Protein and Nucleic Acid Metabolism:

Lecture #20

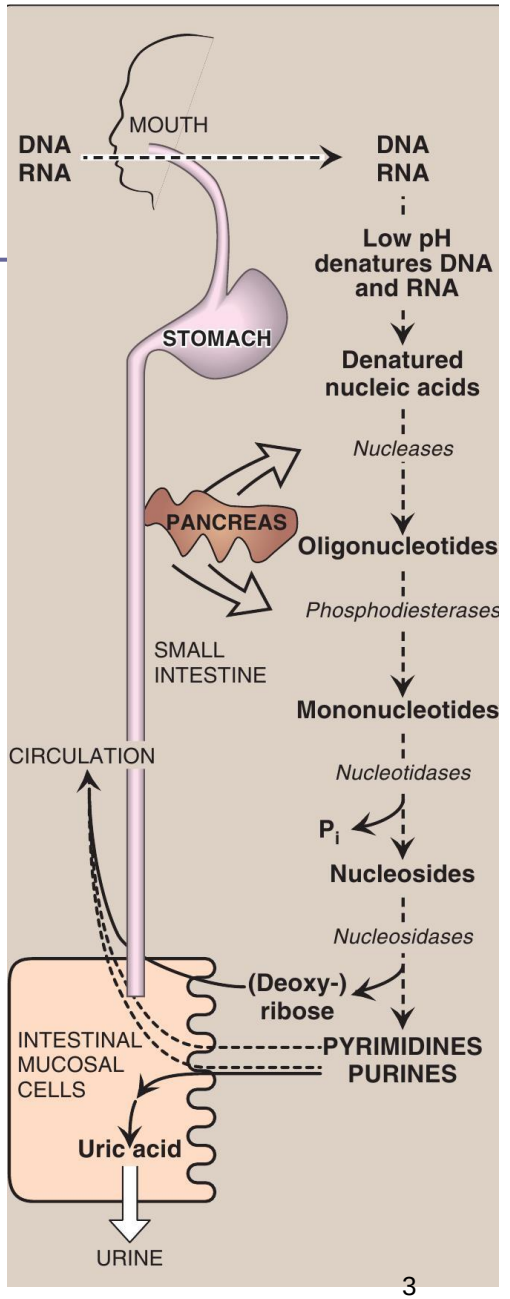
Lecturer: Alexander Koval

Introduction

- The metabolic requirements for the nucleotides and their cognate bases can be met by both dietary intake or synthesis *de novo* from low molecular weight precursors.
- Indeed, the ability to salvage nucleotides from sources within the body alleviates any nutritional requirement for nucleotides, thus the purine and pyrimidine bases are not required in the diet.
  - The salvage pathways are a major source of nucleotides for synthesis of DNA, RNA and enzyme co-factors.

Nucleic Acid Digestion

- Extracellular hydrolysis of ingested nucleic acids occurs through the actions of (**endo)nucleases, phosphodiesterases, nucleotidases** and **nucleosidases**.
  - ***Endonucleases*** degrade DNA and RNA at internal sites leading to the production of oligonucleotides.
  - Oligonucleotides are further digested by ***phosphodiesterases*** yielding free nucleotides.
  - The phosphates are hydrolyzed by ***nucleotidases***, that yield nucleosides.
  - The bases - by ***nucleosidases*,** that yield deoxy(ribose).
  - If the nucleosides and/or bases are not re-utilized the purine bases are further degraded to **uric acid** and the pyrimidines to **β-aminoiosobutyrate, NH_3 and CO_2**.



PRPP Formation

- Both the *salvage* and *de novo* synthesis pathways of purine and pyrimidine biosynthesis lead to production of nucleoside-5'-phosphates through the utilization of an activated sugar intermediate and a class of enzymes called phosphoribosyltransferases.
  - The activated sugar used is **5-phosphoribosyl-1-pyrophosphate, PRPP**.
  - PRPP is generated by the action of **PRPP synthetase** and requires energy in the form of ATP as shown:

ribose-5-phosphate + ATP → PRPP + AMP

  - Note that this reaction releases AMP. Therefore, 2 high energy phosphate equivalents are consumed during the reaction.

