AL-MUSTAQBAL UNIVERSITY
COLLEGE OF SCIENCE
DEPARTMENT OF BIOCHEMISTRY
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Lec - 3

Nucleic Acid Metabolism

INTRODUCTION

Purines and **pyrimidines** are dietary non essential components. Dietary nucleic acids and nucleotides do not provide essential constituents for the biosynthesis of endogenous nucleic acids. Humans can synthesize purine and pyrimidine nucleotides de novo.

BIOSYNTHESIS OF PURINE NUCLEOTIDES

• The two purine nucleotides of nucleic acids are:

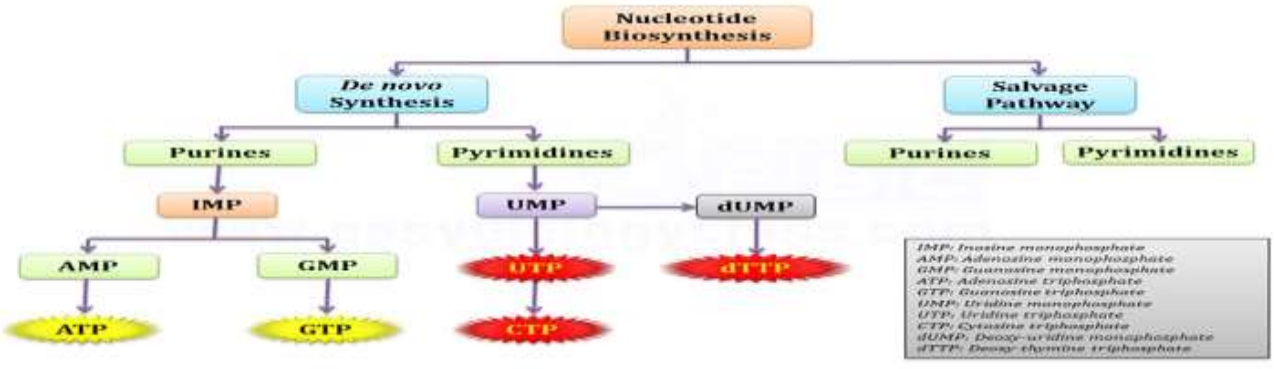
1. Adenosine monophosphate, AMP

2. Guanosine monophosphate, GMP

• Purine nucleotides can be synthesized by two pathways:

1. De novo pathway (New synthesis from amphibolic intermediates).

2. Salvage pathway



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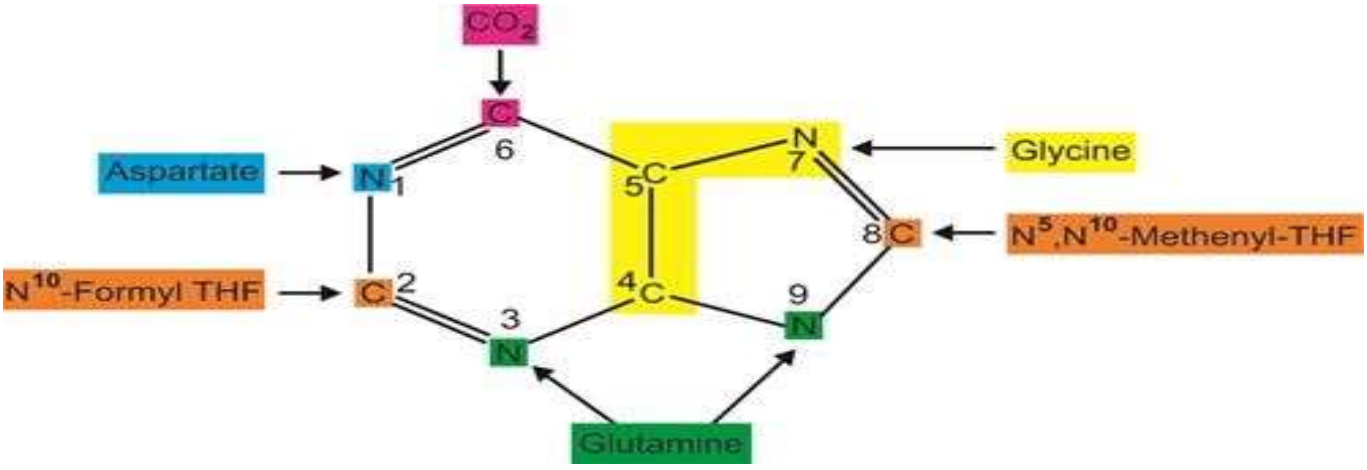
DE NOVO BIOSYNTHESIS OF PURINE NUCLEOTIDES

