Purine and Pyrimidine Metabolism

Purines and pyrimidines are heterocyclic aromatic compounds, which, along with sugar and phosphate groups, form the important components of nucleotides. Purines include adenine and guanine, while pyrimidines include thymine (in DNA), uracil (in RNA), and cytosine. Purine nucleotide synthesis follows a series of reactions using carbon donors, amino acids (e.g., glutamine, aspartate), and bicarbonate. The *de novo* pathway generates inosine monophosphate (IMP), which is the precursor of adenosine monophosphate (AMP) and guanosine monophosphate (GMP). Purine synthesis is regulated in the 1st 2 steps. Synthesis of pyrimidine nucleotides also follows different reactions, producing uridine monophosphate (UMP), which is converted to uridine triphosphate (UTP) and cytidine triphosphate (CTP). For thymine, a part of deoxyribonucleotides, ribonucleoside reductase is required to reduce the ribose moiety. Degradation of nucleotides result in xanthine then uric acid production in purines, while pyrimidines produce the amino acids, β-alanine, and β-aminobutyrate.

Last updated: March 9, 2023

CONTENTS

Overview

Basic terms

Nitrogenous base:

- Purine:
  - Adenine (A)
  - Guanine (G)
- Pyrimidine:
  - Thymine (T)
  - Uracil (U)
  - Cytosine (C)
- Other minor bases:
  - Hypoxanthine
  - Xanthine

Nucleosides: 2 components:

- A nitrogenous base:
  - Adenine, guanine, thymine, and cytosine in DNA
  - Adenine, guanine, uracil, and cytosine in RNA
- Pentose sugar:
  - Ribose
  - Deoxyribose

A beta-*N*-glycosidic bond links the 1st carbon of the pentose sugar and N9 of a purine or N1 of a pyrimidine (e.g., adenosine, guanosine, cytidine, thymidine, uridine, inosine).

Nucleotides: 3 main components:

- Nitrogenous base
- Pentose sugar
- Phosphate groups (varying number)

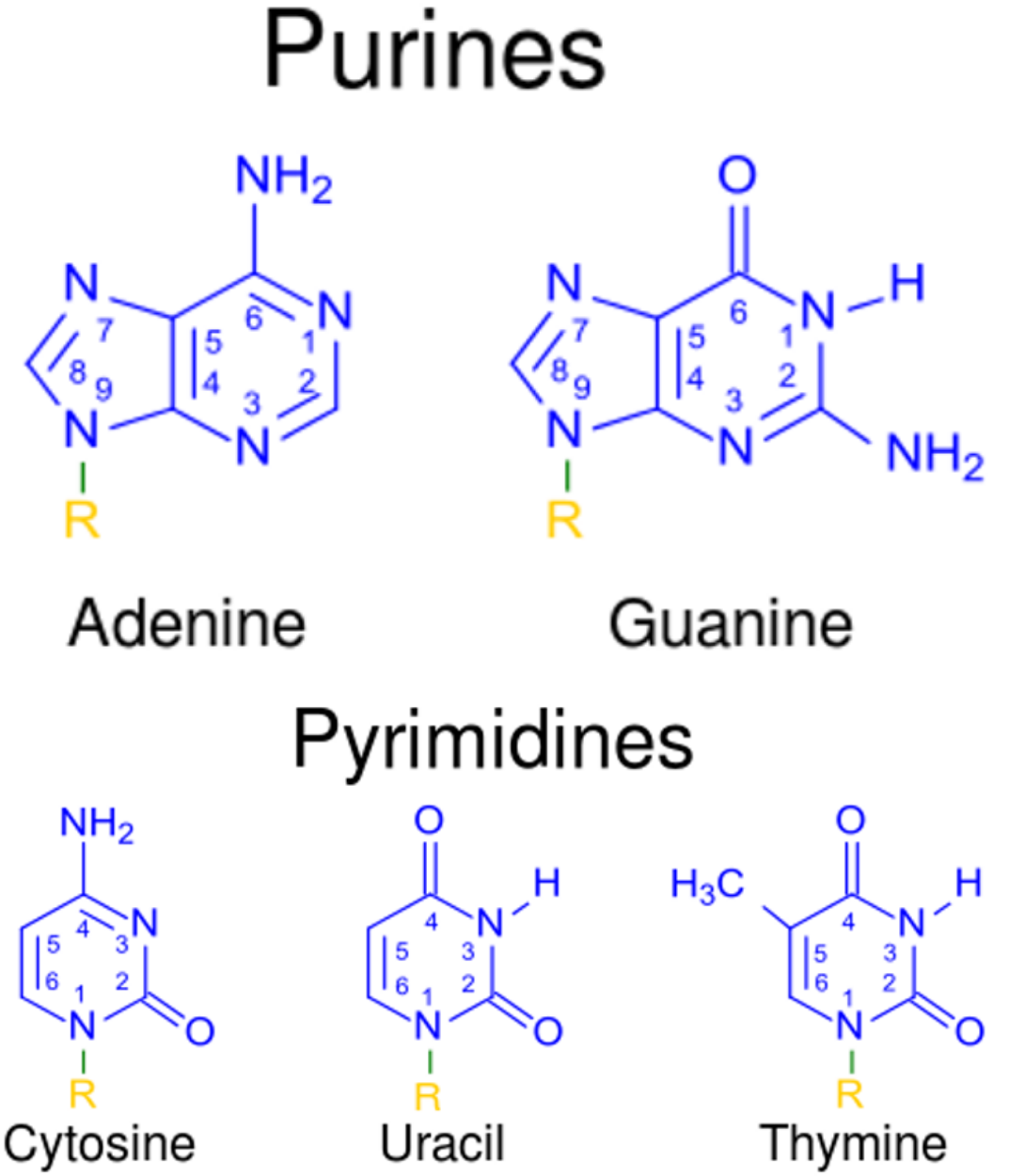
These molecules form the DNA backbone (e.g., adenosine monophosphate, guanosine monophosphate, cytidine monophosphate)

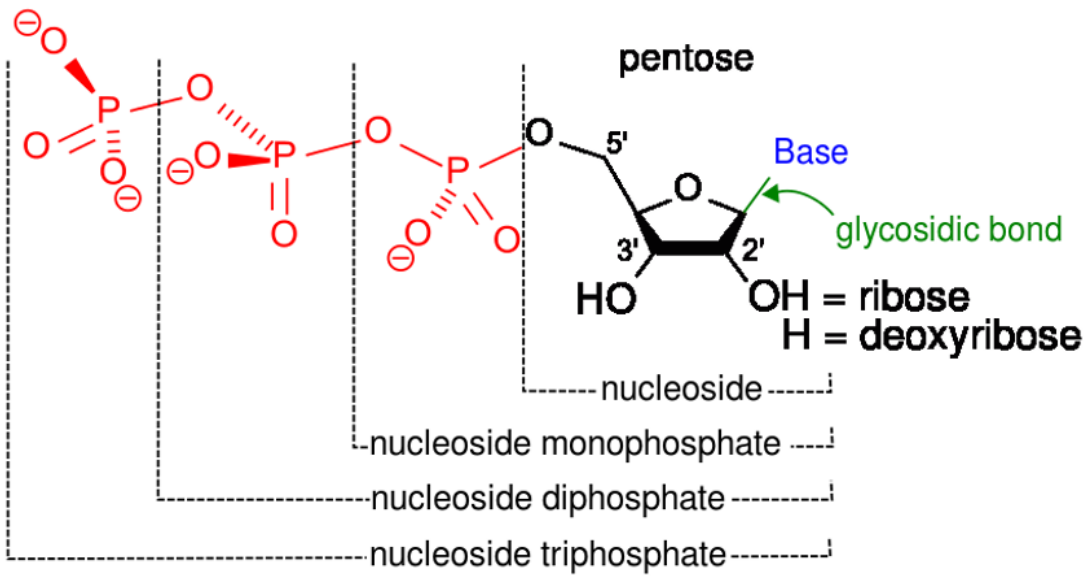
> 1 phosphate groups:

Esterification of the phosphate groups forms the corresponding nucleoside diphosphates and triphosphates (e.g., adenosine triphosphate (ATP), adenosine diphosphate (ADP)).