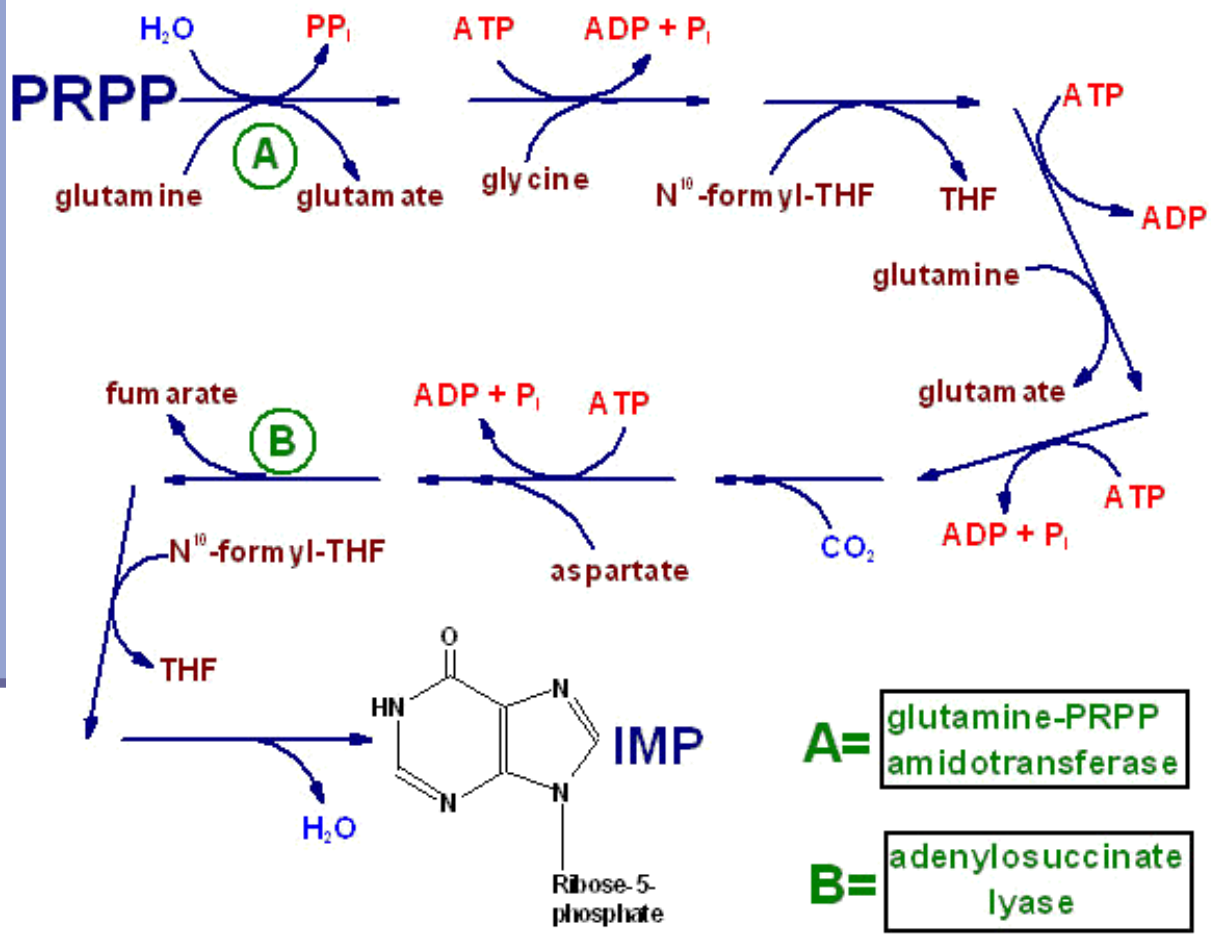
Purine Nucleotide Biosynthesis

- The major site of purine synthesis is in the liver.
- Synthesis of the purine nucleotides begins with PRPP and leads to the first fully formed nucleotide, **inosine 5'-monophosphate (IMP)**.
  - The purine base without the attached ribose moiety is **hypoxanthine.**
  - The purine base is built upon the ribose by several amidotransferase and transformylation reactions.
  - The synthesis of IMP requires five moles of ATP, two moles of glutamine, one mole of glycine, one mole of CO_2, one mole of aspartate and two moles of formate.

