BIOSYNTHESIS OF NUCLEIC ACIDS, CARBOHYDRATES AND LIPIDS

BY: RASAQ NURUDEEN OLAJIDE

LECTURE CONTENT

- INTRODUCTION
- BIOSYNTHESIS OF NUCLEIC ACID
- De NOVO PURINE SYNTHESIS
- REGULATION OF PURINE NUCLEOTIDE BIOSYNTHESIS
- De NOVO SYNTHESIS OF PYRIMIDINE NUCLEOTIDE
- SALVAGE PATHWAYS OF NUCLEOTIDE SYNTHESIS
- BIOSYNTHESIS OF STARCH
- SUCROSE SYNTHESIS
- FATTY ACID BIOSYNTHESIS
- ACETYL-COA CARBOXYLASE REACTION
- β-OXIDATION AND FATTY ACID BIOSYNTHESIS
- FATTY ACID SYNTHASE REACTION
- BIOSYNTHESIS OF TRIACYLGLYCEROL
- BIOSYNTHESIS OF CHOLESTEROL

INTRODUCTION

- **Anabolism also called biosynthesis, is the other set of reactions that constitute metabolism, the other being catabolism/degradation.**
- **In anabolism, 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 ATP and the reducing power of NADPH**
- **Anabolic pathways are divergent.**

BIOSYNTHESIS OF NUCLEIC ACID

- **Nucleotides are biologically ubiquitous substances that participate in nearly all biochemical processes:**
- **There are 2 pathways of nucleotide biosynthesis**

(1) **De Novo pathways**

(2) **Salvage pathways**

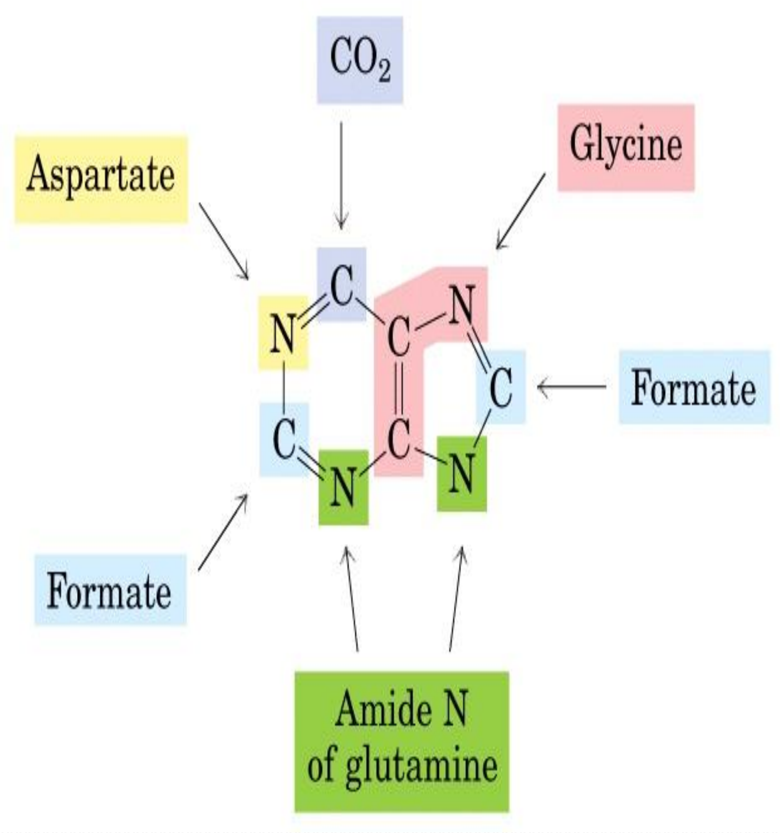
De NOVO PURINE NUCLEOTIDE BIOSYNTHESIS

- **De novo synthesis of nucleotides begins with their metabolic precursors: amino acids, ribose 5-phosphate, Co2 and NH3.**

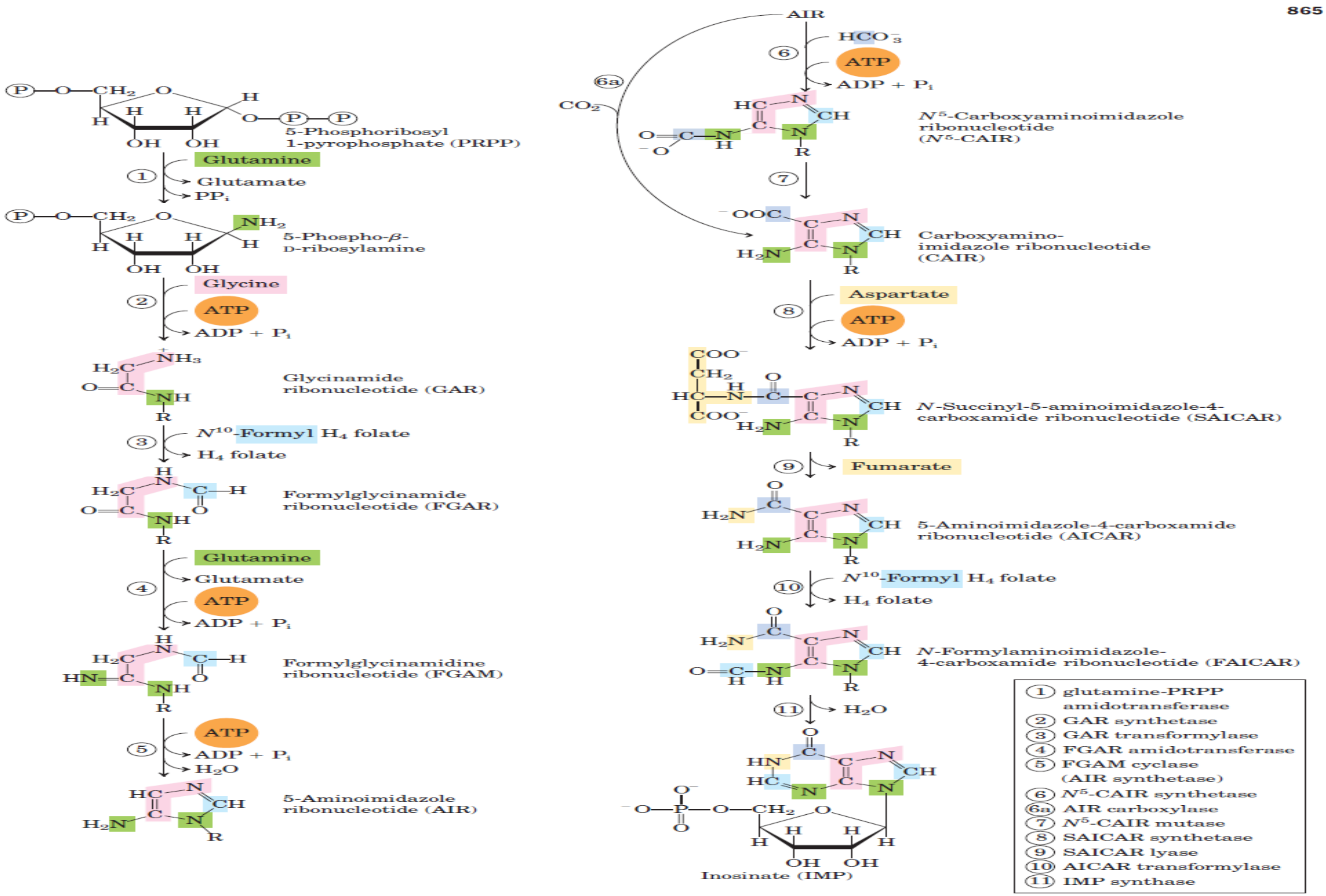
- **The 2 parent purine nucleotides are adenosine 5'-monophospate (AMP, adenylate) and guanosine 5'-monophosphate (GMP, guanylate) containing the purine bases adenine and guanine.**