Nucleic acid:

Polymer of nucleotides (e.g., ribonucleic acid (RNA)).





Mnemonics

- Nucleo**S**ide: base + **S**ugar
- Nucleo**T**ide: base + sugar + phospha**T**e

Biomedical importance

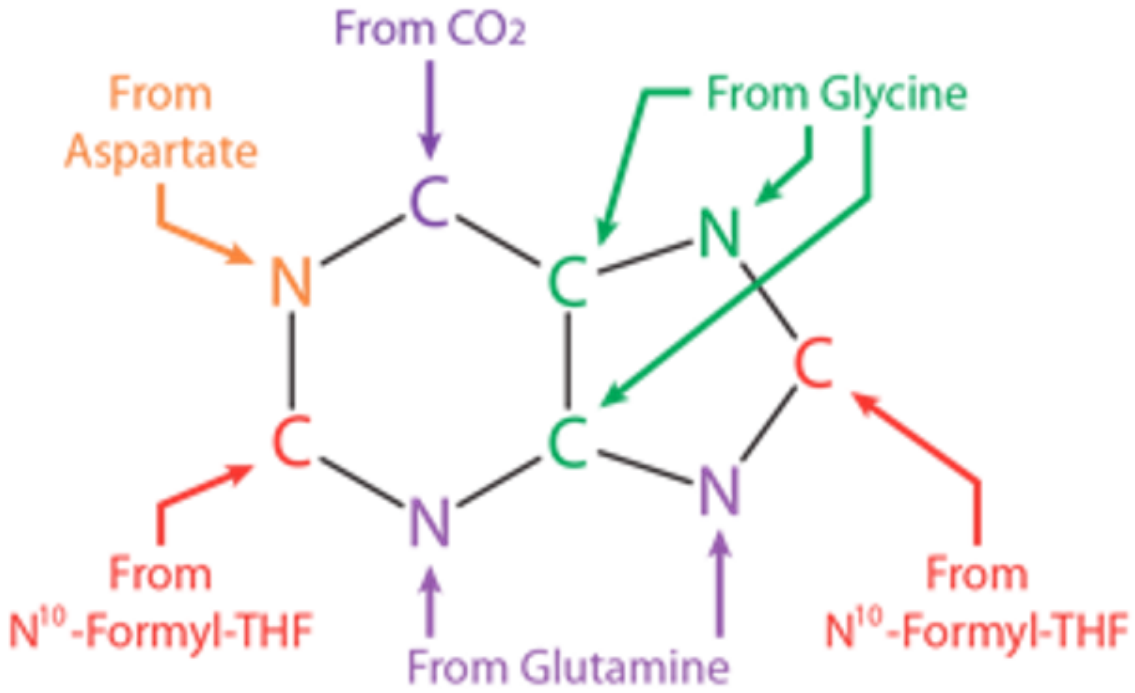
The main functions of nucleotides:

- Form the building blocks of nucleic acids
- Act as cosubstrates and coenzymes in biochemical reactions
- Involved in cell signaling pathways and also act as intracellular second messengers
- Provide chemical energy in the form of nucleoside triphosphates such as ATP (energy in reactions such as amino acid, protein, and cell membrane synthesis)

Synthesis of Purines

Building the structure (*de novo* synthesis)

- Nucleotides are formed from simple molecules: amino acids (e.g., glutamine), carbon donors (e.g., formyl tetrahydrofolate), and bicarbonate.
- Purine nucleotide synthesis is a multireaction process beginning with the conversion of ribose-5-phosphate to 5-phosphoribosyl-1-pyrophosphate (PRPP).
- The major site of synthesis is the liver (intracytoplasmic).



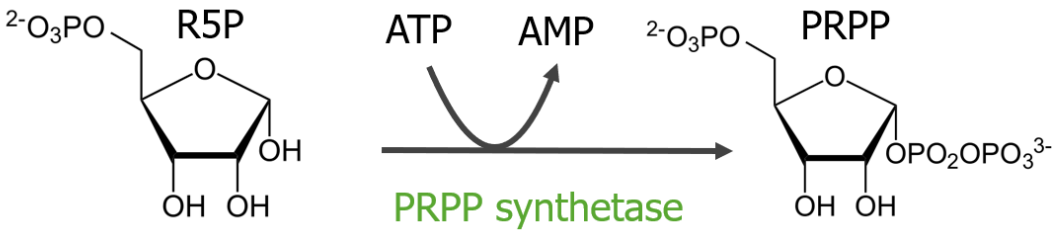
Atom sources for purine synthesis
THF: tetrahydrofolate

Image by Lecturio.

Step 1

Synthesis of PRPP

- PRPP is the substrate for purine synthesis.
- Ribose-5-phosphate is converted to PRPP, with phosphates coming from ATP (reaction of which produces AMP).
- Enzyme: PRPP synthetase/ribose phosphate pyrophosphokinase
- Clinical correlation: PRPP overactivity: X-linked disorder associated with overproduction of nucleotides, manifesting with ↑ uric acid and neurodevelopmental anomalies



Synthesis of phosphoribosyl pyrophosphate (PRPP):
Ribose-5-phosphate (R5P) is converted to PRPP. The phosphates come from ATP and then produce AMP. The enzyme for the conversion is PRPP synthetase.

Image by Lecturio.

Step 2

Formation of 5-phosphoribosylamine (PRA)

- PRPP + glutamine → PRA
- The pyrophosphate group of PRPP is released in this reaction.
- Rate-limiting step
- Enzyme: amidophosphoribosyltransferase
- The enzyme is inhibited by:
    - AMP
    - Guanosine monophosphate (GMP)
    - Inosine monophosphate (IMP)

Step 3

5-Phosphoribosylamine conversion to glycinamide ribonucleotide (GAR)

- Subsequent steps are additions to form 5- or 6-membered ring.
- Glycine is added to PRA to form GAR.
- Glycine contributes C4, C5, and N7.
- Enzyme: GAR synthetase (GARS)/phosphoribosylamine glycine ligase

Step 4

Formylation of GAR to formylglycinamide ribonucleotide (FGAR)

- Formyltetrahydrofolate formylates the amino group of GAR to form FGAR, contributing C8 of purine.
- Enzyme: GAR transformylase/phosphoribosyl glycinamide formyltransferase

Step 5

Conversion of FGAR to formylglycinamidine ribonucleotide (FGAM)

- In this adenosine triphosphate (ATP)-dependent reaction, glutamine donates the N3, forming FGAM.
- Enzyme: FGAM synthetase/phosphoribosyl formyl glycinamide synthase

Step 6

Formation of the purine imidazole ring

- This is an ATP-dependent reaction that leads to the formation and closure of the purine ring.
- 5-Aminoimidazole ribonucleotide (AIR) is formed from this reaction.
- Enzyme: AIR synthetase/phosphoribosyl formyl glycinamide cyclo-ligase

Step 7

Carboxylation of AIR

- This is an ATP-dependent carboxylation of AIR to carboxy aminoimidazole ribonucleotide (CAIR), in the presence of bicarbonate
- C6 of purine is contributed by bicarbonate.
- Enzyme: AIR carboxylase/N5-CAIR synthase

Step 8

Formation of 5-aminoimidazole-4-(N-succinylcarboxamide) ribonucleotide (SAICAR)

- The addition of aspartate forms an amide bond with C6 to form SAICAR.
- N1 of purine is contributed by aspartate.
- Enzyme: SAICAR synthetase/N5-carboxy aminoimidazole ribonucleotide mutase