Purine Nucleotide Biosynthesis (cont'd)

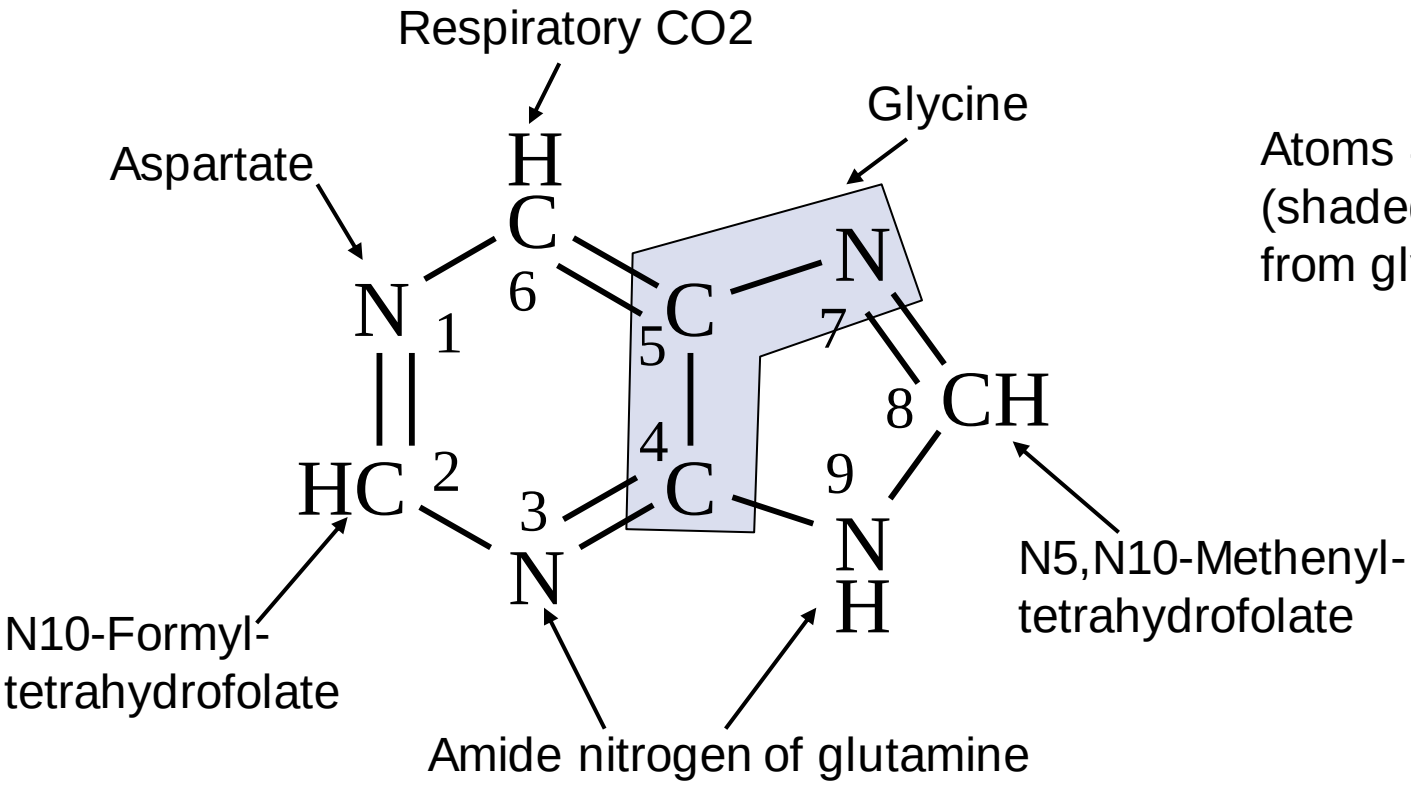
- The formyl moieties are carried on **tetrahydrofolate (THF)** in the form of N^5,N^{10}-methenyl-THF and N^{10}-formyl-THF.
  - IMP represents a branch point for purine biosynthesis, because it can be converted into either AMP or GMP through two distinct reaction pathways.
  - The pathway leading to AMP requires energy in the form of GTP; that leading to GMP requires energy in the form of ATP.
  - The utilization of GTP in the pathway to AMP synthesis allows the cell to control the proportions of AMP and GMP to near equivalence.
  - The accumulation of excess GTP will lead to accelerated AMP synthesis from IMP instead, at the expense of GMP synthesis.
  - Conversely, since the conversion of IMP to GMP requires ATP, the accumulation of excess ATP leads to accelerated synthesis of GMP over that of AMP.

