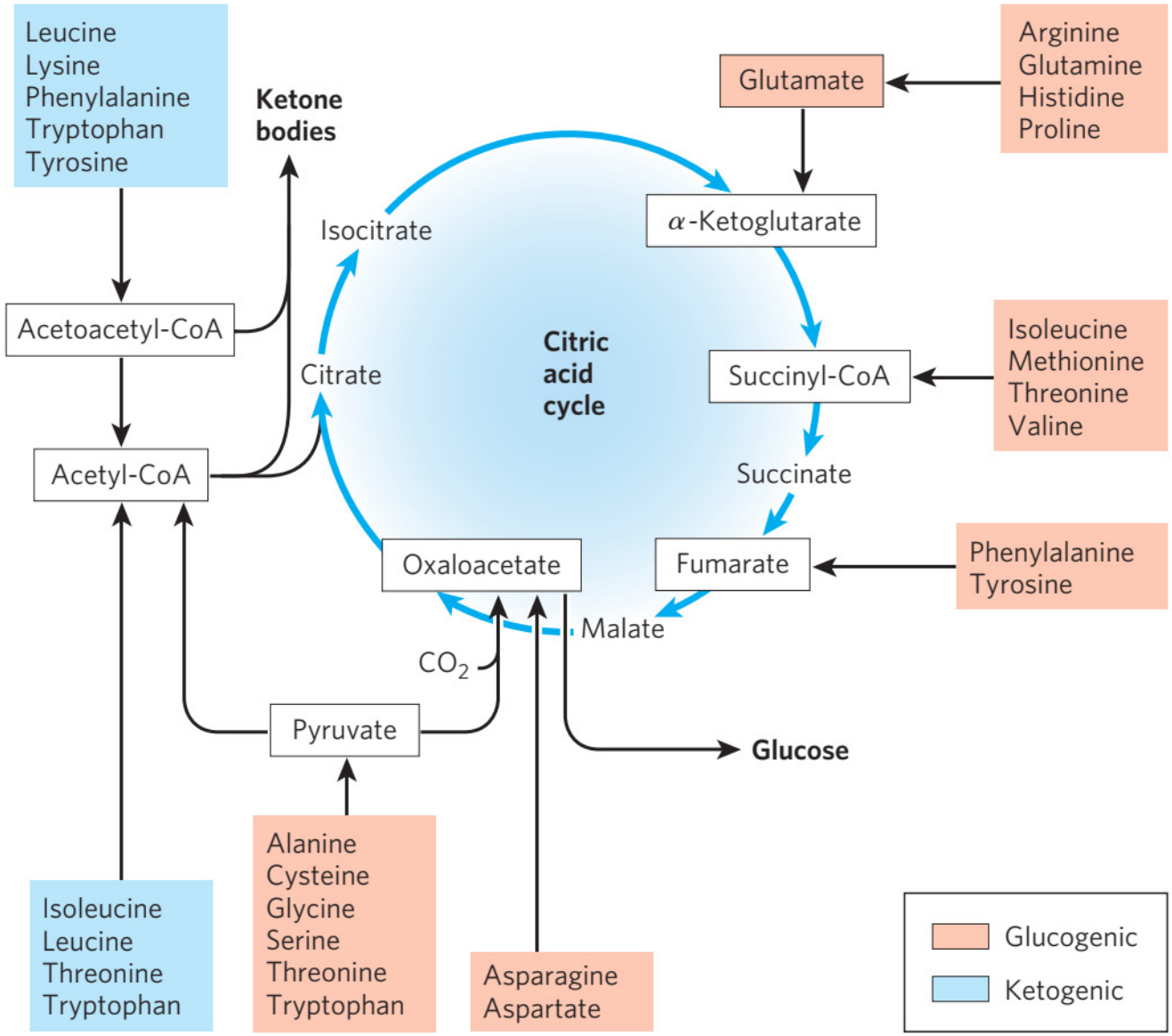
- Excess NH_4 is excreted as ammonia (microbes, bony fishes), urea (most terrestrial vertebrates), or uric acid (birds and terrestrial reptiles).
- Notice that the carbon atoms of urea and uric acid are highly oxidized;
- the organism discards carbon only after extracting most of its available energy of oxidation.

Link between urea cycle and Krebs cycle



The interconnected cycles have been called the "Krebs bicycle." The pathways linking the citric acid and urea cycles are known as the aspartate-argininosuccinate shunt.