Step 9

Elimination of fumarate

- 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) is formed by the cleaving off the fumarate group.
- Enzyme: Adenylosuccinate lyase/5-phosphoribosyl-4-(N-succinyl carboxamide)-5-aminoimidazole lyase

Step 10

Formylation to form 5-formaminoimidazole-4-carboxamide ribonucleotide (FAICAR)

- Formylation occurs by reaction between the amino group of AICAR and N10-formyl tetrahydrofolate to form FAICAR.
- C2 of the purine ring is contributed by N10-formyl tetrahydrofolate.
- Enzyme: AICAR transformylase

Step 11

Cyclization to form IMP

- Inosine monophosphate is formed by the enzymatic closure of the larger ring of FAICAR with the release of water.
- Inosine monophosphate is the precursor of AMP and GMP.
- Enzyme: IMP cyclohydrolase

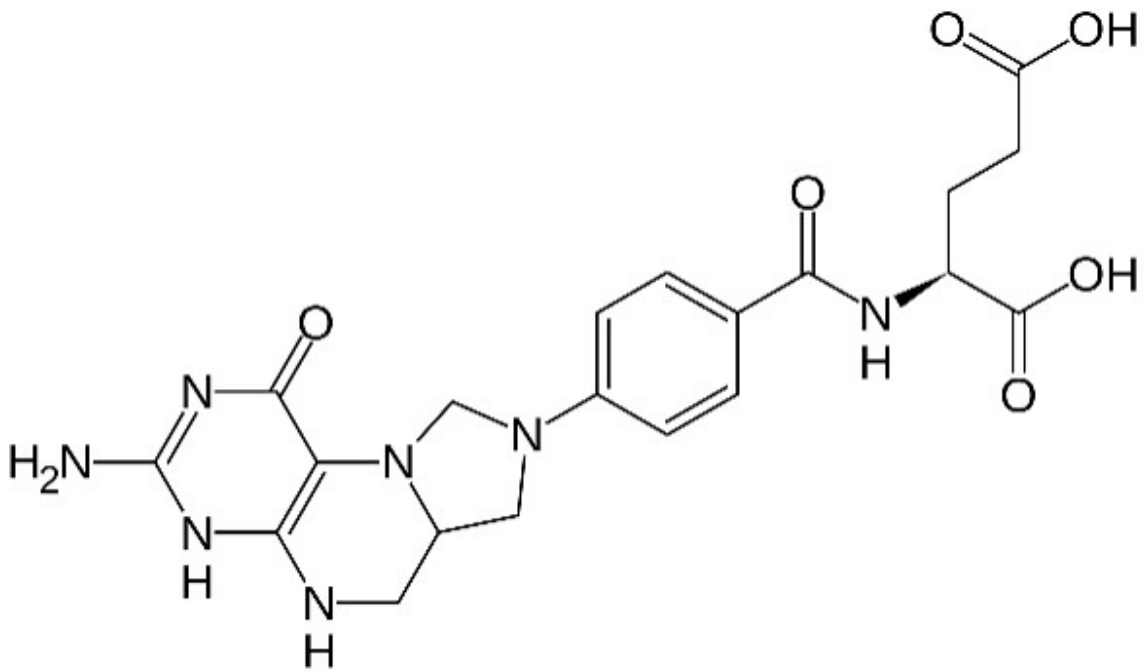
Table: Summary of *de novo* purine synthesis

Step	Reaction	Added atom	Enzyme
1	Ribose-5-phosphate → PRPP	Phosphates (from ATP)	PRPP synthetase
2	PRPP + glutamine → 5-phosphoribosylamine	N9 (from glutamine)	Amidophosphoribosyltransferase
3	PRA conversion to GAR	C4, C5, N7 (from glycine)	GAR synthetase
4	Formylation of GAR to FGAR	C8 (from formyl THF)	GAR transformylase
5	Conversion of FGAR to FGAM	N3 (from glutamine)	FGAM synthetase
6	Ring closure, forming AIR		AIR synthetase
7	Carboxylation of AIR	C6 (from bicarbonate)	AIR carboxylase
8	Formation of SAICAR	N1 (from aspartate)	SAICAR synthetase
9	Fumarate removed AICAR formed		Adenylosuccinate lyase
10	FAICAR formed	C2 (from formyl-THF)	AICAR transformylase
11	IMP formed		IMP cyclohydrolase

AICAR: 5-aminoimidazole-4-carboxamide ribonucleotide
AIR:5-aminoimidazole ribonucleotide
FGAM: formylglycinamidine ribonucleotide
FGAR: formylglycinamide ribonucleotide
GAR: glycinamide ribonucleotide
IMP: inosine monophosphate
PRPP: phosphoribosyl pyrophosphate
PRA: 5-phosphoribosylamine
SAICAR: 5-aminoimidazole-4-(N-succinylcarboxamide) ribonucleotide
THF: tetrahydrofolate

Role of folate

- Folic acid is composed of p-aminobenzoic acid, glutamine, and pteridine and is available for utilization in its active form: tetrahydrofolic acid (TH4).
- Lack of folate leads to decreased nucleotide synthesis.
- 2 important consequences of folic acid deficiency are megaloblastic anemia and spina bifida in newborns (due to maternal folate deficiency).



Structure of folate

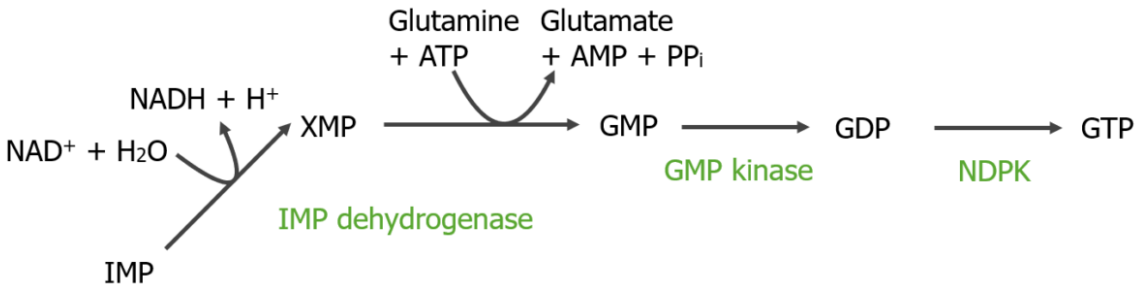
Image by Lecturio.

Adenine and Guanine Formation

Inosine monophosphate is converted to adenine and guanine as AMP and GMP. Formed from GMP, guanosine triphosphate (GTP) provides the energy to convert IMP to AMP.

Synthesis of guanosine monophosphate

- Step 1: dehydrogenation of IMP
  - Dehydrogenation of IMP forms xanthosine monophosphate (XMP).
  - H^+ ions are released (and accepted by NAD^+).
  - Enzyme: IMP dehydrogenase
- Step 2: amidation of XMP
  - Amidation of XMP (amide from glutamine) and hydrolysis of ATP occur, yielding GMP.
  - Enzyme: GMP synthetase
- Clinical correlation:
  - Mycophenolate, an immunosuppressant, inhibits IMP dehydrogenase (IMPDH), reducing proliferation of immune cells.