In de novo pathway, the purine ring formed from precursors is assembled on

ribose-5-phosphate.

Precursors for the De Novo Synthesis of Purine

- Glycine provides C4, C5 and N7
- Aspartate provides N1
- Glutamine provides N3 and N9
- Tetrahydrofolate derivatives furnish C2 and C8
- Carbon dioxide provides C6.



1.The biosynthesis of purine begins with ribose-5- phosphate, derived from pentose phosphate pathway, which is converted to phosphoribosylpyrophosphate PRPP. This reaction is catalyzed by the enzyme **PRPP synthetase**.

ribose-5- phosphate +ATP $\xrightarrow{\text{PRPP synthetase}}$ phosphoribosylpyrophosphate PRPP

2. PRPP is aminated by the addition of the amide group from glutamine to form amino sugar 5-phosphoribosylamine, The enzyme that catalyzes **is PRPP amidotransferase**.

The synthesis of phosphoribosylamine from PRPP is the **first committed (rate limiting) step** in the formation of inosine monophosphate (IMP).

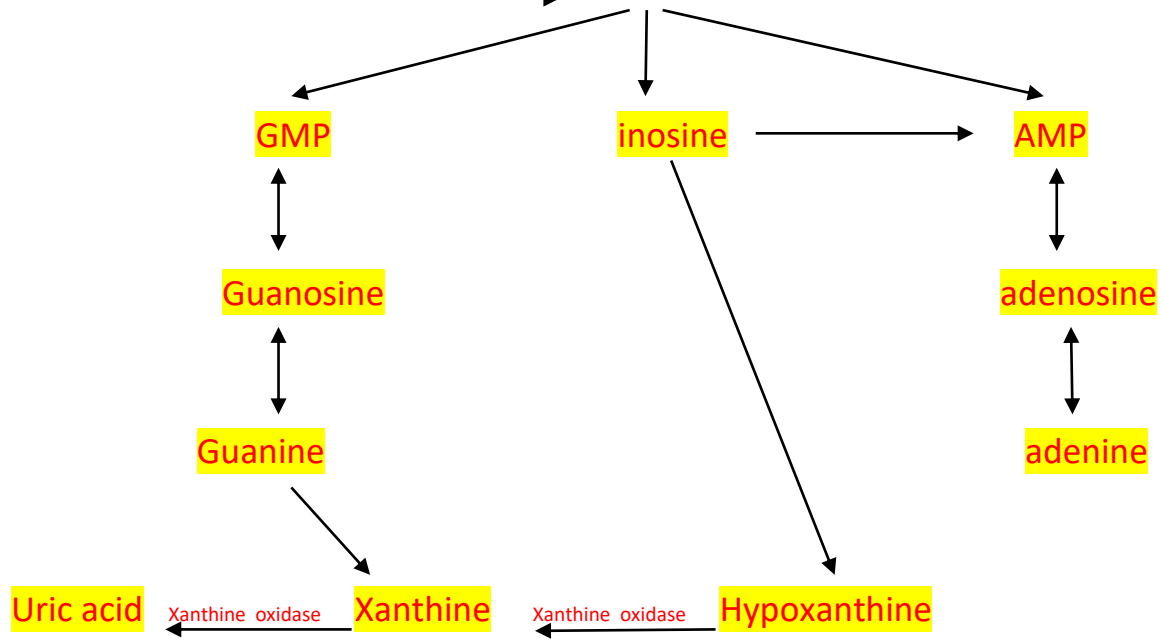
phosphoribosylpyrophosphate PRPP + glutamine —PRPP amidotransferase→ 5-phosphoribosylamine

