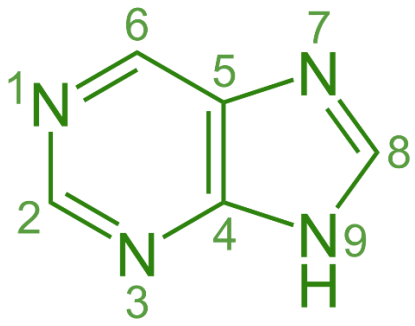
Nucleic acid metabolism

Metabolism of purine nucleotides

Biosynthesis of Purine Nucleotide

Overview

- Purine nucleotides include **adenosine monophosphate (AMP)** and **guanosine monophosphate (GMP)**.
- The purine ring is **built step-by-step directly onto the ribose sugar**, using atoms from multiple precursors.



- **Starting molecule**: Ribose-5-phosphate (from Pentose Phosphate Pathway)
  - **Activated form**: 5-Phosphoribosyl-1-pyrophosphate (PRPP)
  - **Final product of de novo pathway**: Inosine monophosphate (IMP), the precursor to AMP and GMP

Step-by-Step Biosynthesis

1. Formation of PRPP

- **Enzyme**: PRPP synthetase
- **Reaction**: Ribose-5-phosphate + ATP → PRPP
- **Regulation**: Feedback-inhibited by purine nucleotides (AMP, GMP)

2. Formation of 5-Phosphoribosylamine

- **Enzyme**: Glutamine-PRPP amidotransferase
- **Reaction**: PRPP + Glutamine → 5-Phosphoribosylamine + Glutamate + PPi
- **Regulation**: Major control step, inhibited by AMP, GMP, IMP

3–10. Stepwise Formation of IMP

- The atoms of the purine ring come from:

Atom in Purine	Source
N1	Aspartate

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C2, C8	Formate (via N10-formyl-THF)
N3, N9	Glutamine
C4, C5, N7	Glycine
C6	CO_2

Key intermediates:

- Glycine addition
- Formylation
- Cyclization
- Amidation
- Another formylation
- Final ring closure

Final product:

- Inosine monophosphate (IMP)

Conversion of IMP to AMP and GMP

IMP → AMP

- **Enzymes**: Adenylosuccinate synthetase → Adenylosuccinate lyase
- **Requires**: Aspartate and GTP
- **Product**: AMP

IMP → GMP

- **Enzymes**: IMP dehydrogenase → GMP synthetase
- **Requires**: Glutamine and ATP
- **Product**: GMP

Regulation of Purine Biosynthesis

Level	Control
PRPP synthetase	Inhibited by purine nucleotides
Glutamine-PRPP amidotransferase	Inhibited by AMP, GMP, IMP
AMP/GMP Branches	Cross-inhibit each other (GTP drives AMP synthesis and vice versa)

Salvage Pathway for Purines

➢ Reuses free purine bases (adenine, guanine, hypoxanthine):

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Enzymes:

- Hypoxanthine-Guanine Phosphoribosyltransferase (HGPRT)
- Adenine Phosphoribosyltransferase (APRT)

Clinical Note:

- Deficiency of HGPRT leads to **Lesch-Nyhan syndrome**

Purine Catabolism

- Purines are broken down to **uric acid** and excreted in urine.

Pathway:

- AMP → Inosine → Hypoxanthine → Xanthine → Uric Acid
- GMP → Guanine → Xanthine → Uric Acid

Enzyme of interest:

- **Xanthine oxidase**
  - Converts hypoxanthine → xanthine → uric acid

Clinical relevance:

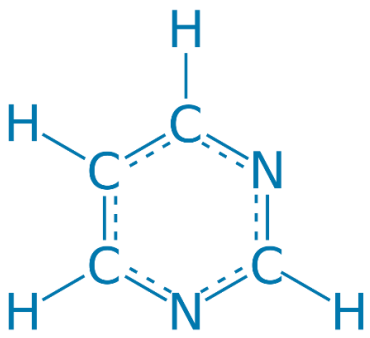
- **Gout**: Accumulation of uric acid crystals in joints (monosodium urate)
  - Painful inflammation, especially in big toe
  - Treated with **allopurinol** (xanthine oxidase inhibitor)

Metabolism of pyrimidine nucleotides

Biosynthesis of Pyrimidine Nucleotide

Overview

- Pyrimidines include **cytidine (CMP)**, **uridine (UMP)**, and **thymidine (TMP)** nucleotides.
  - Unlike purines, the pyrimidine ring is **synthesized first, then attached to PRPP**
  - Final products: UMP → CMP and TMP



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Step-by-Step Biosynthesis

1. Formation of Carbamoyl Phosphate

- **Enzyme**: Carbamoyl phosphate synthetase II (CPS II)
- **Reaction**: Glutamine + CO_2 + 2 ATP → Carbamoyl phosphate
- **Location**: Cytosol (not to be confused with CPS I of the urea cycle)
- **Regulation**: Inhibited by UTP, activated by PRPP

2. Formation of Carbamoyl Aspartate

- **Enzyme**: Aspartate transcarbamoylase (ATCase)
- **Reaction**: Carbamoyl phosphate + Aspartate → Carbamoyl aspartate

3. Formation of Dihydroorotate

- **Enzyme**: Dihydroorotase

4. Oxidation to Orotate

- **Enzyme**: Dihydroorotate dehydrogenase
- **Location**: Mitochondria (only mitochondrial step in this pathway)
- **Reaction**: Dihydroorotate → Orotate

5. Addition of PRPP

- **Enzyme**: Orotate phosphoribosyltransferase
- **Reaction**: Orotate + PRPP → Orotidine monophosphate (OMP)

6. Decarboxylation to UMP

- **Enzyme**: Orotidylate decarboxylase
- **Product**: UMP

UMP → CMP and TMP

UMP → UDP → CTP

- UDP is phosphorylated to UTP
- **Enzyme**: CTP synthetase
- **Requires**: Glutamine and ATP → CTP

UDP → dUMP → dTMP

- UDP is reduced to dUDP by **ribonucleotide reductase**, then converted to dUMP
- **Enzyme**: Thymidylate synthase
- **Reaction**: dUMP → dTMP
- **Requires**: N^5,N^{10}-methylene-THF (tetrahydrofolate derivative)

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Regulation of Pyrimidine Biosynthesis

Level	Control
CPS II	Inhibited by UTP, activated by PRPP
ATCase (bacteria)	Feedback inhibition by CTP
Ribonucleotide reductase	Regulated by dNTP levels

Salvage Pathway for Pyrimidines

- Pyrimidine bases (e.g., uracil, cytosine, thymine) can be reused
- **Enzymes**: Pyrimidine nucleoside phosphorylases
- Less efficient/important than purine salvage

Pyrimidine Catabolism

- Pyrimidines are broken down into **water-soluble products** (unlike purines → uric acid).

Pathway:

- Cytosine, Uracil → **β-alanine**
- Thymine → **β-aminoisobutyric acid**
- All are excreted via the urine

Protein synthesis

What is Translation?

- **Translation** is the biological process by which **ribosomes synthesize proteins** using **messenger RNA (mRNA)** as a template.
- It is the **second step of gene expression**, following transcription.
    - It occurs in the **cytoplasm** of both prokaryotic and eukaryotic cells.
    - It involves three main types of RNA:
        - **mRNA** (messenger RNA): Carries genetic code
        - **tRNA** (transfer RNA): Brings amino acids
        - **rRNA** (ribosomal RNA): Part of the ribosome's structure and catalytic machinery

Major Components of Translation

Component	Function
mRNA	Template with codons that specify amino acids

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