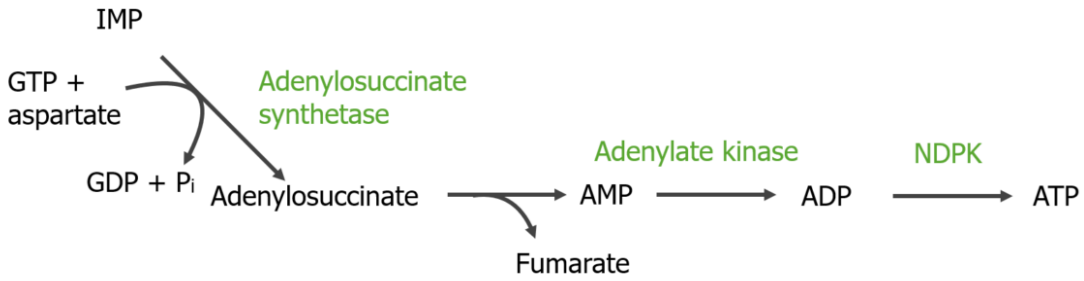


Conversion of IMP to GMP and then to GTP:
NAD+: nicotinamide adenine dinucleotide (oxidized)
NADH: nicotinamide adenine dinucleotide (reduced)
NDPK: nucleoside diphosphate kinase
PPi: pyrophosphate

Image by Lecturio.

Synthesis of AMP

- Step 1: Donation of the amino group by aspartate
  - The amino group of aspartate (links to IMP) + GTP hydrolysis → adenylosuccinate
  - Enzyme: adenylosuccinate synthetase
- Step 2: Elimination of fumarate to form AMP
  - Adenylosuccinate is enzymatically converted to AMP by the removal of fumarate.
  - Enzyme: adenylosuccinase/adenylosuccinate lyase



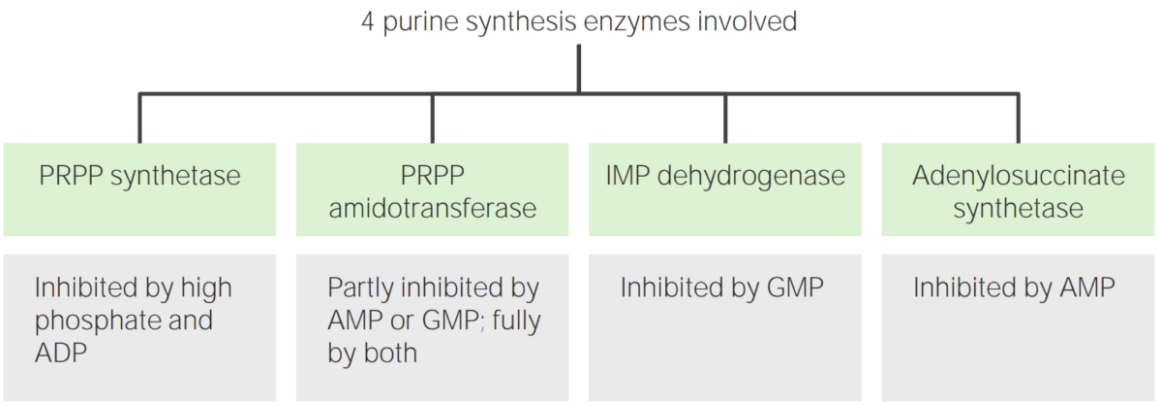
Conversion of IMP to AMP and then to ATP:
NDPK: nucleoside diphosphate kinase
Pi: inorganic phosphate

Image by Lecturio.

Regulation of synthesis

Synthesis of IMP, ATP and GTP is regulated to control the amount of purine nucleotides produced.

- The enzyme PRPP synthetase (step 1) is inhibited by ADP and GDP.
- The enzyme amidophosphoribosyltransferase (step 2) is inhibited by:
  - AMP
  - GMP
  - IMP
- The enzyme adenylosuccinate synthetase (AMP synthesis) is inhibited by AMP.
- The enzyme IMP dehydrogenase (in GMP synthesis) is inhibited by GMP.
- External factors affecting purine synthesis include purine analogs:
  - Thiopurines (inhibit *de novo* purine synthesis)
    - 6-Mercaptopurine (6-MP): antineoplastic and immunosuppressive agent
    - 6-Thioguanine
    - Azathioprine (immunosuppressant): undergoes nonenzymatic reduction into 6-MP
  - Fludarabine
  - Cladribine



Regulators of purine metabolism

Image by Lecturio.

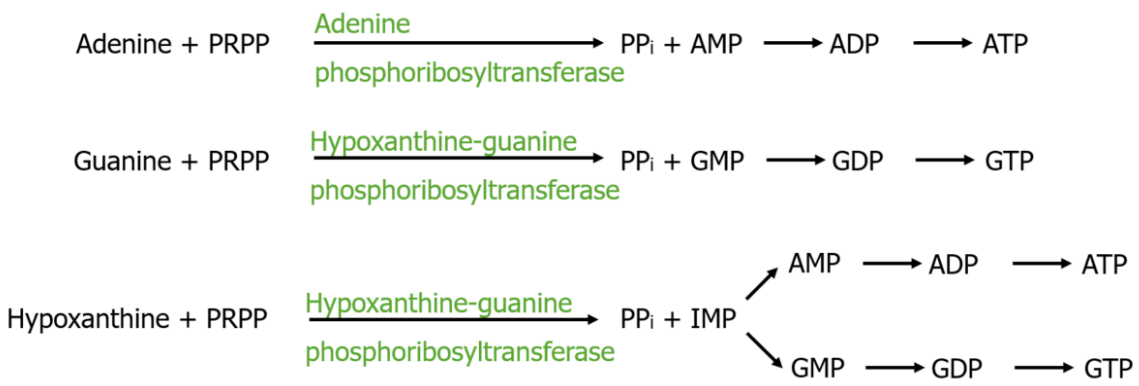
Salvage Pathway of Purines

Building the structure

- Generation of nucleotides from the breakdown of nucleic acids
- Free purines are converted back to their respective nucleotides through salvage pathways.
- PRPP is an essential component in this pathway.
- The 2 main enzymes involved are:
    1. Adenine phosphoribosyltransferase (APRT)
    2. Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)

Reactions

- The brief summary of the salvage pathway is:
    - Adenine + PRPP ⇆ AMP + PPi (enzyme: APRT)
    - Guanine + PRPP ⇆ GMP + PPi (enzyme: HGPRT)
    - Hypoxanthine + PRPP ⇆ IMP + PPi (enzyme: HGPRT)
- Clinical correlation: Lesch-Nyhan syndrome: X-linked recessive disorder caused by defect in HGPRT (unable to salvage purine bases → ↑ uric acid)



The salvage pathway that recycles nucleotides for utilization

Image by Lecturio.

Importance

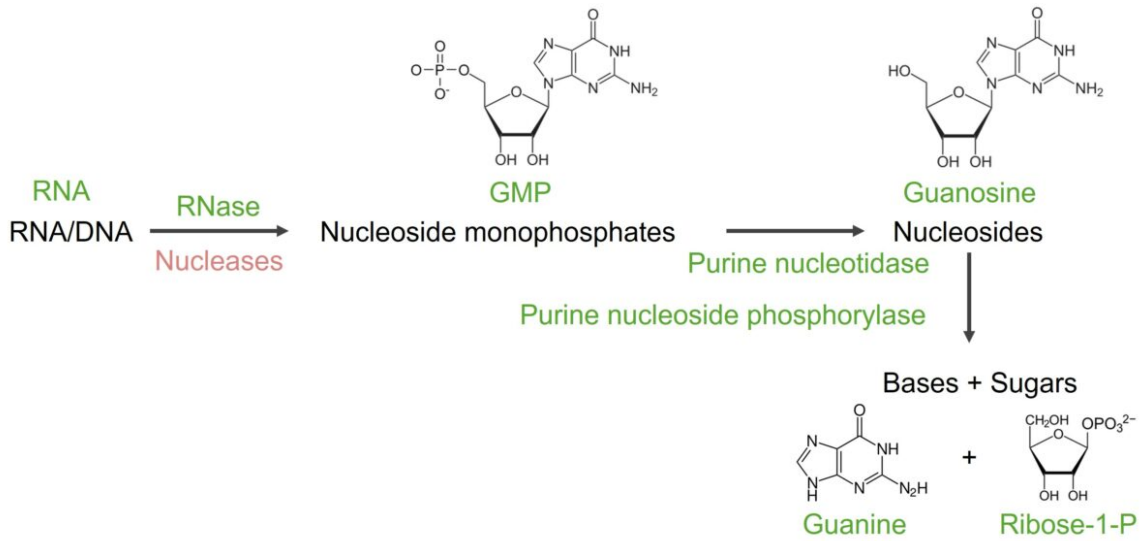
- In tissues like erythrocytes and the brain, the salvage pathway is important owing to the absence of *de novo* purine synthesis.
- The pathway economizes intracellular energy expenditure.