- **Before AMP and GMP are synthesized, the initially synthesized purine derivative is INOSINE monophosphate (IMP)**

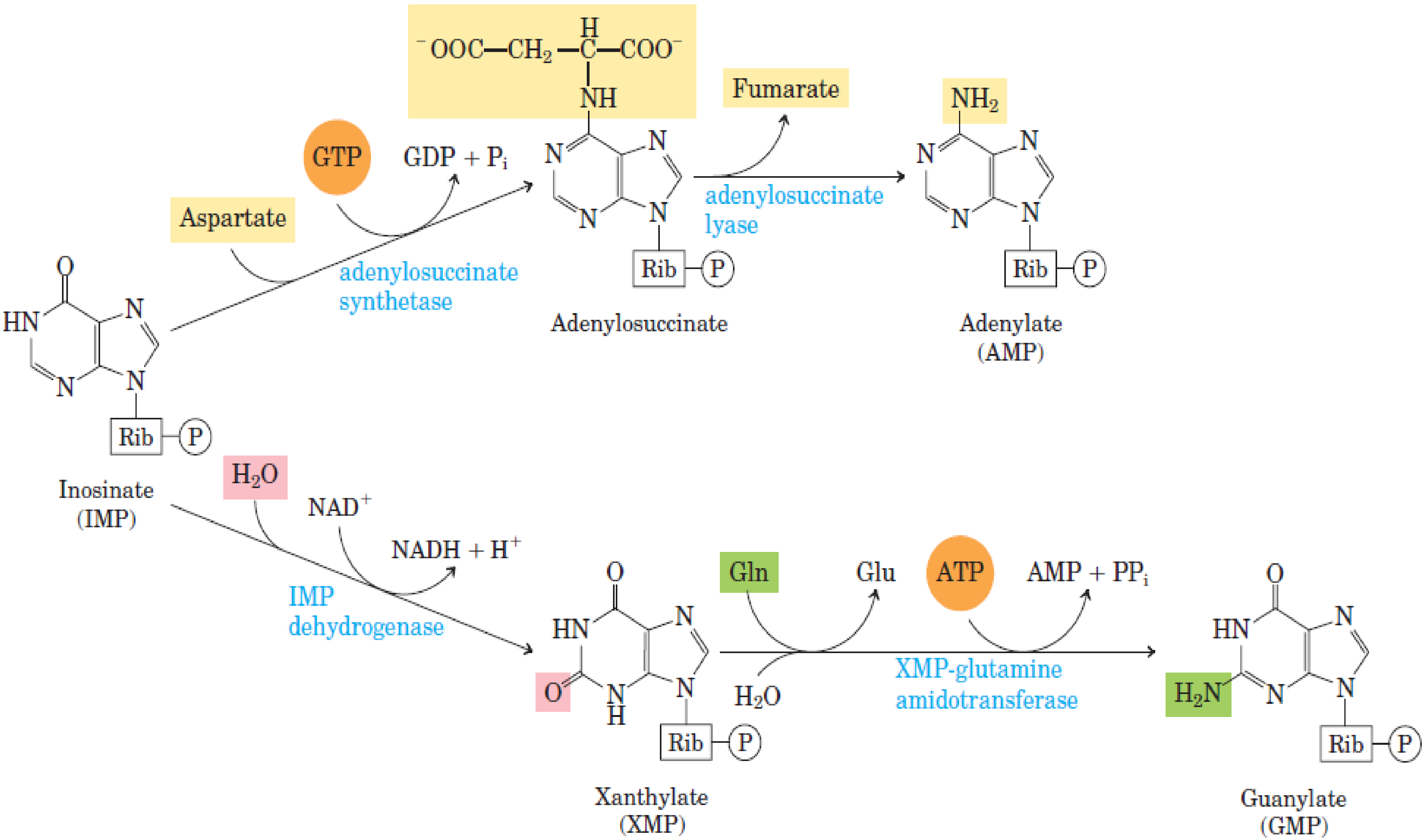
- **Origin of the ring atoms of purine**



