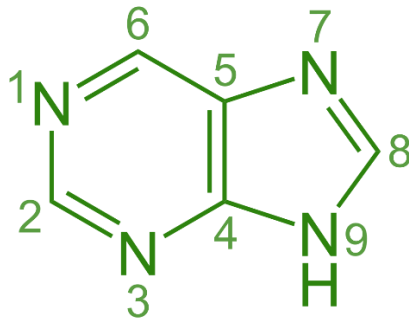


# Nucleic acid metabolism and genetic information transfer

## 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 + P<sub>i</sub>
- **Regulation:** Major control step, inhibited by AMP, GMP, IMP

#### 3. Stepwise Formation of IMP

- The atoms of the purine ring come from:

| Atom in Purine | Source                       |
|----------------|------------------------------|
| N1             | Aspartate                    |
| C2, C8         | Formate (via N10-formyl-THF) |

|            |                 |
|------------|-----------------|
| N3, N9     | Glutamine       |
| C4, C5, N7 | Glycine         |
| C6         | CO <sub>2</sub> |

### 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):

**Enzymes:**

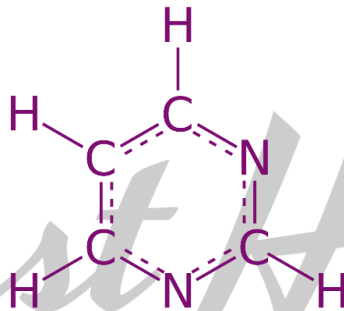
- Hypoxanthine-Guanine Phosphoribosyltransferase (HGPRT)
- Adenine Phosphoribosyltransferase (APRT)

**Clinical Note:**

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

**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

**Step-by-Step Biosynthesis****1. Formation of Carbamoyl Phosphate**

- **Enzyme:** Carbamoyl phosphate synthetase II (CPS II)
- **Reaction:** Glutamine + CO<sub>2</sub> + 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)



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