Catabolism of Purine Nucleotides

Nucleic acid (RNA/DNA) is broken down by nucleases to nucleotides. To degrade purine nucleotides, the phosphate and ribose are removed first, with further reactions leading to xanthine and then to uric acid.

Guanosine monophosphate

- Conversion of nucleotide to nucleoside (GMP to guanosine) by the enzyme nucleotidase, resulting in phosphate removal
- Guanosine is further broken down:
    - Reaction leads to guanine and ribose-1-phosphate.
    - Enzyme: purine nucleoside phosphorylase
- Deamination of guanine leads to the formation of xanthine.

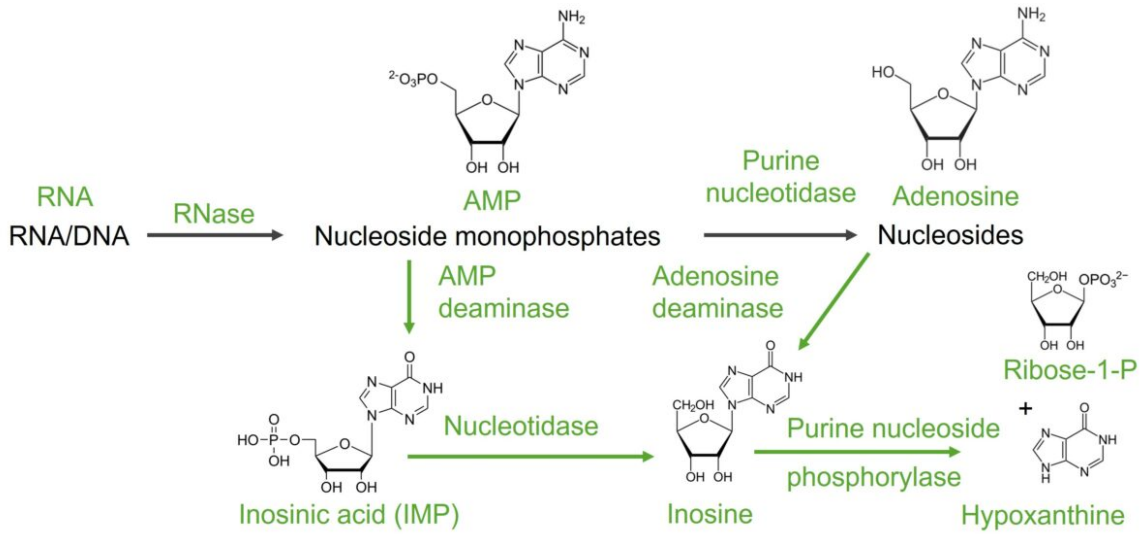


Degradation of guanine

Image by Lecturio.

AMP

- Conversion from nucleic acids (RNA/DNA to AMP to bases) can have different pathways, using different deaminases.
- 1st pathway:
    - AMP → adenosine: catalyzed by the enzyme purine nucleotidase, with removal of the phosphate
    - Adenosine converted to inosine by adenosine deaminase (ADA)
    - Inosine is degraded by purine nucleoside phosphorylase (PNP) to hypoxanthine and ribose-1-phosphate.
    - Hypoxanthine is oxidized to xanthine by xanthine oxidase.
- 2nd pathway:
    - AMP → inosinic acid or IMP: catalyzed by AMP deaminase
    - IMP is converted to inosine by nucleotidase.
    - Inosine is degraded by PNP to hypoxanthine and ribose-1-phosphate.
    - Hypoxanthine is oxidized to xanthine by xanthine oxidase.
- Clinical correlation:
    - ADA deficiency: leads to ↑ deoxy-ATP, deoxy-GTP (toxic to immune cells such as T cells)
    - PNP deficiency: leads to ↑ deoxy-ATP, deoxy-GTP (toxic to immune cells such as T cells) and also associated with developmental delay

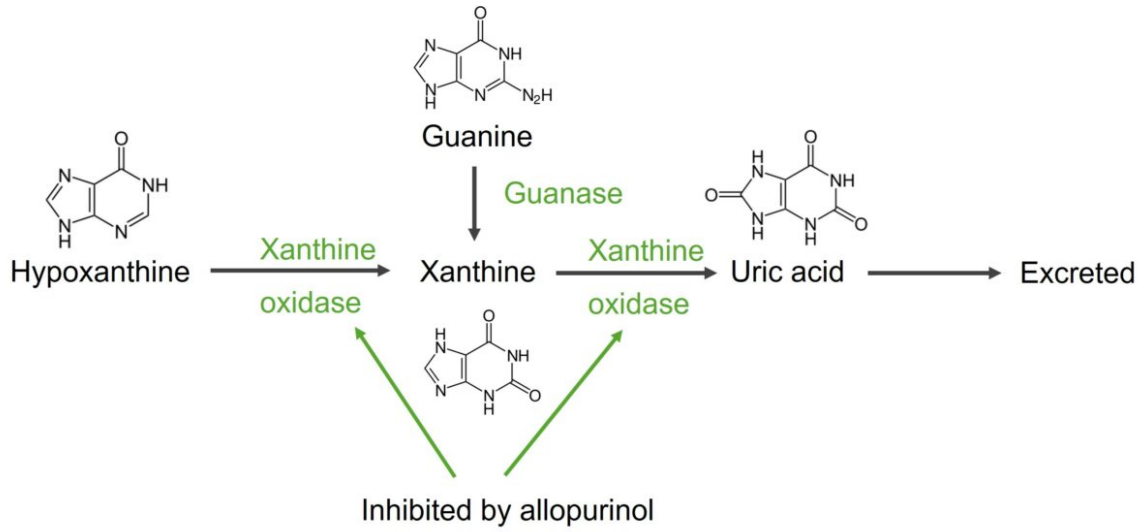


Degradation of adenine

Image by Lecturio.

Xanthine

- Both adenosine and guanosine are converted to xanthine.
    - Adenosine → inosine → hypoxanthine → xanthine
    - Guanosine → guanine → xanthine
- Xanthine oxidase:
    - Catalyzes hypoxanthine to xanthine and xanthine to uric acid reactions
    - The end product, uric acid, is excreted in the urine.
- Clinical correlation: allopurinol, an inhibitor of xanthine oxidase, is used for gout treatment.



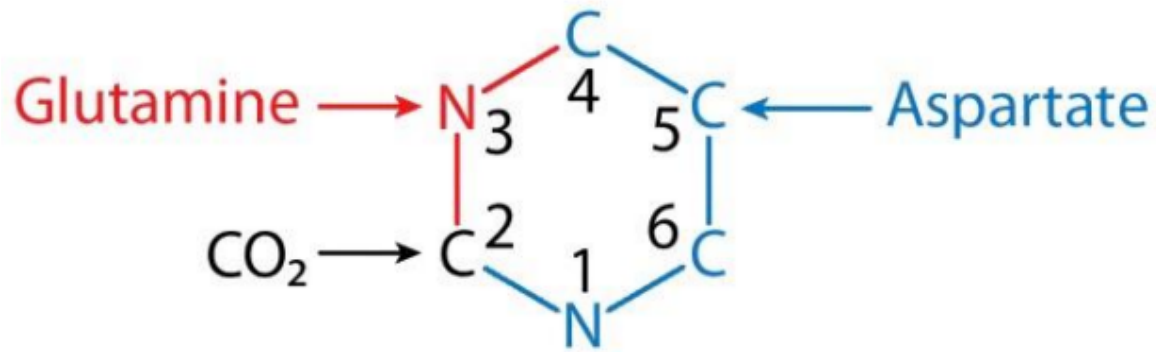
Degradation of guanine and hypoxanthine into uric acid

Image by Lecturio.