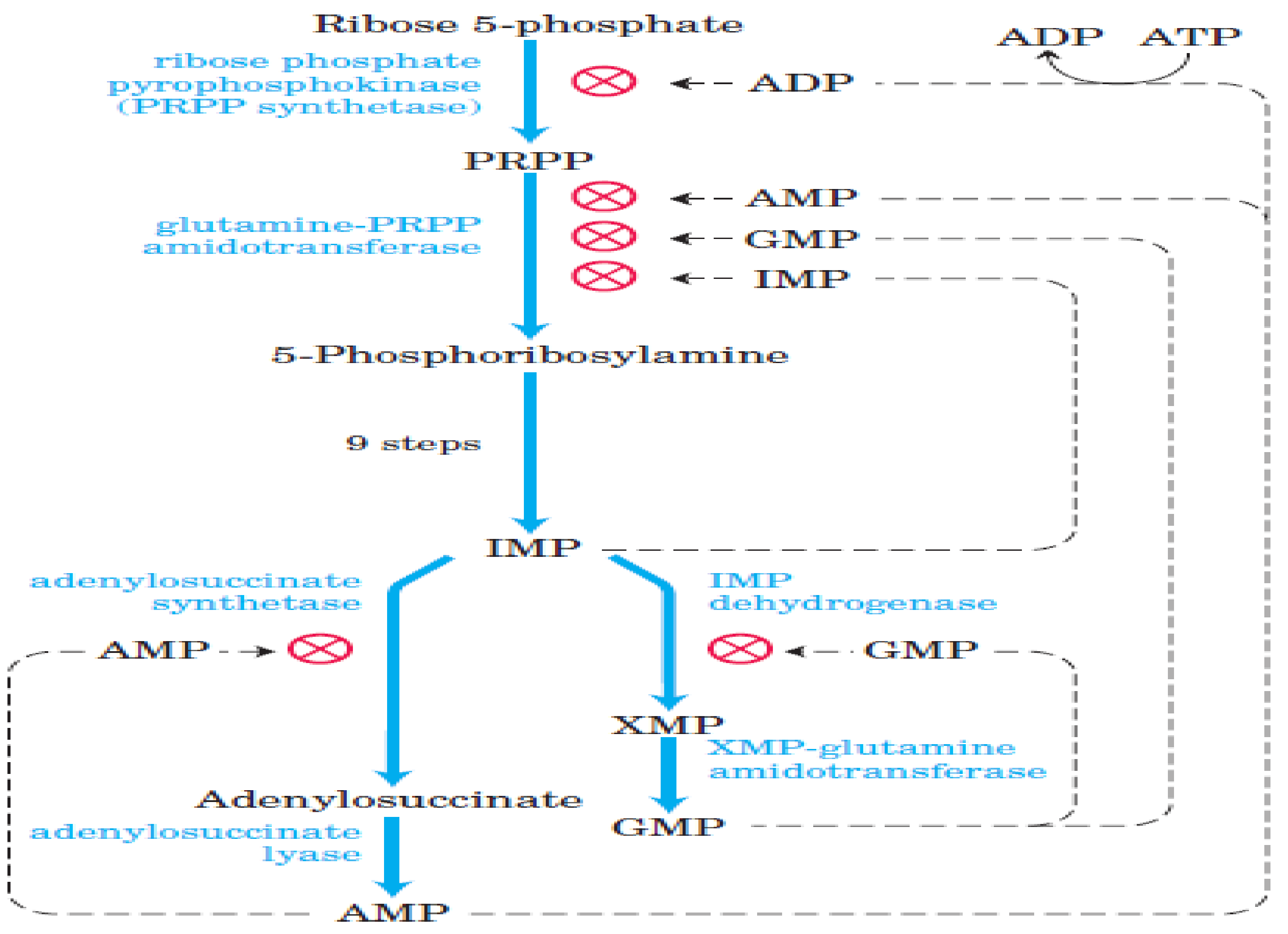
De NOVO PURINE NUCLEOTIDE BIOSYNTHESIS



De NOVO SYNTHESIS OF PURINE CONT'D



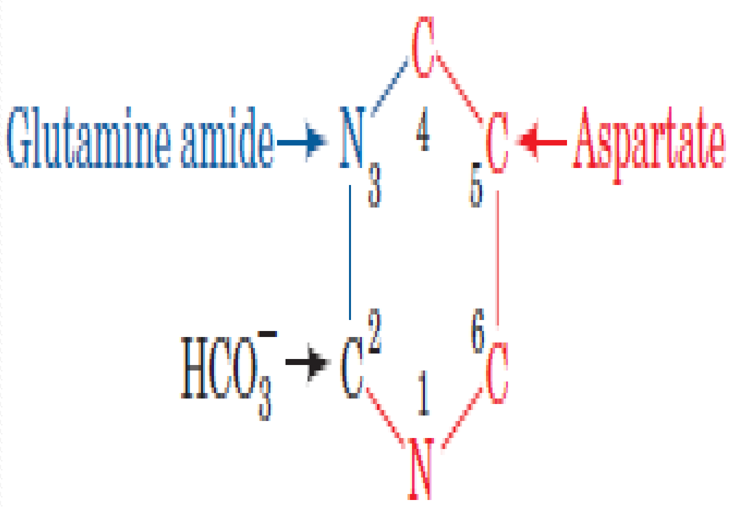
REGULATION OF PURINE NUCLEOTIDE BIOSYNTHESIS



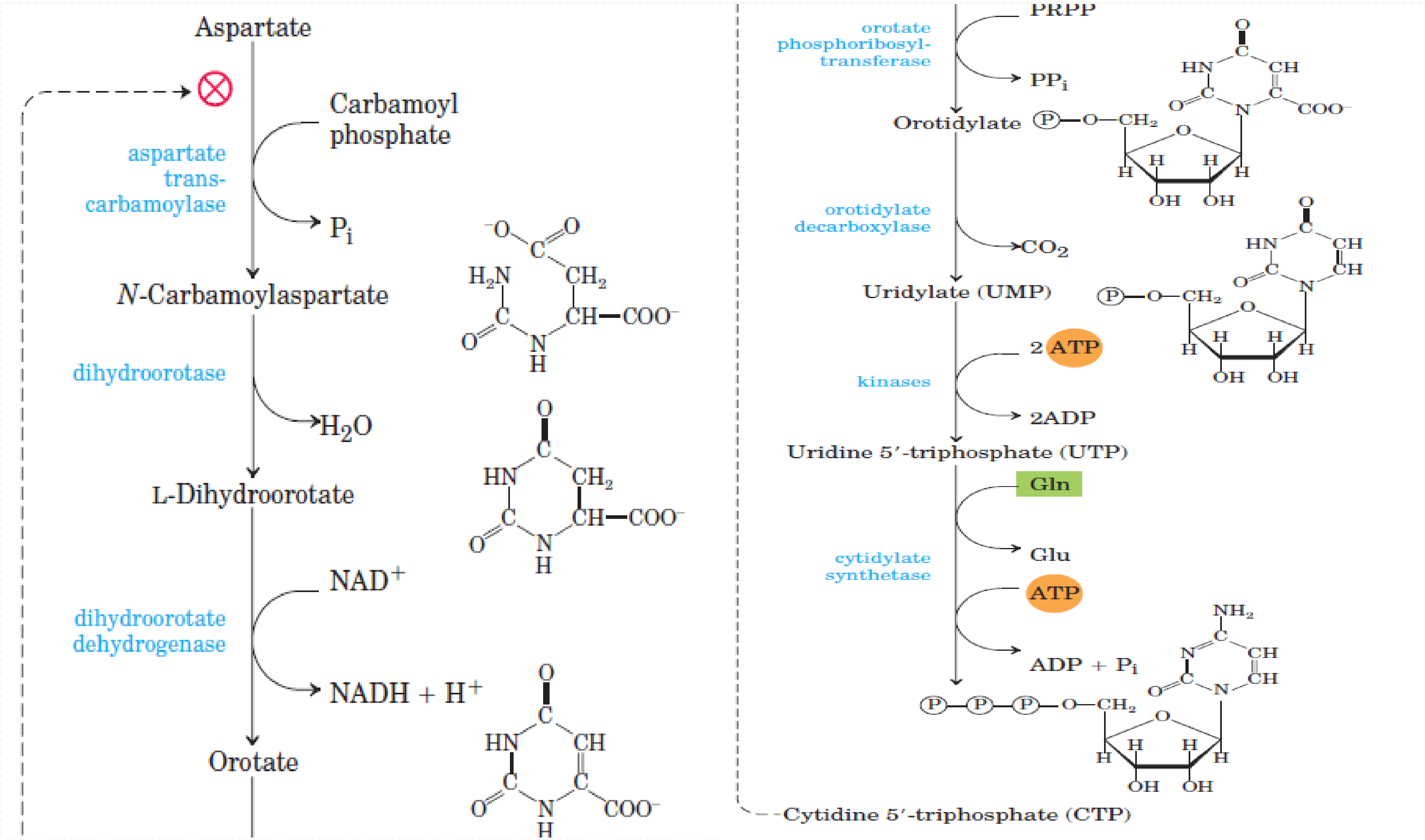
De NOVO SYNTHESIS OF PYRIMIDINE NUCLEOTIDES