3. addition of amino acid glycine to form glycinamide ribosyl 5-phosphate. ATP is consumed in this reaction and the enzyme phosphoribosyl glycinamide synthetase is required.

5-phosphoribosylamine + glycine + ATP —phosphoribosyl glycinamide synthetase→ glycinamide ribosyl 5-P

4. multple enzymtic reactions forms the first purine nucleotide, **inosine monophosphate, IMP.**

glycinamide ribosyl 5-P —multiple enzymatic reactions→ inosine monophosphate IMP.



Regulation of De Novo Synthesis of Purine Nucleotide

• The synthesis of purine nucleotides is controlled by:

– Concentration of PRPP

– Feedback regulation at several sites.

• Increased concentration of PRPP stimulates the purine nucleotides synthesis.

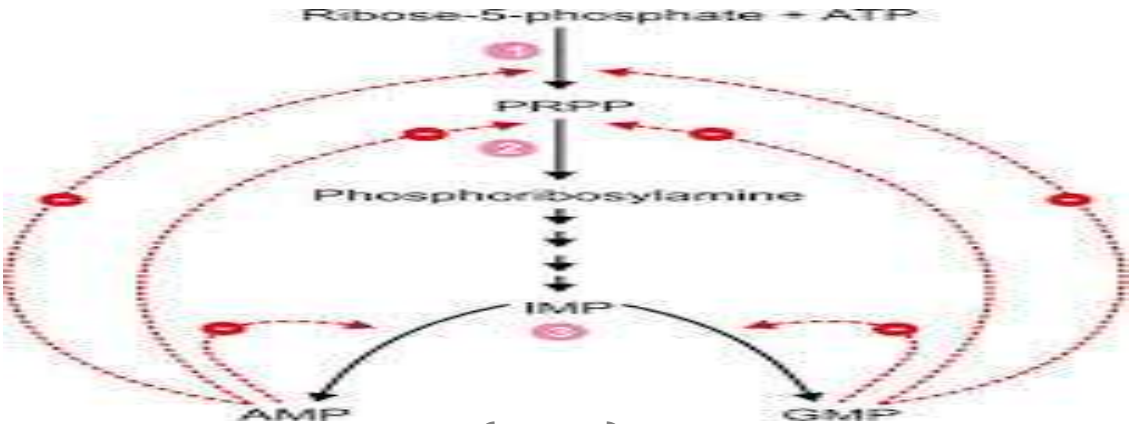
Concentration of PRPP depends on : – Availability of ribose-5-phosphate – On the activity of PRPP synthase.

• Three major feedback mechanisms regulate the overall rate of de novo purine nucleotide synthesis.

1. The step leading to formation of PRPP. This reaction is catalyzed by an allosteric enzyme PRPP synthetase, which is feedback inhibited by purine nucleotides, AMP and GMP .

2. The committed step in purine nucleotide biosynthesis is the conversion of PRPP into phosphoribosylamine by PRPP glutamyl-amido transferase which is feedback inhibited by AMP and GMP.

3. AMP and GMP feedback regulate their formation from IMP. AMP feedback regulates adenylosuccinate synthase and GMP feedback regulates IMP dehydrogenase.



SYNTHESIS OF PURINE NUCLEOTIDES BY SALVAGE PATHWAY

• The pathway involved in the conversion of **free purines to nucleotides** is called salvage pathway (Salvage means property saved from loss).