Pyrimidine Synthesis

Building the structure (*de novo* synthesis)

- Pyrimidine base is synthesized first and then incorporated into the nucleotide (the ring is completed before being linked to ribose-5-phosphate).
- Sources of the carbon and nitrogen atoms of pyrimidine:
  - Glutamine and bicarbonate contribute N3 and C2, respectively, which combine to form carbamoyl phosphate.
  - Aspartate contributes N1, C6, C5, and C4



Sources of the carbon and nitrogen atoms in pyrimidine synthesis

Image by Lecturio.

Step 1

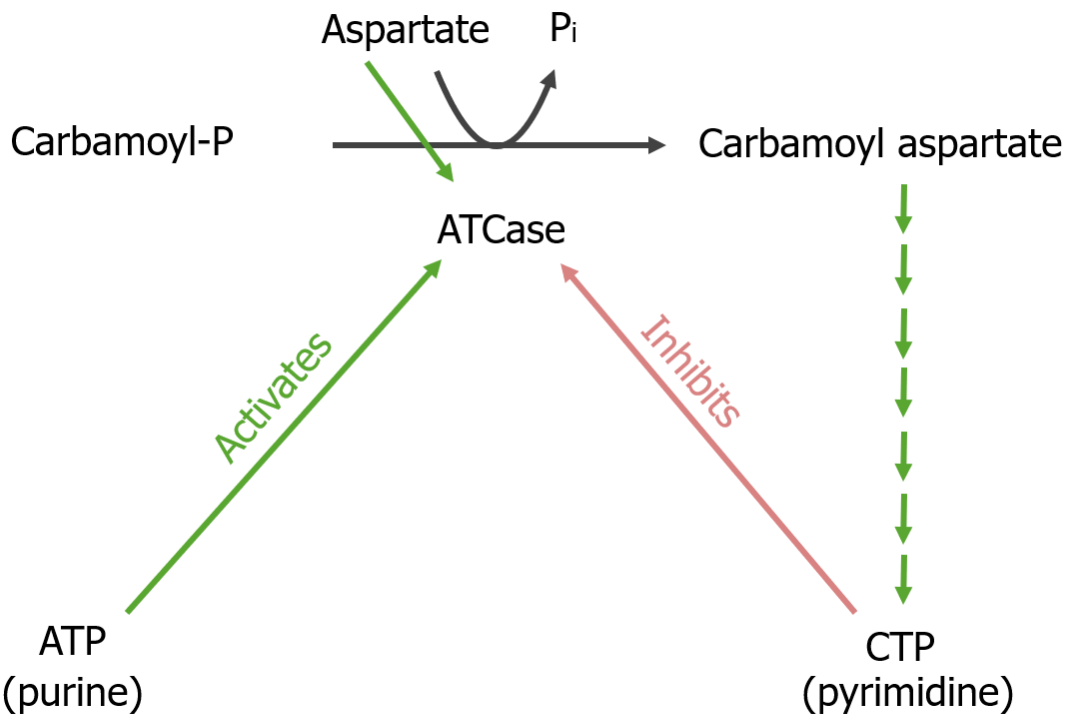
Synthesis of carbamoyl phosphate

- This reaction occurs in the cytoplasm.
- The nitrogen of glutamine and carbon of bicarbonate react to form carbamoyl phosphate.
- Enzyme: carbamoyl phosphate synthetase II

Step 2

Synthesis of carbamoyl aspartate

- Rate-limiting step
- Carbamoyl phosphate reacts with aspartate to yield carbamoyl aspartate.
- Atoms C2 and N3 are derived from carbamoyl phosphate.
- Enzyme: aspartyl transcarbamoylase (ATCase)
    - Activated by ATP
    - Inhibited by cytidine triphosphate (CTP)



Rate-limiting step of pyrimidine synthesis:
Reaction converts carbamoyl phosphate to carbamoyl aspartate, catalyzed by aspartyl transcarbamoylase (ATCase). Subsequent reactions eventually lead to the end product, cytidine triphosphate (CTP). The ATCase is activated by ATP and inhibited by CTP.

Image by Lecturio.

Step 3

Formation of the pyrimidine ring

- A molecule of water is eliminated, and carbamoyl aspartate is converted to a ring compound (dihydroorotate).
- Enzyme: dihydroorotase

Step 4

Oxidation of dihydroorotate

- Removal of hydrogen atoms (dehydrogenation) from the C5 and C6 positions produces orotic acid.
- Enzyme: dihydroorotate dehydrogenase
- Coenzyme: NAD

Step 5

Formation of orotidine-5-monophosphate (OMP)

- Orotic acid + ribose-5-phosphate → orotidine monophosphate or orotidylic acid
- PRPP is the donor of ribose-5-phosphate.
- Enzyme: orotate phosphoribosyltransferase (OPRT)

Step 6

Decarboxylation to form uridine monophosphate (UMP)

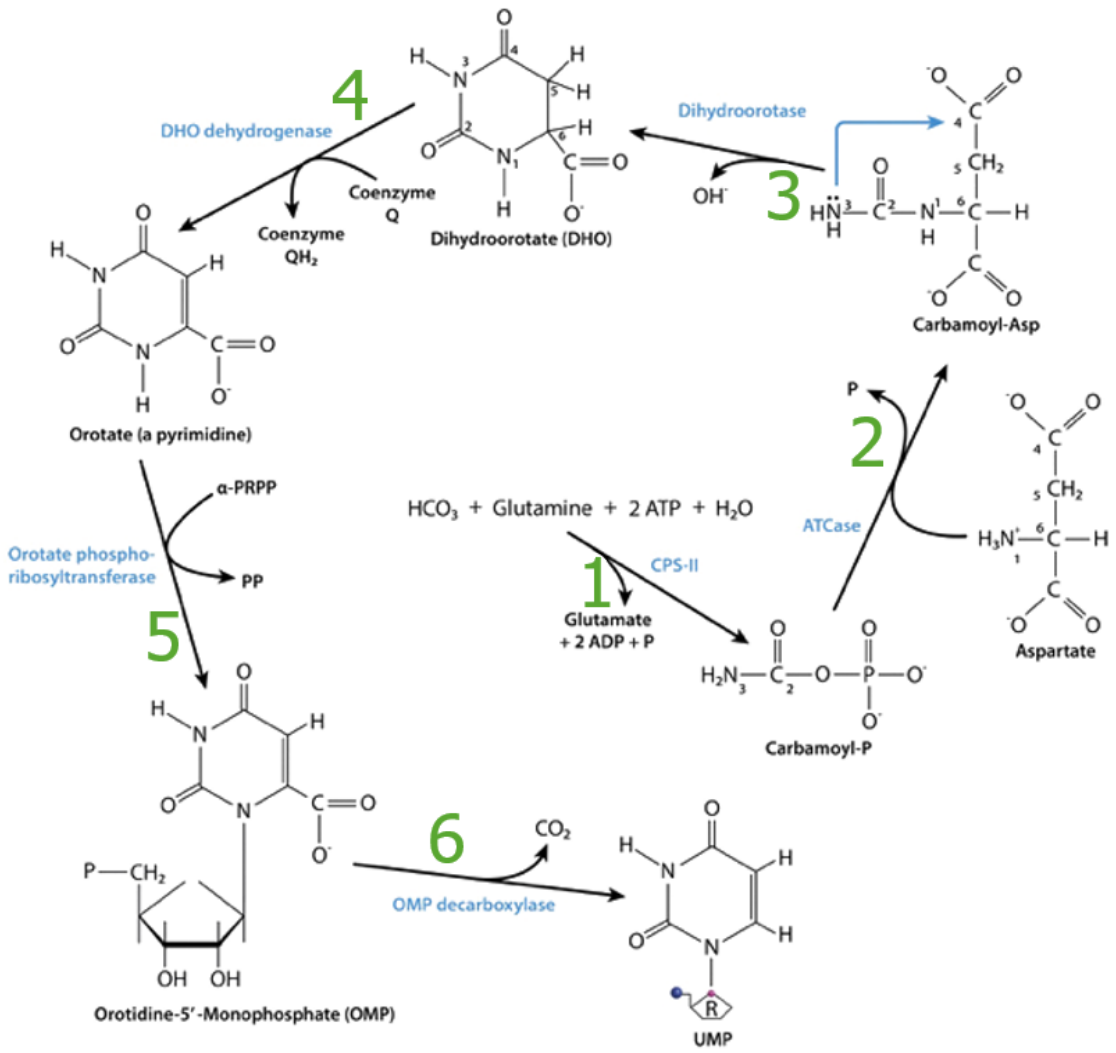
- Orotidine monophosphate undergoes decarboxylation.
- UMP is produced by the removal of C1 in the form of CO_2 , making uridine the first pyrimidine to be synthesized.
- Enzyme: OMP decarboxylase
- Subsequent steps form the triphosphates uridine triphosphate (UTP) and cytidine triphosphate (CTP).