Link between amino acid catabolism and Krebs cycle

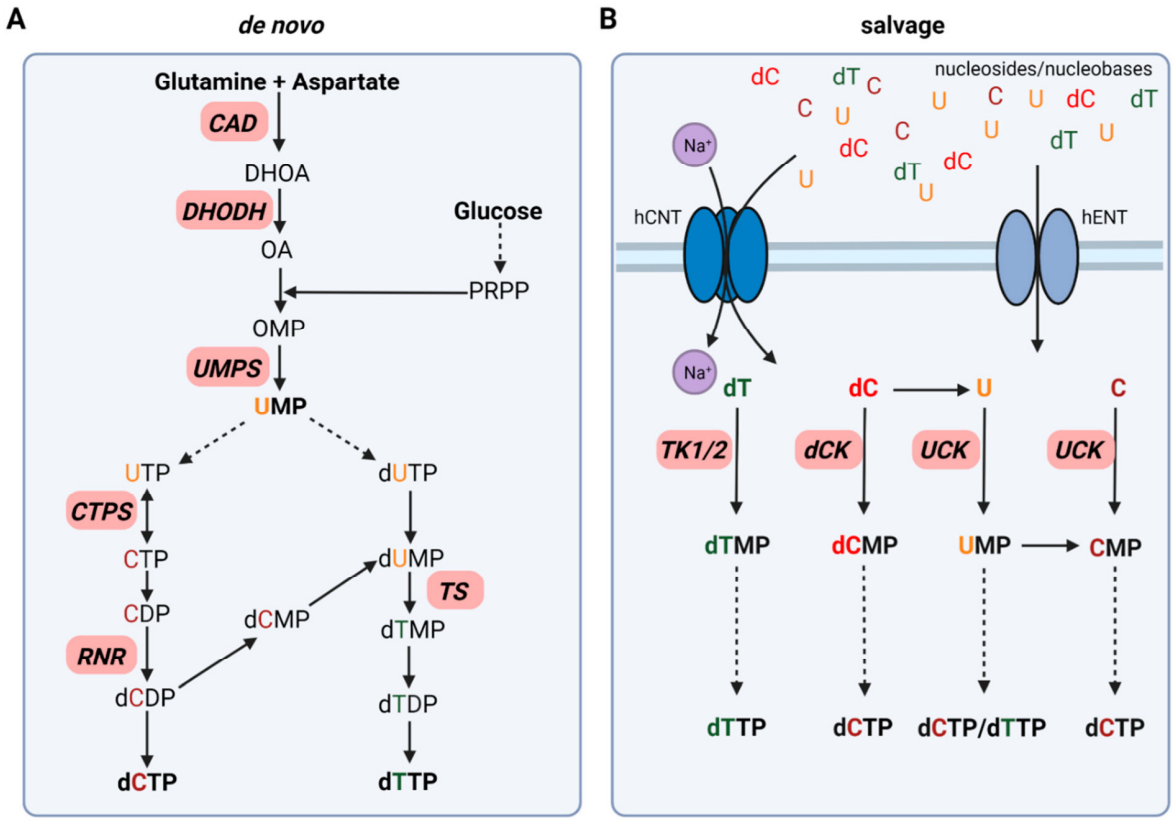


Amino acids are grouped according to their major degradative end product

- Ketogenic amino acid
- Glucogenic amino acid
- Only 2 amino acids, leucine and lysine, are solely ketogenic.

4. Nucleotide metabolism

- 2 types of pathways
  - *De novo* pathway: synthesis of nucleotides begins with amino acids, ribose 5-phosphate, CO_2, and NH_3.
  - Salvage pathway: recycle the free bases and nucleosides released from nucleic acid breakdown