- **Pyrimidine nucleotides are made from Aspartate, PRPP and carbamoyl phosphate**
- **The common pyrimidine ribonucleotides are CMP or Cytidylate, UMP or Uridylate and TMP or Thymidylate**
- **The six-membered pyrimidine ring is made first and then attached to ribose 5 phosphate**

- **Biosynthetic origin of pyrimidine ring atom**

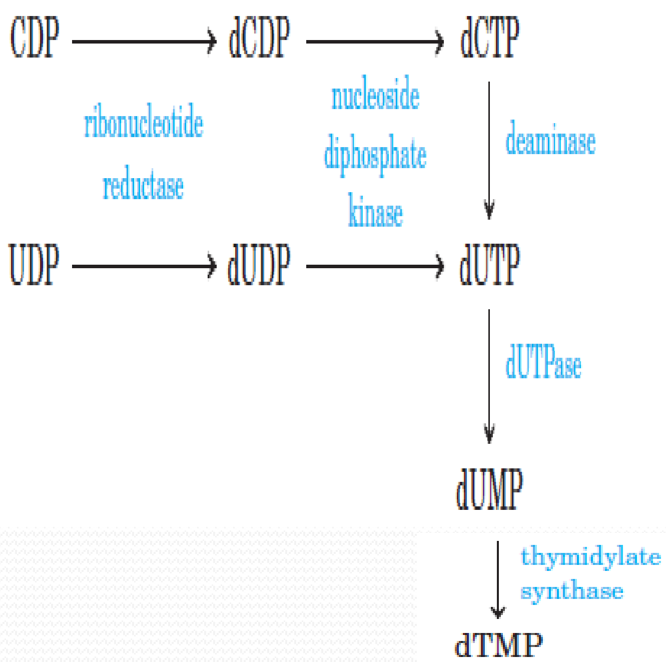


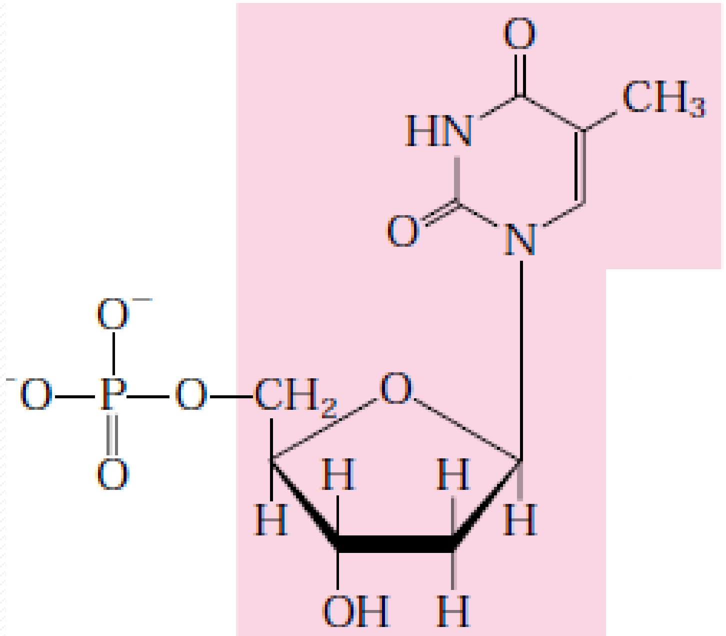
De NOVO PYRIMIDINE SYNTHESIS CONT'D



DE NOVO SYNTHESIS OF PYRIMIDINE NUCLEOTIDES CONT'D

- **Thymidylate is derived from dCDP and dUMP**





Deoxythymidylate (deoxythymidine 5′-monophosphate)

T, dT, dTMP

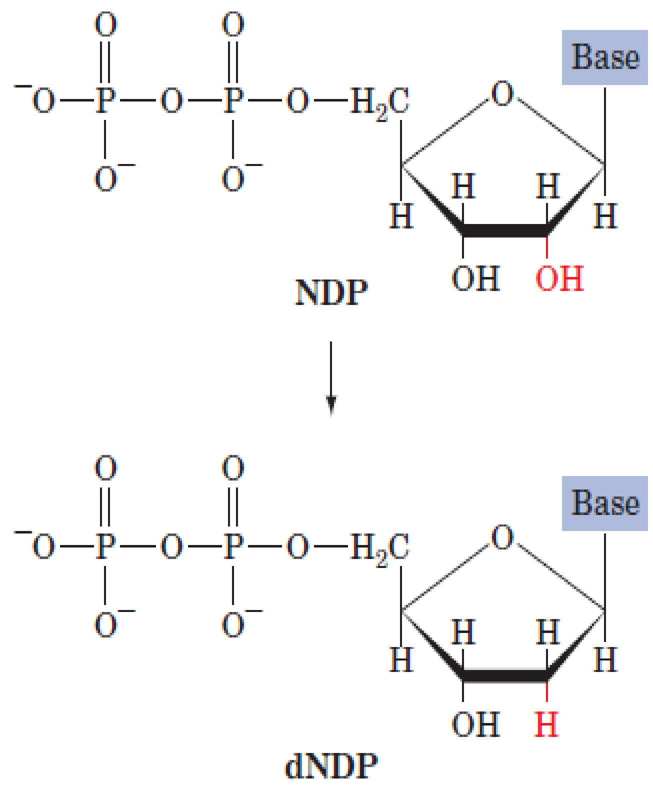
Deoxythymidine

NUCLEOTIDE BIOSYNTHESIS CONT'D

- **Nucleotides to be used in biosynthesis are generally converted to nucleoside triphosphate**
- **The conversion pathways are common to all cells.**
- **Phosphorylation of AMP to ADP is promoted by adenylate kinase**

$$\text{ATP} + \text{AMP} \rightleftharpoons 2\text{ADP}$$

- **The ADP formed is phosphorylated to ATP by the glycolytic enzymes or through oxidative phosphorylation**
- **Deoxy-ribonucleotides, the building blocks of DNA, are derived from the corresponding ribonucleotides by reduction at the 2' carbon atom of the D-ribose to form the 2-deoxy derivative in a reaction catalyzed by ribonucleotide reductase.**