Note: The last 2 enzymes in this pathway, OPRT and OMP decarboxylase, are located on the same polypeptide, **UMP synthase**. UMP synthase catalyzes the conversion of orotic acid to UMP.

Table: Summary of *de novo* pyrimidine synthesis

Step	Enzyme	Product
1	Carbamoyl phosphate synthetase II	Carbamoyl phosphate
2	Aspartyl transcarbamoylase*	Carbamoyl aspartate
3	Dihydroorotase	Dihydroorotic acid
4	Dihydroorotate dehydrogenase	Orotic acid
5	Orotate phosphoribosyltransferase	OMP
6	OMP decarboxylase	Uridine monophosphate

**catalyzes the rate-limiting step*
OMP: orotidine-5-monophosphate



Summary of pyrimidine synthesis, enzymes:
1. CPS II: carbamoyl phosphate synthetase II
2. ATCase: aspartyl transcarbamoylase
3. Dihydroorotase
4. Dihydroorotate (DHO) dehydrogenase
5. Orotate phosphoribosyltransferase
6. Orotidine-5-monophosphate (OMP) decarboxylase

Image by Lecturio.

Synthesis of uridine triphosphate and cytidine triphosphate

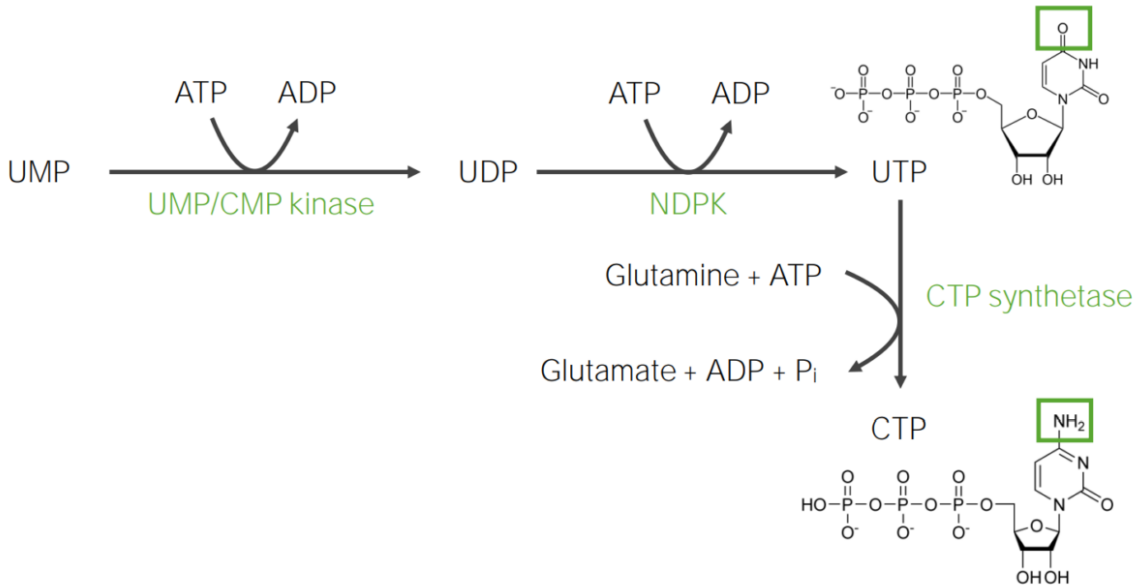
UTP and CTP are used in the synthesis of RNA.

UTP:

- Step 1:
  - Phosphorylation of UMP by ATP produces uridine diphosphate (UDP)
  - Enzyme: nucleoside monophosphate kinase (UMP/CMP kinase)
- Step 2:
  - UDP is phosphorylated to uridine triphosphate (UTP) by ATP.
  - Enzyme: nucleoside diphosphate kinase (NDPK)

CTP:

- UTP is converted to CTP (cytidine triphosphate) by the addition of an amino group from glutamine.
- This reaction requires ATP.
- Enzyme: CTP synthetase
    - Activated by GTP
    - Inhibited by CTP



Synthesis of UTP and CTP (triphosphates)

Image by Lecturio.

Deoxyribonucleotides and thymine

DNA is different from RNA, as DNA has deoxyribose, instead of ribose, and thymine (5-methyluracil), instead of uracil.

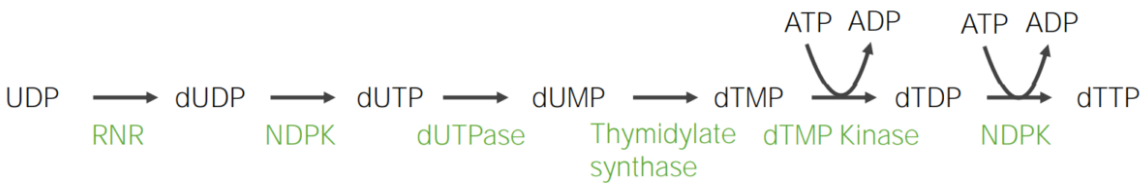
Deoxyribonucleotides are generated from their corresponding ribonucleotides.

- Ribonucleotide reductases (RNRs) reduce ribonucleoside diphosphates (NDPs) to deoxyribonucleoside diphosphates (dNDPs).
- dNDPs in turn, are converted to deoxyribonucleoside triphosphates (dNTPs) by nucleoside diphosphate kinase (NDPK).

Thymine is a pyrimidine present in DNA; thus, the ribose moiety of the corresponding nucleotide requires reduction.

- Step 1:
  - UDP → dUDP
  - Enzyme: ribonucleotide reductase
- Step 2:
  - dUDP → dUTP
  - Enzyme: NDPK
- Step 3:
  - dUTP → deoxyuridine monophosphate (dUMP)
  - Enzyme: dUTP diphosphohydrolase
- Step 4:
  - dUMP is methylated to deoxythymidine monophosphate (dTMP).
  - Enzyme: thymidylate synthase
  - Requires methylene tetrahydrofolate (as the methyl donor)
- Step 5:
  - dTMP is phosphorylated to dTTP (by ATP).
  - Phosphorylation occurs in 2 rounds.