Purine Nucleotides Biosynthesis (cont'd)



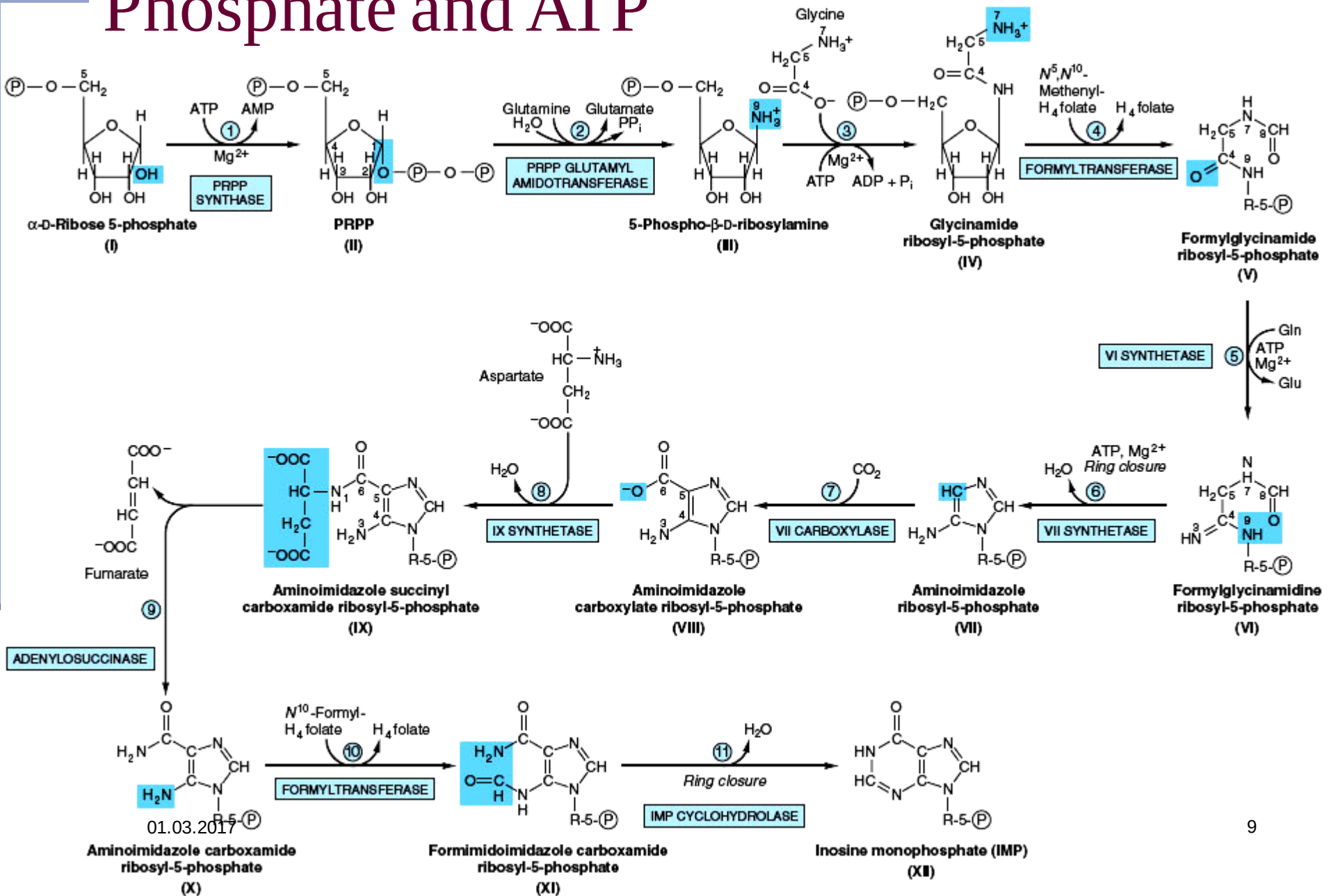
- Synthesis of the first fully formed purine nucleotide **IMP** begins with **PRPP**.
- The two indicated enzymes (A and B) are those catalyzing the rate limiting step and the reaction necessary for the **purine nucleotide cycle,** respectively.