• Free purine bases **(adenine, guanine and hypoxanthine)** are formed in cells during the metabolic degradation of nucleic acids and nucleotides. However, free purines are salvaged and used over again to remake purine nucleotides. This occurs by a pathway that is quite different from the de novo biosynthesis of purine nucleotides described earlier, in which the purine ring system is assembled step by step on ribose-5-phosphate in a long series of reactions.

• The salvage pathway is much simpler and requires far less energy than does de novo synthesis. It consists of a single reaction.

Salvage Reaction

i. PRPP is the starting material in this pathway; it is also a substrate for de novo synthesis. Hence these two pathways are closely interrelated.

ii. The free purines are salvaged by two different enzymes;

adenine phospho ribosyl transferase (APRTase) and

hypoxanthine guanine phosphoribosyl transferase (HGPRTase).

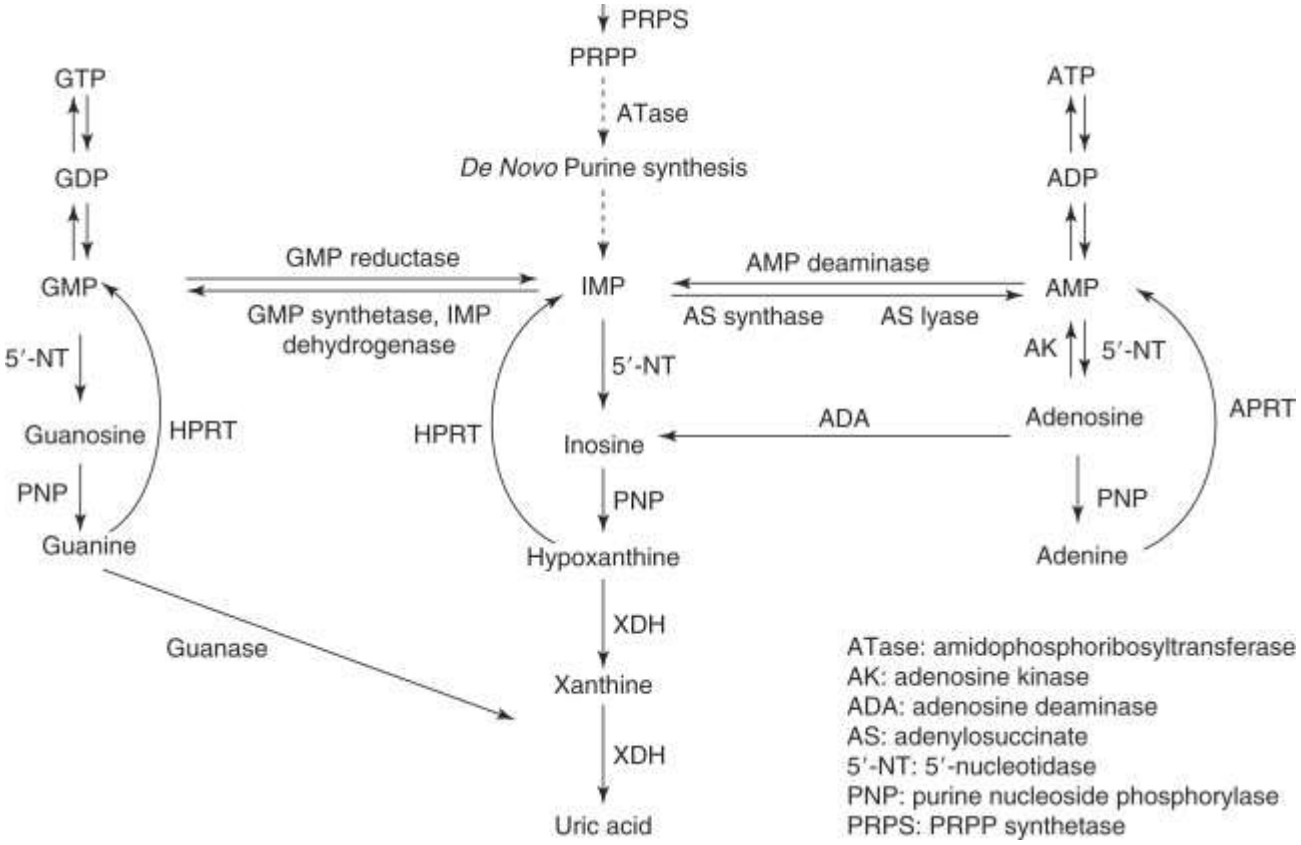
iii. The pathway is of special importance in tissues like RBCs and brain where the de novo pathway is not operating. The salvage pathway economizes intracellular energy expenditure.