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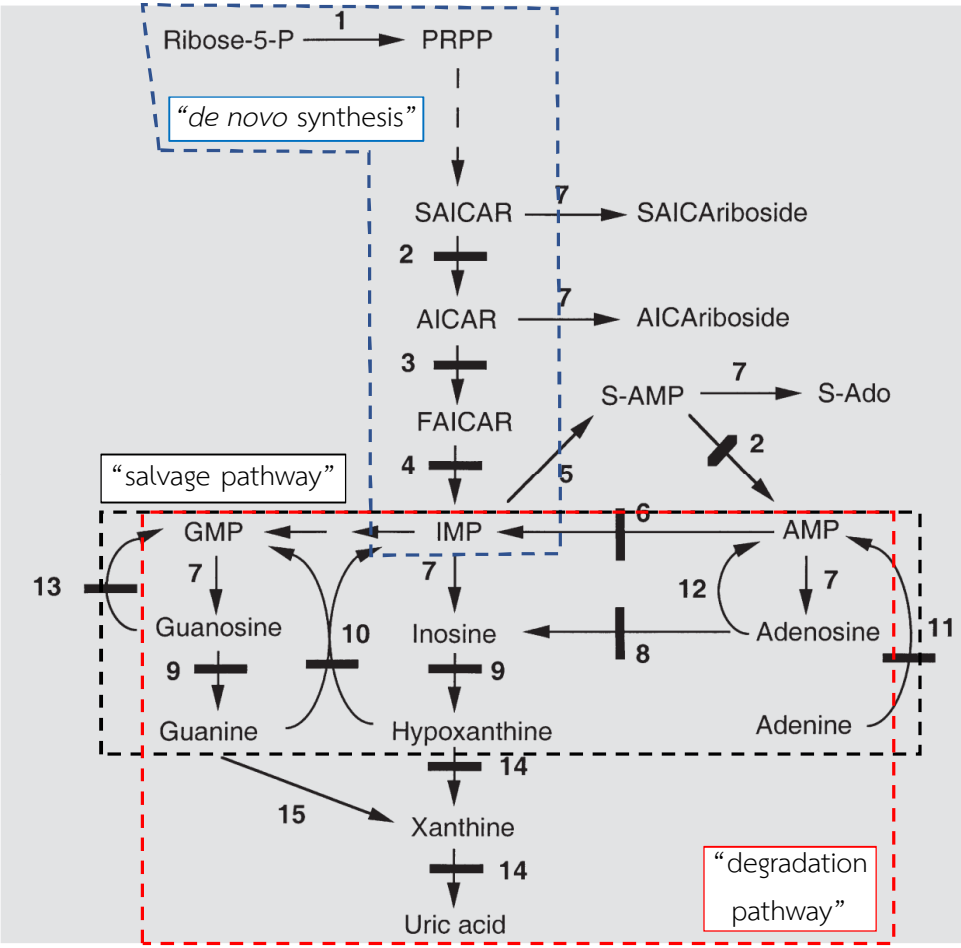
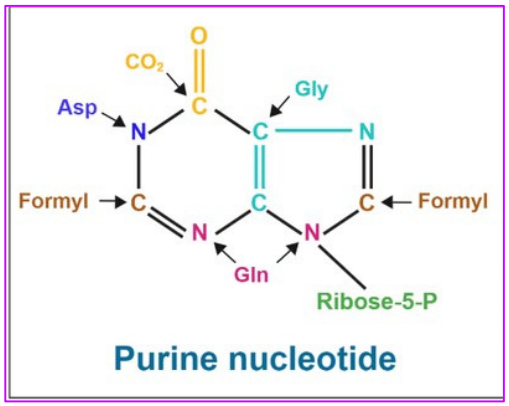
4. Nucleotide metabolism: Purine metabolism