Sources of the Nitrogen and Carbon Atoms of the Purine Ring

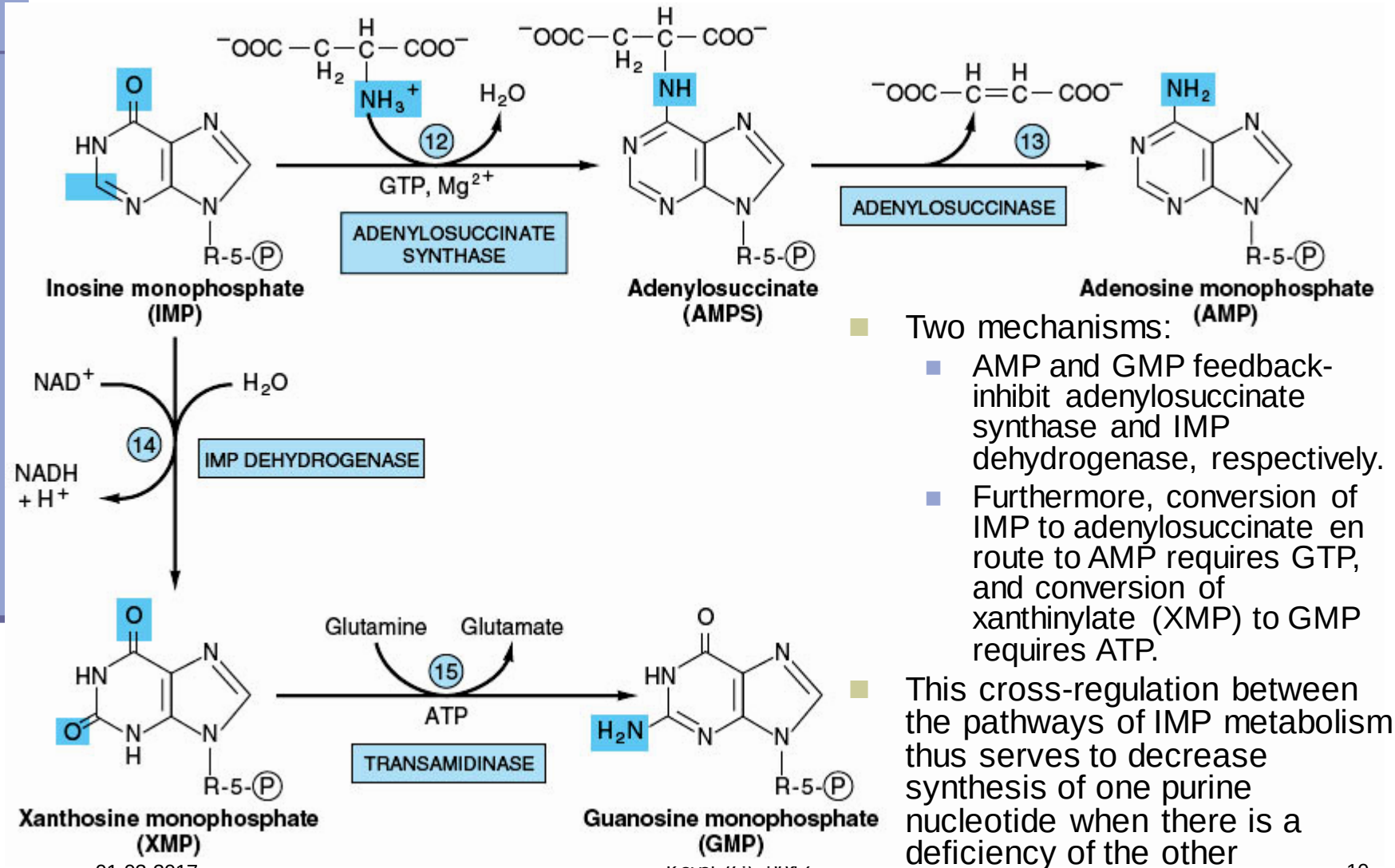


Atoms 4, 5, and 7 (shaded) derive from glycine.

