.

BIOSYNTHESIS OF PYRIMIDINE RIBONUCLEOTIDES

The synthesis of pyrimidines is a much simpler process compared to that of purines. Aspartate, glutamine (amide group) and CO_2 contribute to atoms in the formation of pyrimidine ring.

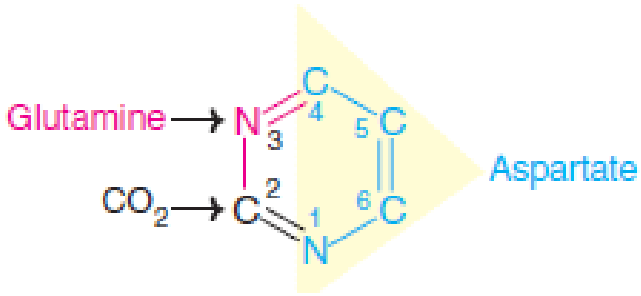

Figure 1: Sources of individual atoms in Pyrimidine ring

Pyrimidine ring is first synthesized and then attached to ribose 5-phosphate. This is in contrast to purine nucleotide synthesis where in purine ring is built upon a pre-existing ribose-5 phosphate. The pathway of pyrimidine synthesis is depicted in **Figure 2**, and the salient features are described below:

1. Glutamine transfers its amido nitrogen to CO_2 to produce carbamoyl phosphate. This reactionis ATP-dependent and is catalysed by cytosomal enzyme carbamoyl phosphate synthetase II (CPS II). CPS II is activated by ATP and PRPP and inhibited by UTP.
2. Carbamoyl phosphate condenses with aspartate to form carbamoyl aspartate. This reaction is catalysed by aspartate transcarbamoylase.
3. Dihydroorotase catalyses the pyrimidine ring closure with a loss of H_2O. The three enzymes—CPS II, aspartate transcarbamoylase and dihydroorotase are the domains (functional units) of the same protein. This is a good example of a **multifunctional enzyme.**
4. The next step in pyrimidine synthesis is an NAD^+ dependent dehydrogenation, leading to the formation of orotate.
5. Ribose 5-phosphate is now added to orotate to produce orotidine monophosphate (OMP). This reaction is catalysed by orotate phosphoribosyltransferase.

6. OMP undergoes decarboxylation to uridine mono-phosphate (UMP). Orotate phosphoribosyltransferase and OMP decarboxylase are **domains** of a single protein.
7. By an ATP-dependent kinase reaction, UMP is converted to UDP which serves as a precursor for the synthesis of dUMP, dTMP, UTP and CTP.
8. Ribonucleotide reductase converts UDP to dUDP by a thioredoxin-dependent reaction.
9. Thymidylate synthetase catalyses the transfer of a methyl group from N_5, N_{10}-methylene tetrahydrofolate to produce deoxythymidine monophosphate (dTMP).
10. UDP undergoes an ATP-dependent kinase reaction to produce UTP.
11. Cytidine triphosphate (CTP) is synthesized from UTP by amination. CTP synthetase is the enzyme and glutamine provides the nitrogen.