Salvage pathway is summarized below:

Adenine + PRPP $\xrightarrow{\text{APRTase}}$ **AMP + PPi**

Guanine + PRPP ——HGPRTase——→ GMP + PPi

Hypoxanthine + PRPP ——HGPRTase——→ IMP + PPi



CATABOLISM OF PURINE NUCLEOTIDES

The end product of purines (adenine and guanine) in humans is sparingly soluble uric acid .

• Purine nucleotides (AMP and GMP) are degraded by a pathway, in which the phosphate group is removed by the action of nucleotidase; to yield the nucleoside, adenosine or guanosine.

• Adenosine is then deaminated to inosine by adenosine deaminase.

• Inosine is then hydrolyzed by purine nucleoside phosphorylase to yield its purine base hypoxanthine and ribose-1-phosphate.

• Hypoxanthine is oxidized successively to xanthine and then uric acid, by xanthine oxidase. In this reaction, molecular oxygen is reduced to H_2O_2, which is decomposed to H_2O and O , by catalase.

• Guanosine is cleaved to guanine and ribose-1- phosphate by phosphorylase enzyme.

• Guanine undergoes hydrolytic removal of its amino group by guanase to yield xanthine, which is converted to uric acid by xanthine oxidase.

DE NOVO BIOSYNTHESIS OF PYRIMIDINE NUCLEOTIDES

The pyrimidine nucleotides are:

1. Cytidine monophosphate CMP

2. Uridine monophosphate UMP

3. Thymidine monophosphate TMP.

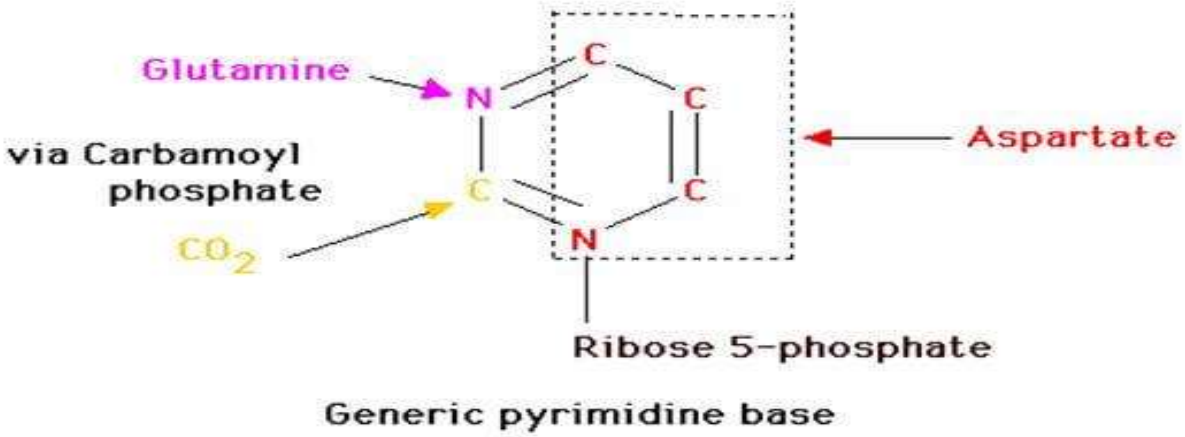
Unlike the synthesis of purine nucleotide, six membered pyrimidine ring is made first and then attached to ribose phosphate, which is donated by PRPP.