PURINE AND PYRIMIDINE BASES ARE RECYCLED BY SALVAGE PATHWAYS

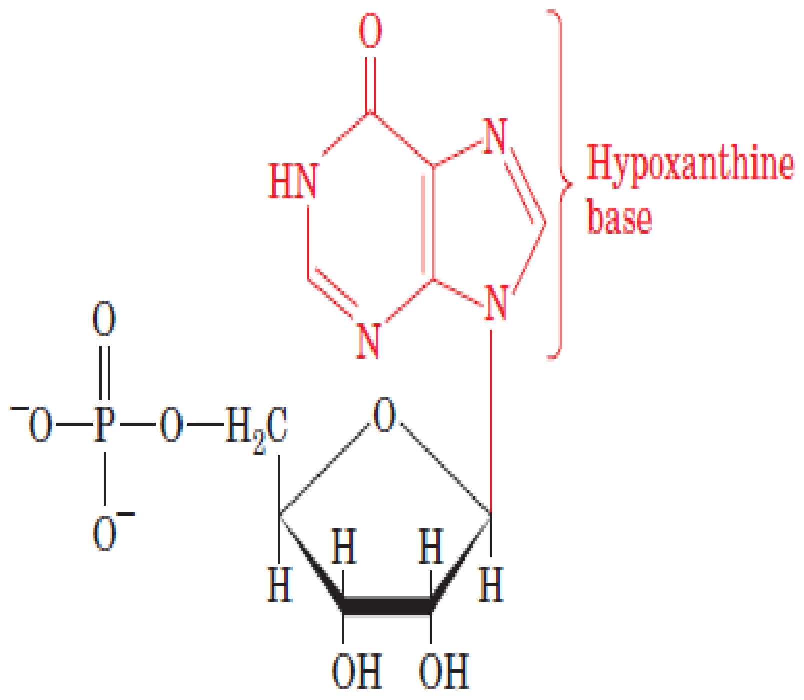
- **Free purine and pyrimidine bases are constantly released in cells during the metabolic degradation of nucleotides**
- **Free purines are in large part salvaged and reused to make nucleotides, in a pathway much simpler than the denovo synthesis of purine nucleotides**
- **In mammals, purines are salvaged by two different enzymes, ADENINE PHOSPHORIBOSYLTRANSFERASE (APRT) catalyzes AMP formation through the transfer of adenine to PRPP with the release of ppi**

$$\text{Adenine} + \text{PRPP} \rightleftharpoons \text{AMP} + \text{PP}_i$$

- **HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE (HGPRT) catalyzes the analogous reaction for both hypoxanthine and guanine**

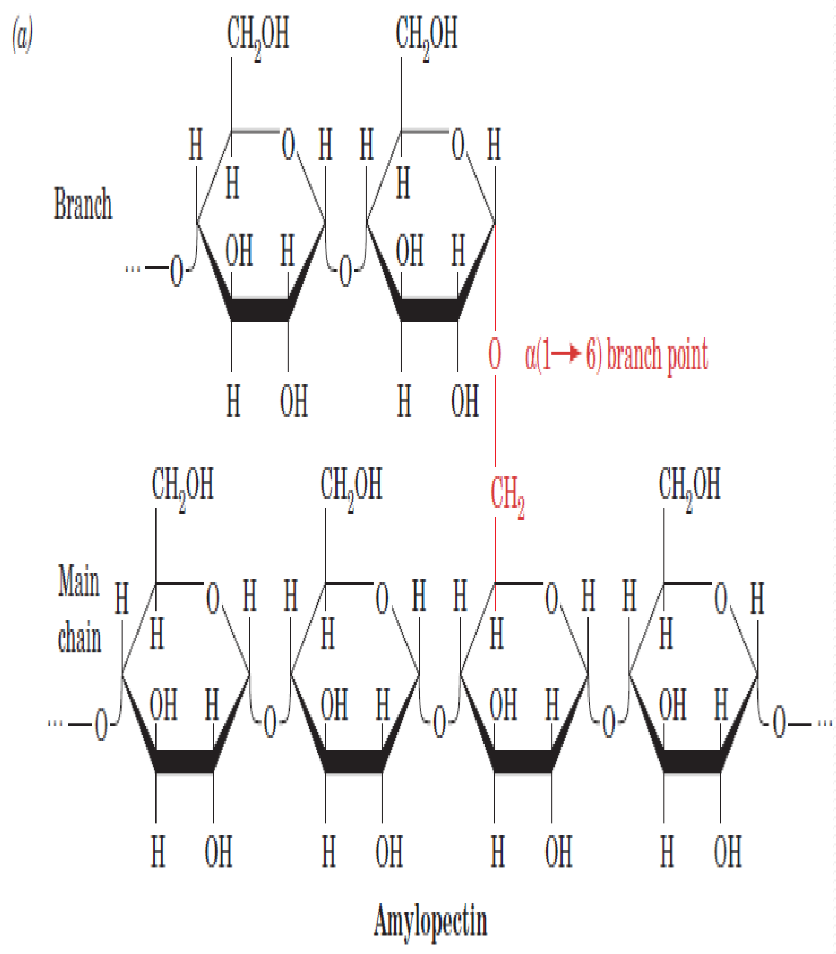
$$\text{Hypoxanthine} + \text{PRPP} \rightleftharpoons \text{IMP} + \text{PP}_i$$
$$\text{Guanine} + \text{PRPP} \rightleftharpoons \text{GMP} + \text{PP}_i$$

- **A similar salvage pathway exists for pyrimidine bases in microbes and possibly in mammals**



Inosine monophosphate (IMP)

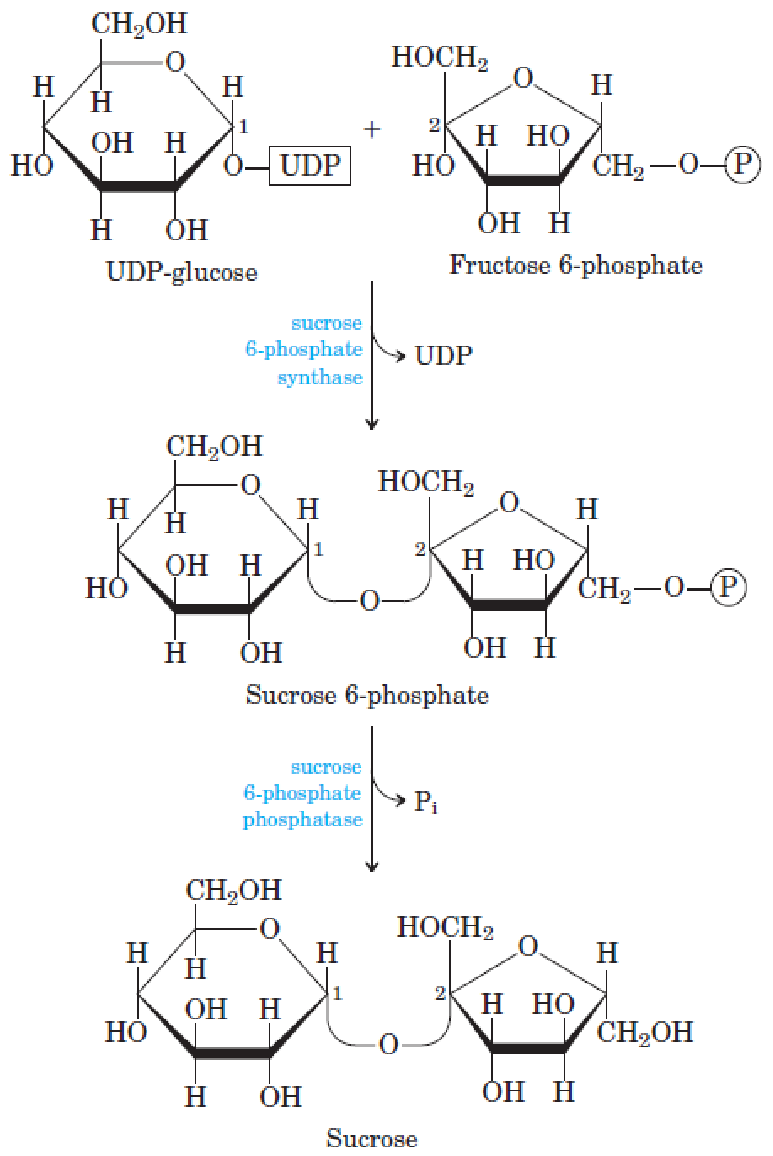
BIOSYNTHESIS OF STARCH



- **An activated nucleotide sugar, ADP-glucose, is formed by condensation of glucose 1-phosphate with ATP in a reaction made essentially irreversible by the inorganic pyrophosphatase in plastids.**
- **Starch synthase then transfers glucose residues from ADP-glucose to preexisting starch molecules at non reducing ends.**