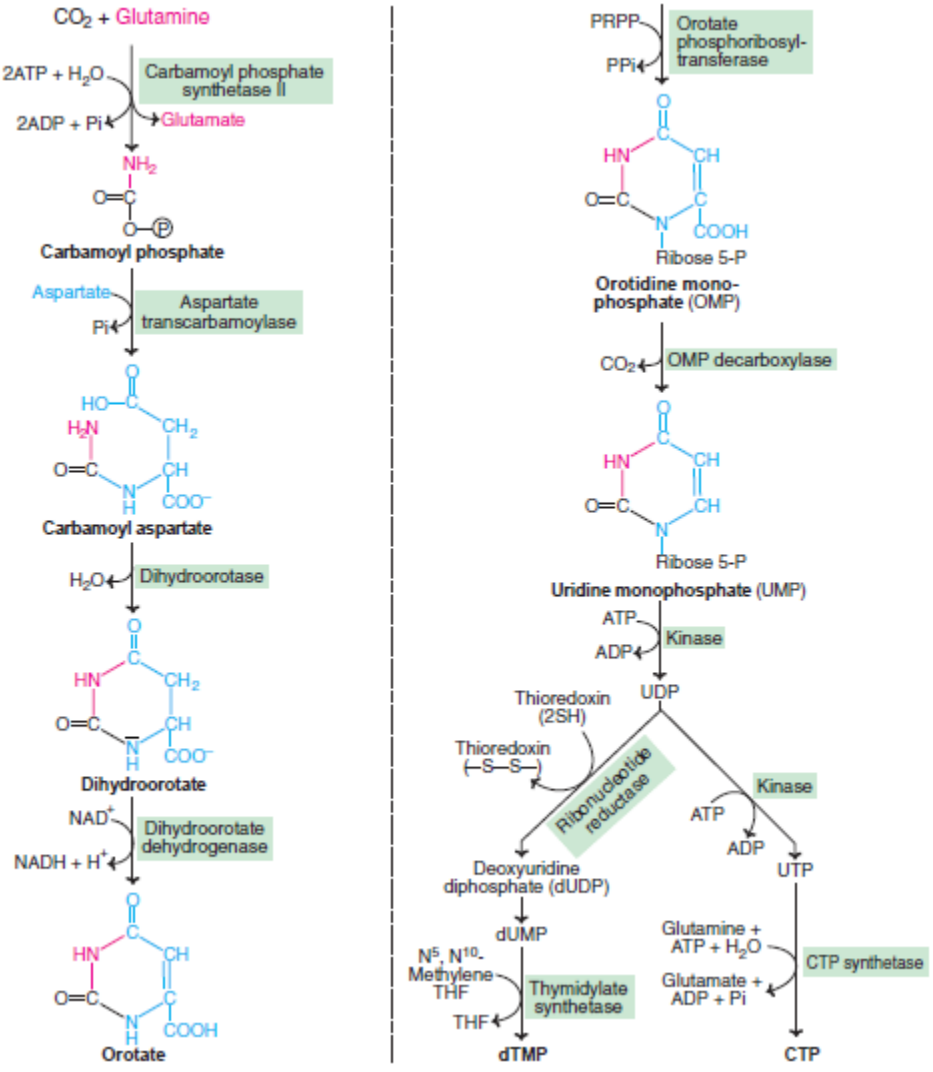

Figure 2 : Metabolic pathway for the synthesis of pyrimidine nucleotides.

Regulation of pyrimidine synthesis

In bacteria, **aspartate transcarbamoylase** (ATCase) catalyses a **committed step** in pyrimidine biosynthesis. ATCase is a good example of an enzyme controlled by **feedback mechanism** by the end product CTP. In certain bacteria, UTP also inhibits ATCase. ATP, however, stimulates ATCase activity.

Carbamoyl phosphate synthetase II (CPS II) is the regulatory enzyme of pyrimidine synthesis in animals. It is activated by PRPP and ATP and inhibited by UDP and UTP. OMP decarboxylase, inhibited by UMP and CMP, also controls pyrimidine formation.

Catabolism of pyrimidine nucleotide

The pathways for degradation of pyrimidines generally lead to NH_4^+ production and thus to urea synthesis. Thymine, for example, is degraded to methylmalonylsemialdehyde an intermediate of valine catabolism (Figure 3) . It is further degraded through propionyl-CoA and methylmalonyl-CoA to succinyl-CoA .

Salvage pathway

The pyrimidines (like purines) can also serve as precursors in the salvage pathway to be converted to the respective nucleotides. This reaction is catalysed by pyrimidine phosphoribosyltransferase which utilizes PRPP as the source of ribose 5-phosphate.

Disorders of pyrimidine metabolism

Orotic aciduria : This is a rare metabolic disorder characterized by the excretion of orotic acid in urine, severe anemia and retarded growth. It is due to the deficiency of the enzymes **orotate phosphoribosyl transferase** and **OMP decarboxylase** of pyrimidine synthesis (**Figure 2**). Both these enzyme activities are present on a single protein as domains (**bifunctional enzyme**). Feeding **diet rich in uridine** and/or **cytidine** is an **effective treatment** for orotic aciduria. These compounds provide (through phosphorylation) pyrimidine nucleotides required for DNA and RNA synthesis. Besides this, UTP inhibits carbamoyl phosphate synthetase II and blocks synthesis of orotic acid.

Reye's syndrome : This is considered as a secondary orotic aciduria. It is believed that a defect in ornithine transcarbamoylase (of urea cycle) causes the accumulation of carbamoyl phosphate. This is then diverted for the increased synthesis and excretion of orotic acid.

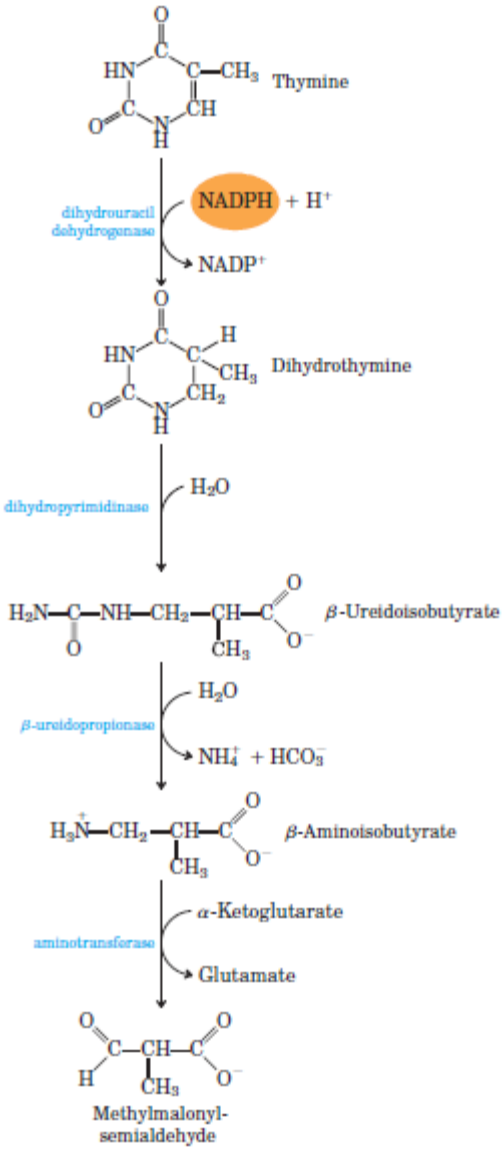

Figure 3: Catabolism of a pyrimidine. Shown here is the pathway for thymine. The methylmalonylsemialdehyde is further degraded to succinyl-CoA.