Precursors for the De Novo Synthesis of Pyrimidine

• Glutamine provides N3

• Aspartic acid furnishes C4, C5, C6 and N1

• Carbon dioxide provides C2.



Major Steps for De Novo Synthesis of Pyrimidine Nucleotide

1. Pyrimidine biosynthesis starts with the formation of carbamoyl phosphate from glutamine, ATP and CO2. This reaction is catalyzed by cytosolic carbamoyl phosphate synthase- II (CPS-II) an enzyme different from mitochondrial carbamoyl phosphate synthase-l (CPS-I) required in the synthesis of urea.

Glutamine+ ATP +CO2 $\xrightarrow{\text{(CPS-II)}}$ carbamoyl phosphate

2. Condensation of carbamoyl phosphate with aspartate forms carbamoyl aspartate in a reaction catalyzed by aspartate transcarbamoylase and is the committed step in the biosynthesis of pyrimidine.

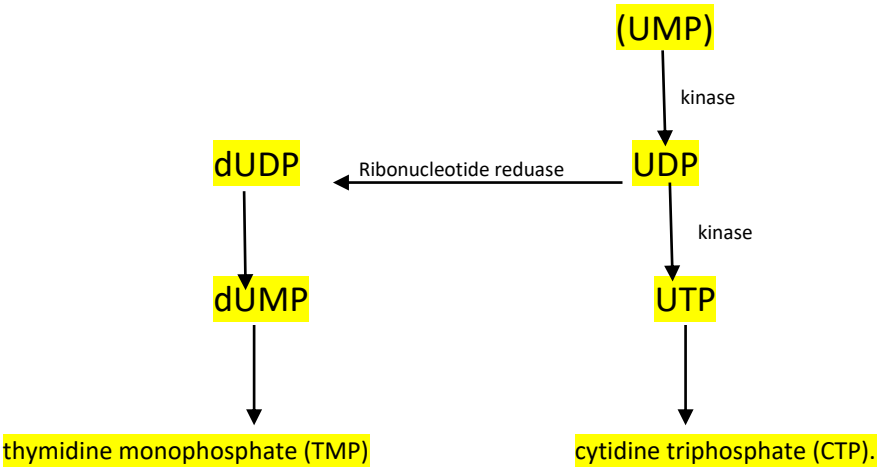
carbamoyl phosphate + aspartate $\xrightarrow{\text{aspartate transcarbamoylase}}$ carbamoyl aspartate

3. By removal of water from carbamoyl aspartate, catalyzed by dihydro-orotase, the pyrimidine ring is closed with formation of dihydro-orotic acid.

carbamoyl aspartate $\xrightarrow{\text{dihydro-orotase}}$ dihydro-orotic acid

$\xrightarrow{H_2O}$

dihydro-orotic acid + PRPP



Regulation of De Novo Synthesis of PyrImidine Nucleotides

The first two enzymes carbamoyl phosphate synthaseII and aspartate transcarbamoylase are allosteric enzymes and are regulated allosterically

• Carbamoyl phosphate synthase-II, reaction 1 is feed- back inhibited by UTP and activated by PRPP.

• Aspartate transcarbamoylase, reaction 2, is feedback inhibited by CTP and activated by AT

CATABOLISM OF PYRIMIDINE NUCLEOTIDES

Unlike the purines which degraded to sparingly soluble product, uric acid, the end products of pyrimidine catabolism are highly water soluble:

• CO_2

• NH_3

• β-alanine

• β-aminoisobutyrate Humans probably transaminate β-aminoisobutyrate to methylmalonate semialdehyde which is then converted to succinyl-CoA via methylmalonyl-CoA. βalanine can serve as precursor of acetyl-CoA.