SUCROSE BIOSYNTHESIS

- **Sucrose is synthesized in the cytosol, beginning with dihydroxyacetone phosphate(DHAP)and glyceraldehyde 3-phosphate(GAP) exported from the chloroplast into the cytosol**
- **Condensation of two triose phosphates will eventually lead to fructose 6-phosphate as in gluconeogenesis**



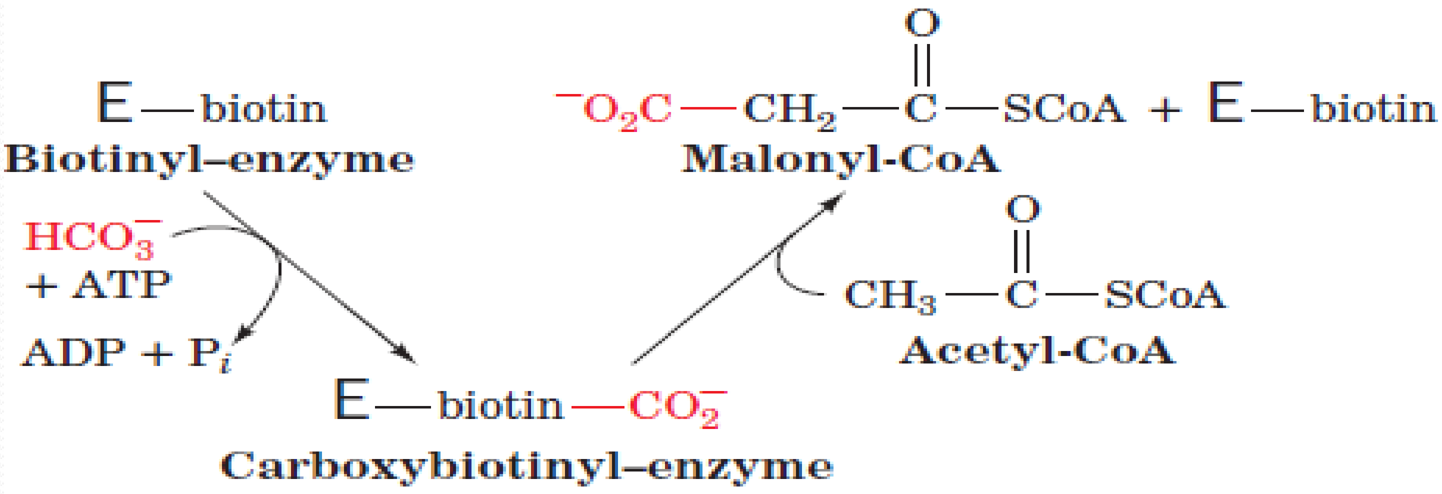
FATTY ACID BIOSYNTHESIS

- **Fatty acid biosynthesis occurs through condensation of C2 units. The reverse of the β-oxidation process**
- **Acetyl coA is the precursor of the condensation reaction**
- **In the biosynthetic pathway, the condensation reaction is coupled to the hydrolysis of ATP, thereby driving the reaction to completion**
- **The process involves two steps**

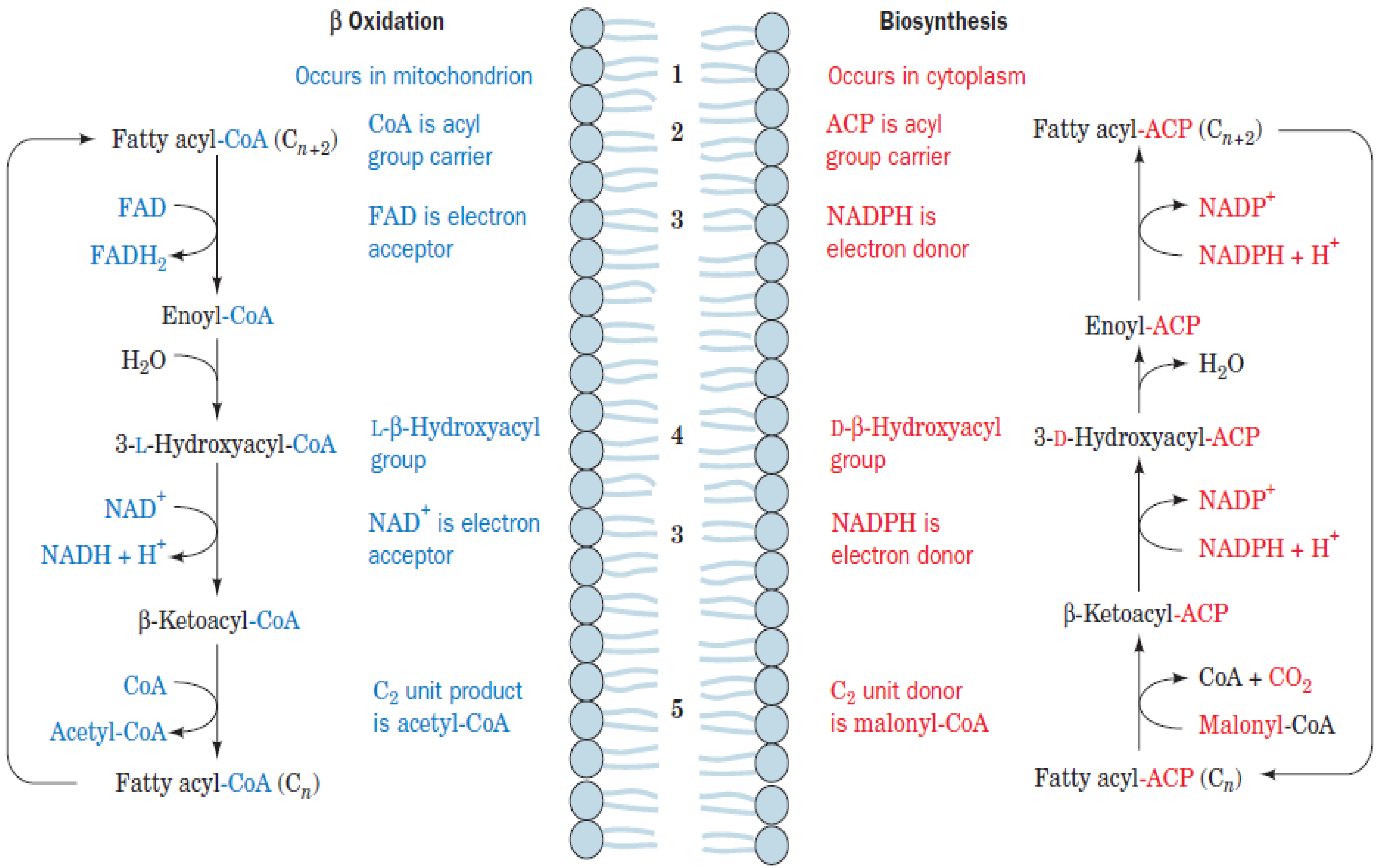
(1) The ATP dependent carboxylation of acetyl-coA to form malonyl coA and (2) the exergonic decarboxylation of the malonyl group in the condensation reaction catalyzed by fatty acid synthase