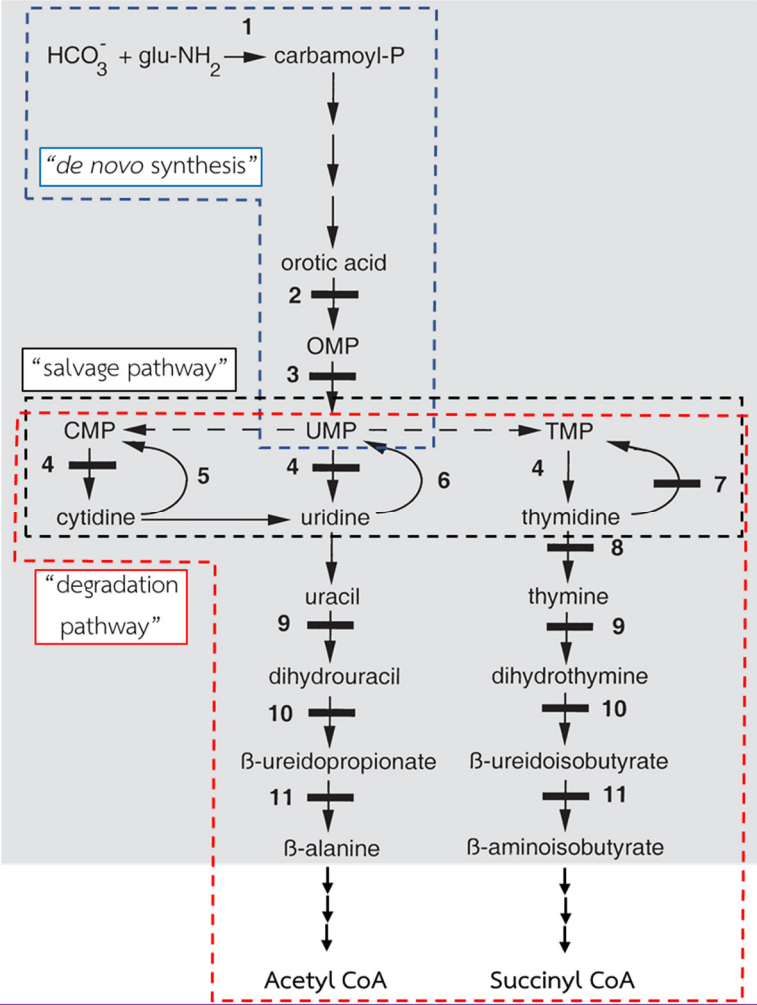
Villa E and Ali E, Cancers, 2019.

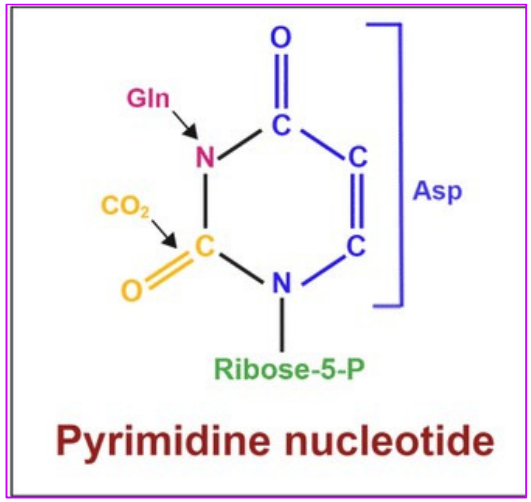
Fig. 35.1. Pathways of purine metabolism. *AICAR*, aminoimidazolecarboxamide ribotide; *AMP*, adenosine monophosphate; *FAICAR*, formylaminoimidazolecarboxamide ribotide; *GMP*, guanosine monophosphate; *IMP*, inosine monophosphate; *P*, phosphate; *PRPP*, phosphoribosyl pyrophosphate, *S-Ado*, succinyladenosine; *SAICAR*, succinylaminoimidazolecarboxamide ribotide; *S-AMP*, adenylosuccinate, *XMP*, xanthosine monophosphate. **1**, PRPP synthetase; **2**, adenylosuccinase (adenylosuccinate lyase); **3**, AICAR transformylase; **4**, IMP cyclohydrolase (3 and 4 form ATIC); **5**, adenylosuccinate synthetase; **6**, AMP deaminase; **7**, 5′-nucleotidase(s), **8**, adenosine deaminase; **9**, purine nucleoside phosphorylase; **10**, hypoxanthine-guanine phosphoribosyltransferase; **11**, adenine phosphoribosyltransferase; **12**, adenosine kinase; **13**, guanosine kinase; **14**, xanthine oxidase (dehydrogenase). Enzyme defects are indicated by *solid bars* across the arrows

Step 14 is catalyzed by xanthine oxidase enzyme and can be inhibited by allopurinol drug (anti-hyperuricemic drug).

Hoffmann GF., et al. Inborn metabolic Diseases, Diagnosis and treatment, 4th ed., 2006

