Nucleic acids metabolism

Nucleotide structure

- Nucleotides are composed of a nitrogenous base, a pentose monosaccharide, and one, two, or three phosphate groups.
- The nitrogen-containing bases belong to two families of compounds: the purines and the pyrimidines.

Both DNA and RNA contain the same purine bases: adenine (A) and guanine (G). Both DNA and RNA contain the pyrimidine cytosine (C), but they differ in their second pyrimidine base: DNA contains thymine (T), whereas RNA contains uracil (U).

Nucleosides

The addition of a pentose sugar to a base produces a nucleoside. If the sugar is ribose, a ribonucleoside is produced; if the sugar is
2-deoxyribose, a deoxyribonucleoside is produced. The ribonucleosides of A, G, C, and U are named adenosine, guanosine, cytidine, and uridine.

**Nucleotides**

The addition of one or more phosphate groups to a nucleoside produces a nucleotide.

**Digestion of nucleic acids**

- The nucleic acids in the diet are hydrolysed to a mixture of nucleotides by ribonuclease and deoxyribonuclease presents in pancreatic and intestinal secritions.
- Then the nucleotidases librate the phosphate from nucleotides.
- The resulting nucleosides are hydrolysed by nucleosidases forming free bases and pentose sugars.
- Even when humans consume a diet rich in nucleoproteins, dietary purines and pyrimidines are not incorporated directly into tissue nucleic acids. Humans synthesize the nucleic acids, ATP, NAD+, coenzyme A, from amphibolic intermediates.

![Diagram of nucleic acid digestion](image)
Biosynthesis of purine nucleotides

- The purine nucleotides are synthesised by most of the tissues.
- The major site is the liver. This pathway operates in the cytoplasm.
- The major pathway is denoted as de novo synthesis, because the purine ring is synthesis from different small components and from different sources.
- During de novo synthesis, purine ring is build up on a ribose-5- phosphate molecule.

There are ten steps in the de novo synthesis pathway.
Synthesis of Purine Nucleotides

Synthesis of nucleotides requires a source of Ribose 5-phosphate. This compound is produced from glucose 6-phosphate via the pentose phosphate pathway.

\[
\text{Glucose 6-phosphate} \rightarrow \text{Ribose 5-phosphate} \rightarrow \text{PRPP}
\]

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Formation of (phosphoribosyl pyrophosphate) PRPP

The atoms of the purine ring are contributed by a number of compounds, including amino acids (aspartic acid, glycine, and glutamine), CO\textsubscript{2}, and N\textsuperscript{10}–formyltetrahydrofolate.
The purine ring is constructed by a series of reactions that add the donated carbons and nitrogens to a preformed ribose 5-phosphate.

**Salvage pathway**

- This pathway ensures the recycling of purines formed by degradation of nucleotides.
- Nucleosides and deoxy-nucleosides can also be salvaged.
- PRPP is the starting material in this pathway. It is also a substrate for de novo synthesis. Hence, these two pathways are closely inter-related.
- The pathway is of importance in tissues like RBCs and brain where the denovo pathway is not operating.
Degradation of purine nucleosides

The end product of purine nucleotide catabolism is uric acid (Urate).

This degradation is taking place mainly in the liver.

![Uric Acid](image)

- Normal blood level of uric acid ranges from 2-5 mg/dl in females, and 3-7 mg/dl in males.
- Nucleic acid content is more in non-vegetarian diet.

Pyrimidine nucleotide synthesis

- The pyrimidine ring (unlike the purine) is synthesised as free pyrimidine and then it is incorporated into the nucleotide.
- De novo pyrimidine biosynthesis begins with the formation of carbamoyl phosphate from the amide group of glutamine, CO2, and a phosphoryl group of ATP.
- The reaction occurs in cytoplasm (in urea cycle, the reaction is in mitochondria).
- Carbomyl phosphate and aspartate combine to form carbamoyl aspartate. Then oritic acid is formed.
- Ribose-5- phosphate is added to oritic acid as PRPP
- Oritidine-5-phosphate is formed by decarboxylation; uridine monophosphate is produced.

Carbamoyl phosphate becomes part of the pyrimidine ring. The remaining atoms of the ring are added as a unit in the form of aspartate. The resulting N-carbamoyl aspartate is converted to a free pyrimidine base, orotate, by ring closure and oxidation. The base is then joined to PRPP to form a nucleoside monophosphate, orotidine monophosphate (OMP). Uridine monophosphate (UMP) is derived directly from OMP by decarboxylation.
Nucleotide catabolism and Salvage

Nucleotide turnover occurs continuously in cells. Breakdown of DNA and RNA releases nucleoside 5’-monophosphates, which can be hydrolyzed by 5’-nucleotidases to yield nucleosides. Although both purine and pyrimidine nucleosides can be degraded to waste products that are excreted, the catabolic pathways have branch points in most cells at which the components of nucleotides can be salvaged.
Diseases associated with purine degradation

Gout

- Gout is a disorder characterized by high levels of uric acid. The end product of purine catabolism in blood (hyperuricemia), as a result of either the overproduction or underexcretion of uric acid. The hyperuricemia leads to the deposition of monosodium urate crystals in the joints, and an inflammatory response to the crystals, causing first acute and then to chronic gouty arthritis.

Diseases associated with pyrimidine metabolism

Orotic aciduria

- Excessive excretion of orotic acid in urine. It causes a characteristic form of anemia and may be associated with mental and physical retardation.