ACETYL COA CARBOXYLASE REACTION

- **Acetyl coA carboxylase catalyzes the first committed step of fatty acid biosynthesis**
- **It catalyzes the formation of malonyl-coA from acetyl-coA and bicarbonate in an ATP dependent reaction which is essentially irreversible**



COMPARISON OF FATTY ACID OXIDATION AND BIOSYNTHESIS



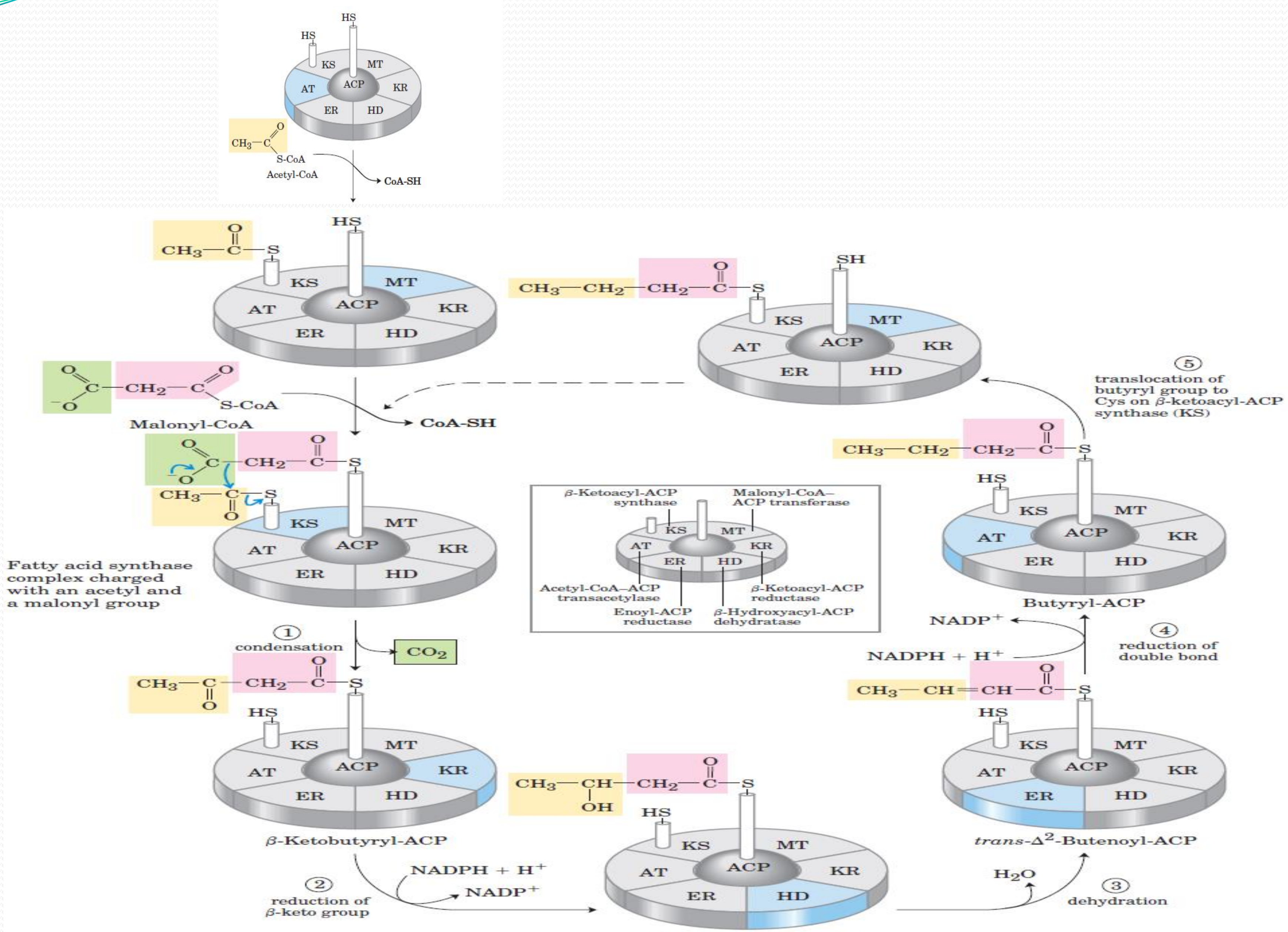
FATTY ACID SYNTHESIS PROCEEDS IN A REPEATING REACTION SEQUENCE

- **The long carbon chains of fatty acids are assembled in a repeating four step sequence**
- **A saturated acyl group produced by this set of reactions becomes the substrate for subsequent condensation with an activated malonyl group**
- **With each passage through the cycle, the fatty acyl chain is extended by two carbons, when the chain length reaches 16 carbons, the product palmitate leaves the cycle. Carbons C-16 and C-15 are from acetyl coA used to prime the system at the outset**
- **All the reactions in the synthetic process are catalyzed by a multienzyme complex, FATTY ACID SYNTHASE**
- **The core of the fatty acid synthase synthase consists of seven separate polypepetides.**
- **The proteins act together to catalyze the formation of fatty acids from acetyl coA and malonyl coA**