4. Nucleotide metabolism: Pyrimidine metabolism

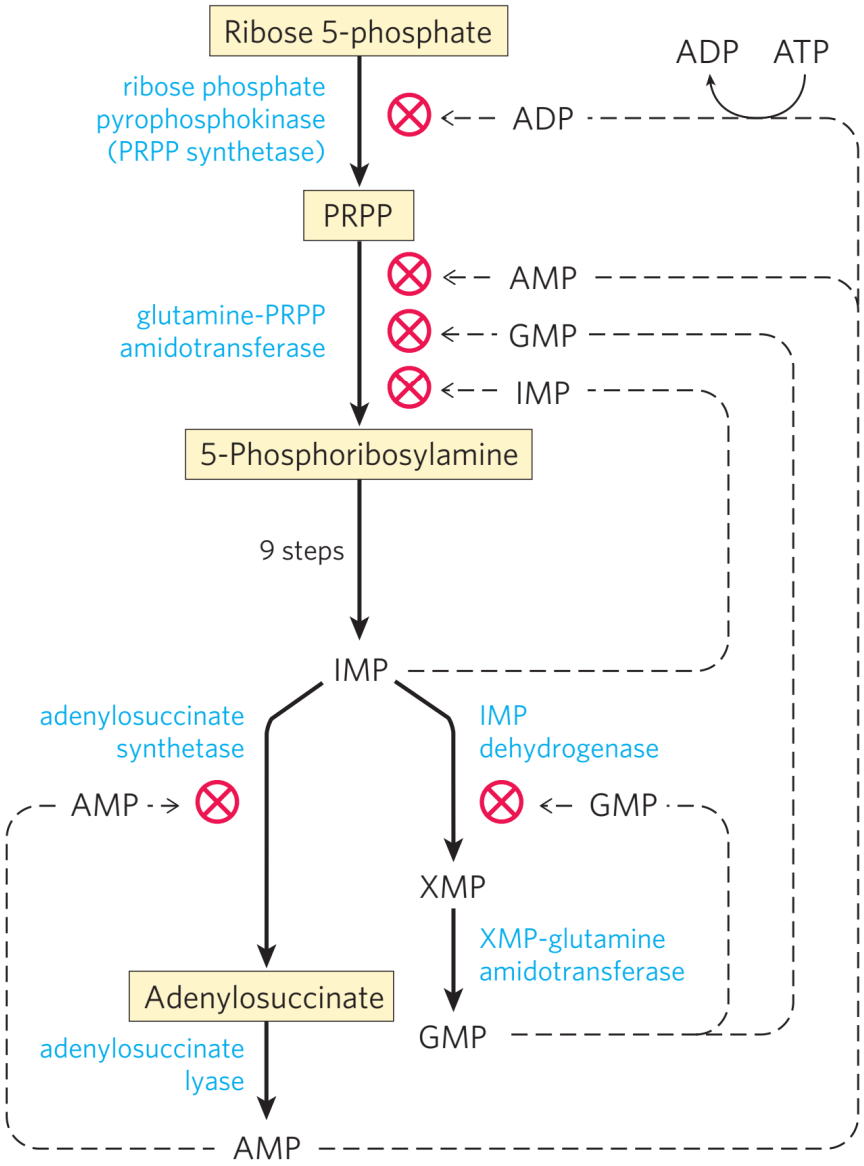




Villa E and Ali E, Cancers, 2019.

Fig. 35.3. Pathways of pyrimidine metabolism. *CMP*, cytidine monophosphate; *glu-NH$_2$*, glutamine; *OMP*, orotidine monophosphate; *PRPP*, phosphoribosylpyrophosphate; *TMP*, thymidine monophosphate; *UMP*, uridine monophosphate. **1**, carbamoylphosphate synthetase; **2**, orotate phosphoribosyltransferase; **3**, orotidine decarboxylase (**2** and **3** form UMP synthase); **4**, pyrimidine (cytosolic) 5′-nucleotidase; **5**, cytidine kinase; **6**, uridine kinase; **7**, thymidine kinase; **8**, thymidine phosphorylase; **9**, dihydropyrimidine dehydrogenase; **10**, dihydropyrimidinase; **11**, ureidopropionase. Enzyme deficiencies are indicated by *solid bars* across the arrows

Hoffmann GF., et al. Inborn metabolic Diseases, Diagnosis and treatment, 4th ed., 2006



Regulations of biosynthesis of adenine and guanine nucleotide

3 major feedback mechanisms regulating the *de novo* purine nucleotide synthesis

- R-5-P → PRPP
- PRPP → 5-phosphoribosylamine
  Whenever either AMP or GMP accumulates to excess, the first step in its biosynthesis from PRPP is partially inhibited.
- IMP → XMP and IMP → adenylosuccinate

PRPP = Phosphoribosyl diphosphate

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3. Lieberman M and Peet A, Marks' Basic Medical Biochemistry; a Clinical approach, 5th edition, 2017.

Thank you

If you may have any questions, please send an e-mail to kulthidava@kku.ac.th

Post-test will be available on e-learning from 20-28 June 2024.