Purine Biosynthesis from Ribose 5-Phosphate and ATP



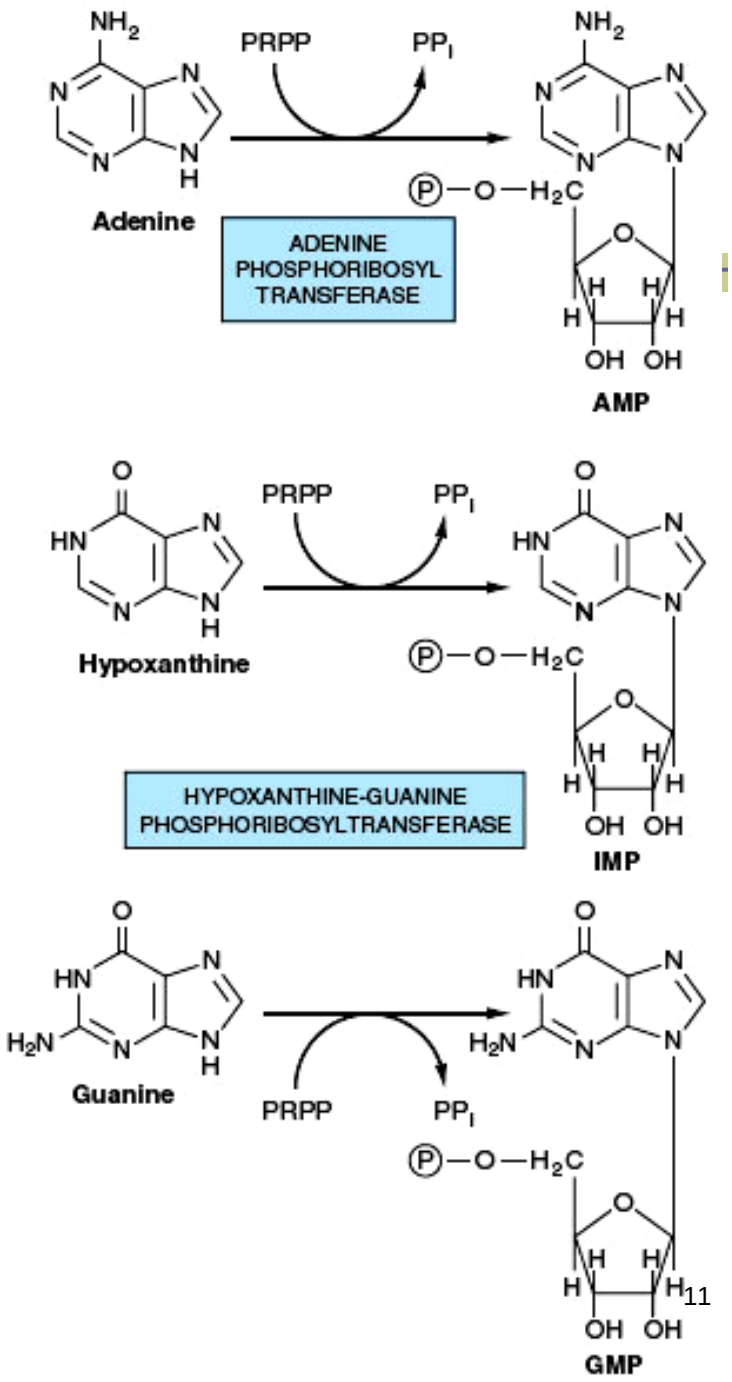
Conversion of IMP to AMP and GMP



- Two mechanisms:
  - AMP and GMP feedback-inhibit adenylosuccinate synthase and IMP dehydrogenase, respectively.
  - Furthermore, conversion of IMP to adenylosuccinate en route to AMP requires GTP, and conversion of xanthinylate (XMP) to GMP requires ATP.
- This cross-regulation between the pathways of IMP metabolism thus serves to decrease synthesis of one purine nucleotide when there is a deficiency of the other nucleotide.

Phosphoribosylation of Adenine, Hypoxanthine, and Guanine

- AMP and GMP also inhibit hypoxanthine-guanine phosphoribosyltransferase, which converts hypoxanthine and guanine to IMP and GMP, and GMP feedback-inhibits PRPP glutamyl amidotransferase.