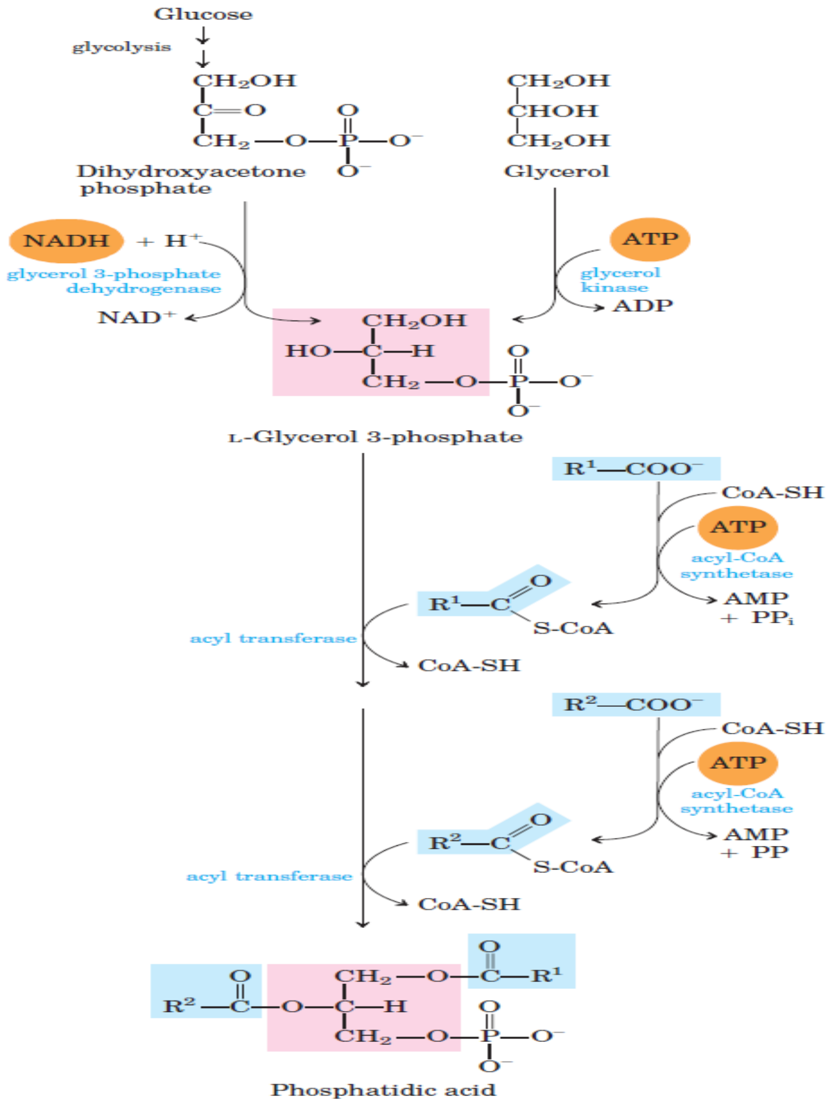
TABLE 21-1 Proteins of the Fatty Acid Synthase Complex of *E. coli*

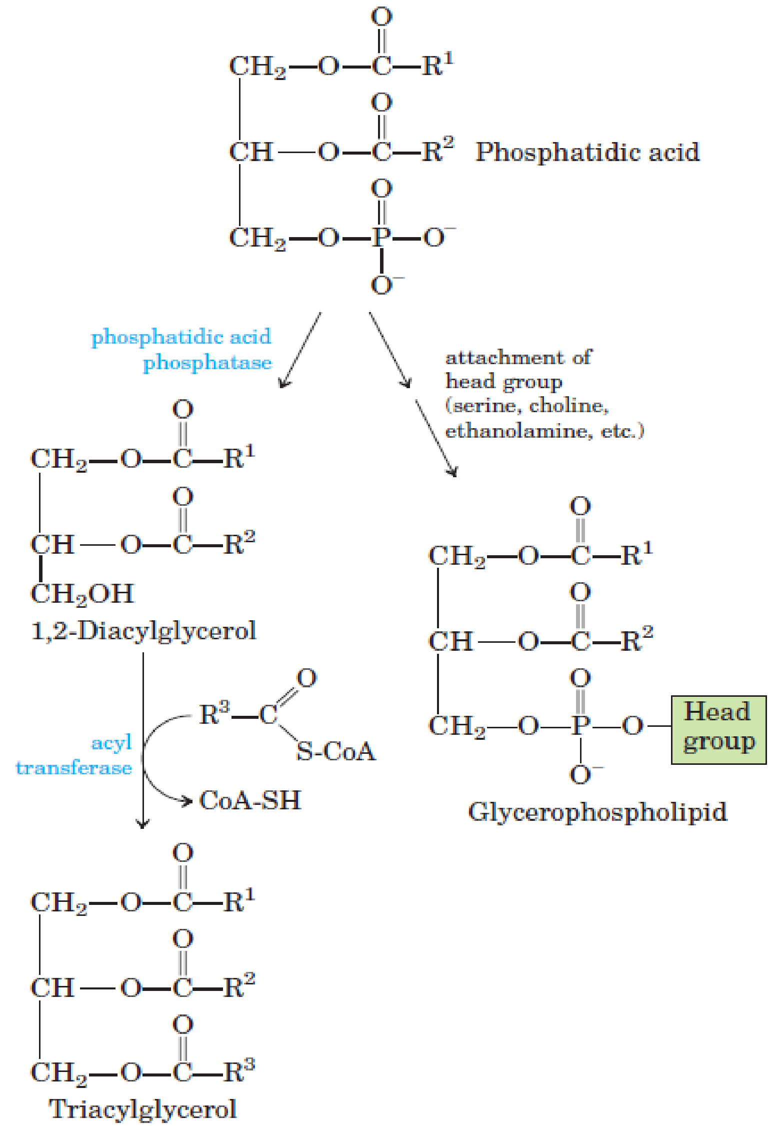
Component	*Function*
Acyl carrier protein (ACP)	Carries acyl groups in thioester linkage
Acetyl-CoA-ACP transacetylase (AT)	Transfers acyl group from CoA to Cys residue of KS
β-Ketoacyl-ACP synthase (KS)	Condenses acyl and malonyl groups (KS has at least three isozymes)
Malonyl-CoA-ACP transferase (MT)	Transfers malonyl group from CoA to ACP
β-Ketoacyl-ACP reductase (KR)	Reduces β-keto group to β-hydroxyl group
β-Hydroxyacyl-ACP dehydratase (HD)	Removes H_2O from β-hydroxyacyl-ACP, creating double bond
Enoyl-ACP reductase (ER)	Reduces double bond, forming saturated acyl-ACP

FATTY ACID SYNTHASE REACTION



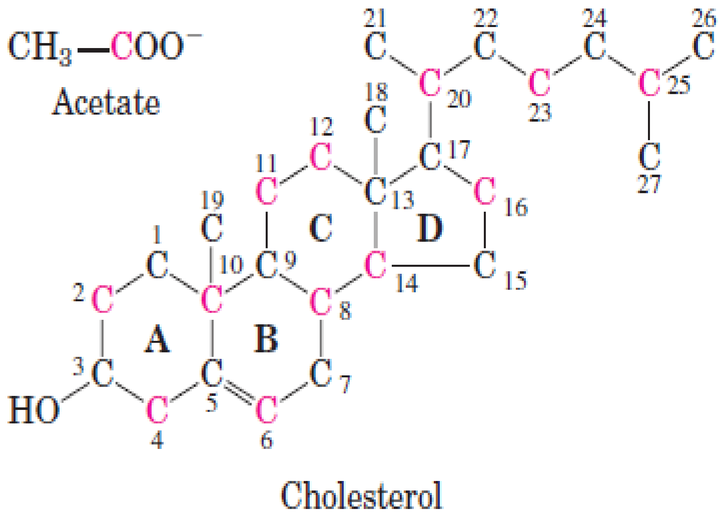
BIOSYNTHESIS OF TRIACYLGLYCEROL





BIOSYNTHESIS OF CHOLESTEROL

- The structure of this 27-carbon compound (cholesterol) suggests a complex biosynthetic pathway, but all of its carbon atoms are provided by a single precursor-acetate



- Cholesterol synthesis takes place in four stages