Clinical correlation: 5-fluorouracil: antimetabolite agent (used in cancers) that inhibits thymidylate synthase and decreases DNA synthesis



Formation of thymine in the form of deoxythymidine triphosphate (dTTP)
dTDP: deoxythymidine diphosphate
dTMP: deoxythymidine monophosphate
dTTP: deoxythymidine triphosphate
dUDP: deoxyuridine diphosphate
dUMP: deoxyuridine monophosphate
dUTPase: deoxyuridine triphosphatase
NDPK: nucleoside diphosphate kinase
RNR: ribonucleotide reductase
UDP: uridine diphosphate

Image by Lecturio.

Regulation of synthesis

- The enzyme, carbamoyl phosphate synthetase (CPS) II in step 1:
    - Activated by PRPP and ATP
    - Inhibited by UTP and UDP
- The enzyme, ATCase in step 2 is allosterically inhibited by CTP.
- The enzyme, OMP decarboxylase (step 6) is inhibited by UMP.
- External factors include pyrimidine analogs (used as antineoplastic agents):
    - 5-fluorouracil
    - Capecitabine
    - Cytarabine
    - Gemcitabine

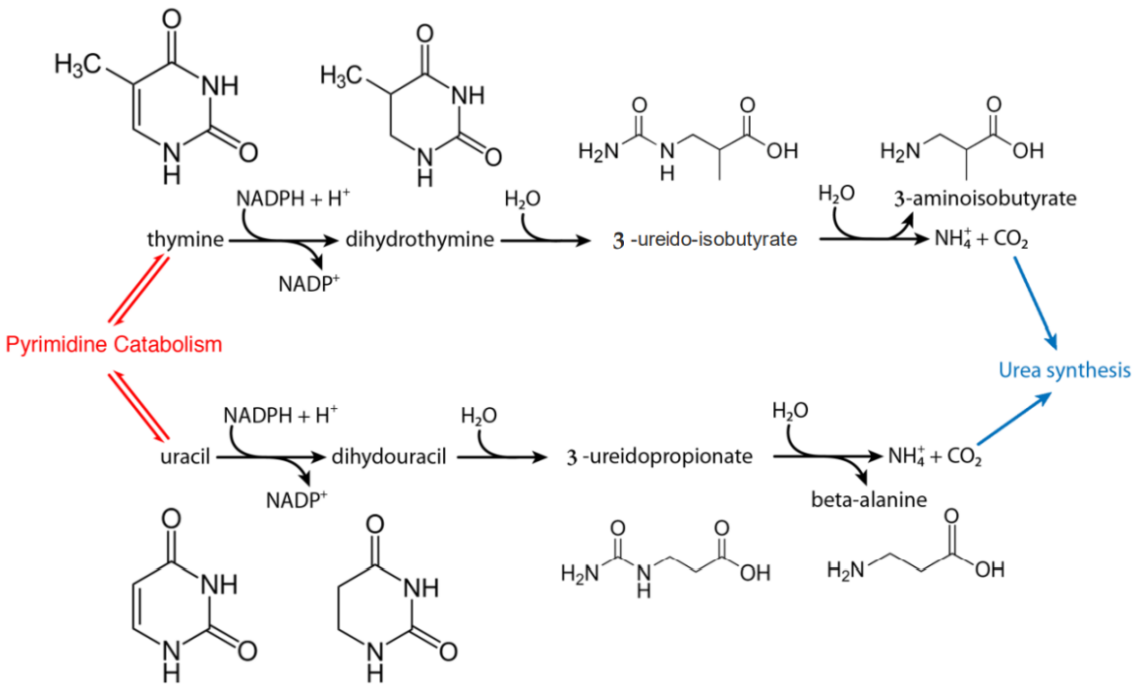
Salvage pathway of pyrimidine nucleotides

- Like purines, pyrimidines are recycled from the derivative intermediates of nucleic acids.
- Reactions convert ribonucleosides (uridine, cytidine) and deoxyribonucleosides (thymidine, deoxycytidine) to nucleotides.
- Kinases or phosphoryltransferases catalyze phosphoryl group transfer (from ATP) to the diphosphates, producing triphosphates:
    - NDP + ATP → NTP + ADP
    - dNDP + ATP → dNTP + ADP

Catabolism of Pyrimidine Nucleotides

Animal cells break down pyrimidine nucleotides to the nitrogenous bases, with the resultant uracil and thymine degraded (via reduction) in the liver.

- As in purine nucleotides, nucleic acid (RNA/DNA) is broken down by nucleases to nucleotides.
- Cytosine is degraded to uracil by the removal of an amino group.
- Both uracil and thymine are then reduced to dihydrouracil and dihydrothymine, respectively, which undergo reactions to the end products:
    - Dihydrouracil → β-alanine
    - Dihydrothymine → β-aminobutyrate
    - Reaction catalyzed by: hepatic β-ureidopropionase
    - β-aminobutyrate and β-alanine are further used in amino acid metabolism.
    - The ammonium ions (NH_4^+) released from the breakdown are used in the urea cycle.



Degradation of uracil and thymine
NADPH: nicotinamide adenine dinucleotide phosphate

Image by Lecturio.

Disorders of Nucleotide Metabolism

Table: Disorders of purine metabolism

Disorder	Defective enzyme	Nature of defect	Manifestations
Hyperuricemia/ gout	• ↑ PRPP synthetase • ↓ HGPRT	↑ Uric acid	Inflamed and painful joints
Lesch-Nyhan syndrome	↓ HGPRT	Lack of enzyme → defective purine salvage pathway	• Delayed puberty • Self-mutilation • Developmental delay • Impaired renal function
SCID	↓ ADA	Lack of enzyme → ↓ immune cells	• Repeated infections , recurrent deep skin, or organ abscesses • Mucocutaneous candidiasis • Failure to thrive
Renal lithiasis	↓ APRT	Autosomal recessive mutation → defective purine salvage pathway	• Renal colic • Recurrent urinary infections • Nausea • Vomiting
Xanthinuria	↓ Xanthine oxidase	Hypouricemia	• Nephrolithiasis • Acute kidney injury

ADA: adenosine deaminase
APRT: adenine phosphoribosyltransferase
HGPRT: hypoxanthine guanine phosphoribosyltransferase
PRPP: phosphoribosyl pyrophosphate
SCID: severe combined immunodeficiency

Table: Disorders of pyrimidine metabolism

Disorder	Defective enzyme	Manifestations
Orotic aciduria	• OPRT • OMP decarboxylase	• Failure to thrive • Developmental delay • Megaloblastic anemia
Drug-induced orotic aciduria	OMP decarboxylase	• Caused by allopurinol and 6-azauridine • Increased excretion of orotic acid

OMP: orotidine-5-monophosphate
OPRT: orotate phosphoribosyltransferase

References

1. Moffatt, B. A., Ashihara, H. (2002). Purine and pyrimidine nucleotide synthesis and metabolism. https://doi.org/10.1199/tab.0018 (https://doi.org/10.1199/tab.0018)
2. Pedley, A. M., Benkovic, S. J. (2017). A new view into the regulation of purine metabolism: the purinosome. Trends in Biochemical Sciences **42:**141–154. https://doi.org/10.1016/j.tibs.2016.09.009 (https://doi.org/10.1016/j.tibs.2016.09.009)
3. Rodwell V.W. (2018). Metabolism of purine & pyrimidine nucleotides. Chapter 33 of Rodwell V.W., et al. (Ed.), Harper's Illustrated Biochemistry, 31st ed. McGraw-Hill. https://accessmedicine.mhmedical.com/content.aspx?bookid=2386&sectionid=187833691 (https://accessmedicine.mhmedical.com/content.aspx?bookid=2386&sectionid=187833691)
4. Swanson, T., et al. (2010) Nucleotide and porphyrin metabolism. In: Swanson, T., et al. (Eds.), Biochemistry, Molecular Biology and Genetics, 5th ed. Lippincott, Williams & Wilkins, pp. 203–208.