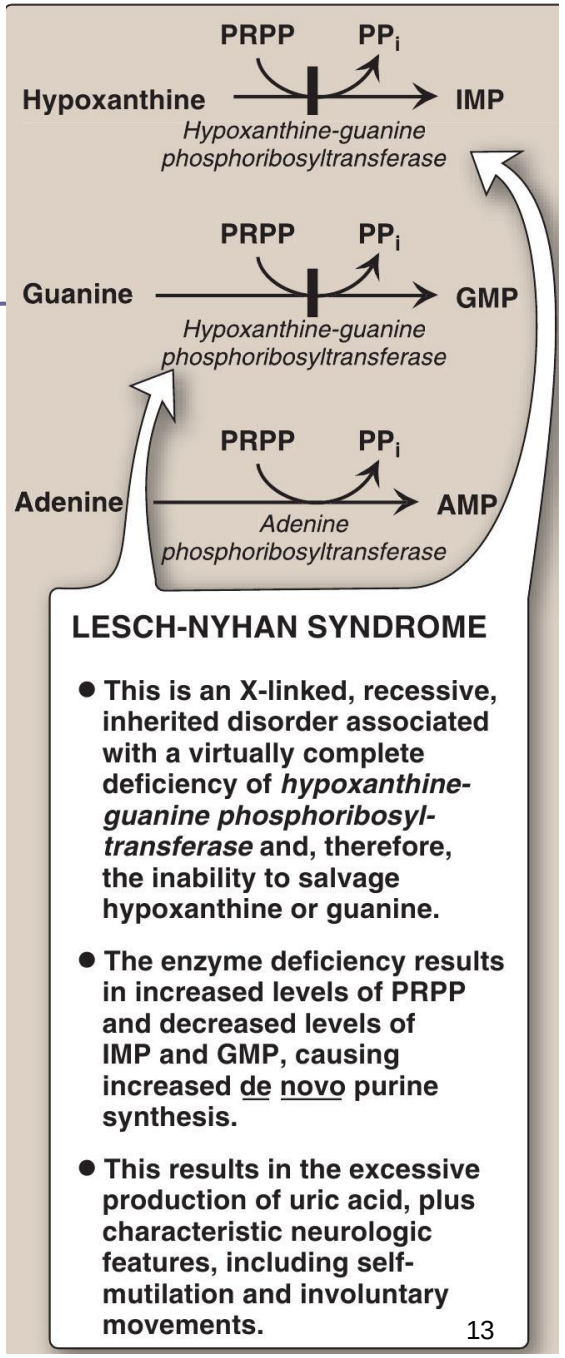


Regulation of Purine Nucleotide Synthesis

- The essential rate limiting steps in purine biosynthesis occur at the first two steps of the pathway. The synthesis of PRPP by PRPP synthetase is feed-back inhibited by purine-5'-nucleotides (predominantly AMP and GMP). Combinatorial effects of those two nucleotides are greatest, e.g., inhibition is maximal when the correct concentration of both adenine and guanine nucleotides is achieved.
- The amidotransferase reaction catalyzed by PRPP amidotransferase is also feed-back inhibited allosterically by binding ATP, ADP and AMP at one inhibitory site and GTP, GDP and GMP at another. Conversely the activity of the enzyme is stimulated by PRPP.
- Additionally, purine biosynthesis is regulated in the branch pathways from IMP to AMP and GMP. The accumulation of excess ATP leads to accelerated synthesis of GMP, and excess GTP leads to accelerated synthesis of AMP.

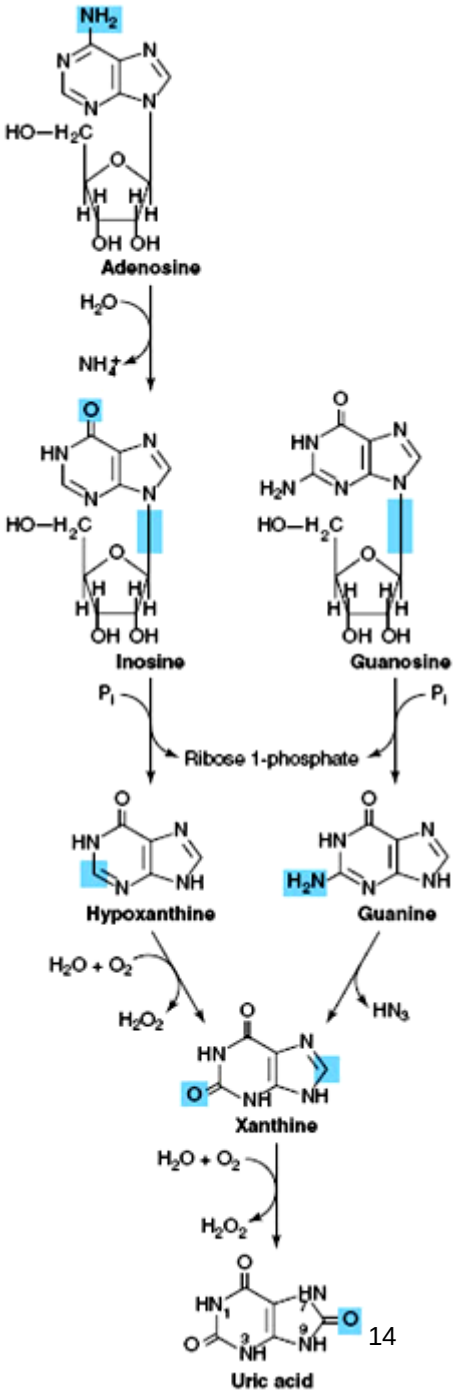
Catabolism and Salvage of Purine Nucleotides

- Catabolism of the purine nucleotides leads to the production of **uric acid** (insoluble, excreted in the urine as sodium urate crystals).
- The synthesis of nucleotides from the purine bases and purine nucleosides takes place in a series of steps known as the **salvage pathways**. The free purine bases – adenine, guanine, and hypoxanthine – can be reconverted to their corresponding nucleotides by phosphoribosylation. Two key transferase enzymes are involved in the salvage of purines: *adenosine phosphoribosyltransferase (APRT)*, and *hypoxanthine-guanine phosphoribosyltransferase (HGPRT)*, which catalyze the following reactions:



Purine Catabolism

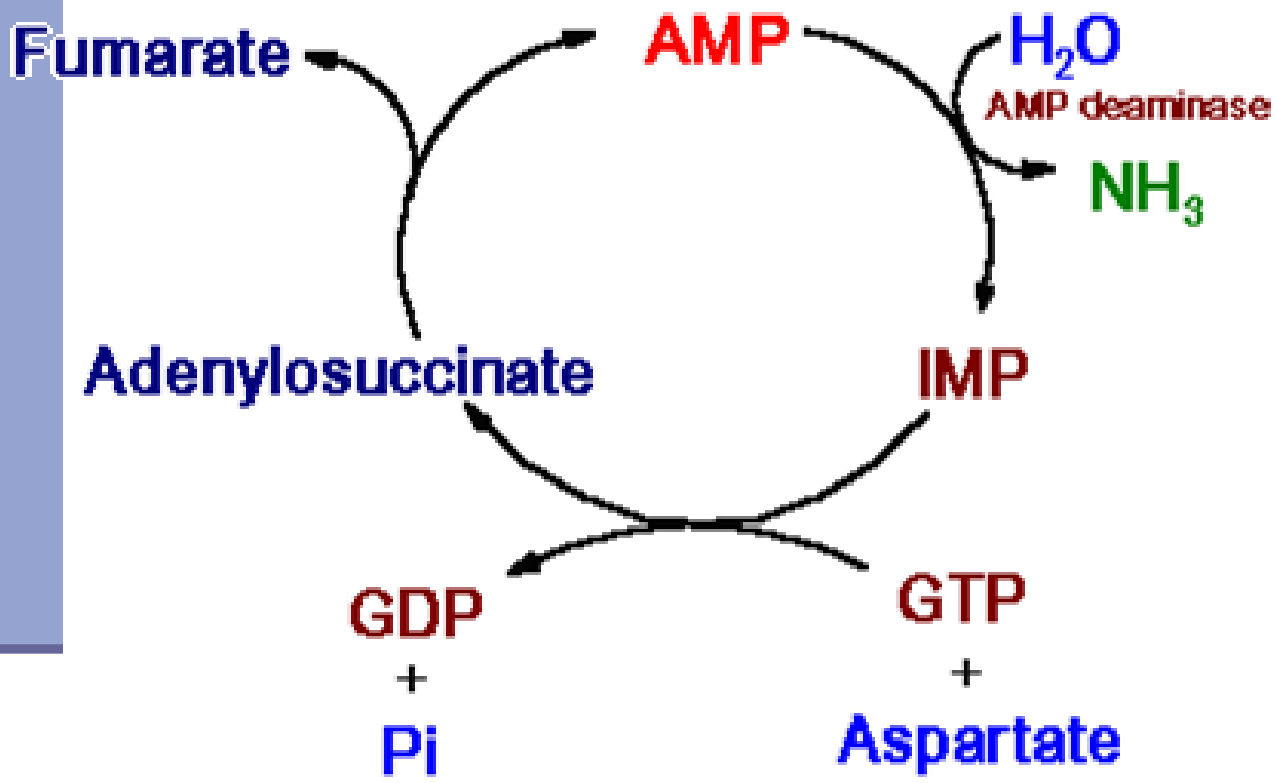
- Formation of uric acid from purine nucleosides by way of the purine bases hypoxanthine, xanthine, and guanine.
- Purine deoxyribonucleosides are degraded by the same catabolic pathway and enzymes, all of which exist in the mucosa of the mammalian gastrointestinal tract.



Purine Nucleotide Cycle

- Purine nucleotide phosphorylases can also contribute to the salvage of the bases through a reversal of the catabolism pathways. However, this pathway is less significant than those catalyzed by the phosphoribosyltransferases.
- The synthesis of AMP from IMP and the salvage of IMP via AMP catabolism have the net effect of deaminating aspartate to fumarate. This process has been termed the **purine nucleotide cycle** (see diagram below). This cycle is very important in muscle cells. Increases in muscle activity create a demand for an increase in the TCA cycle, in order to generate more NADH for the production of ATP. However, muscle lacks most of the enzymes of the major anapleurotic reactions. Muscle replenishes TCA-cycle intermediates in the form of fumarate generated by the purine nucleotide cycle.

Purine Nucleotide Cycle (cont'd)



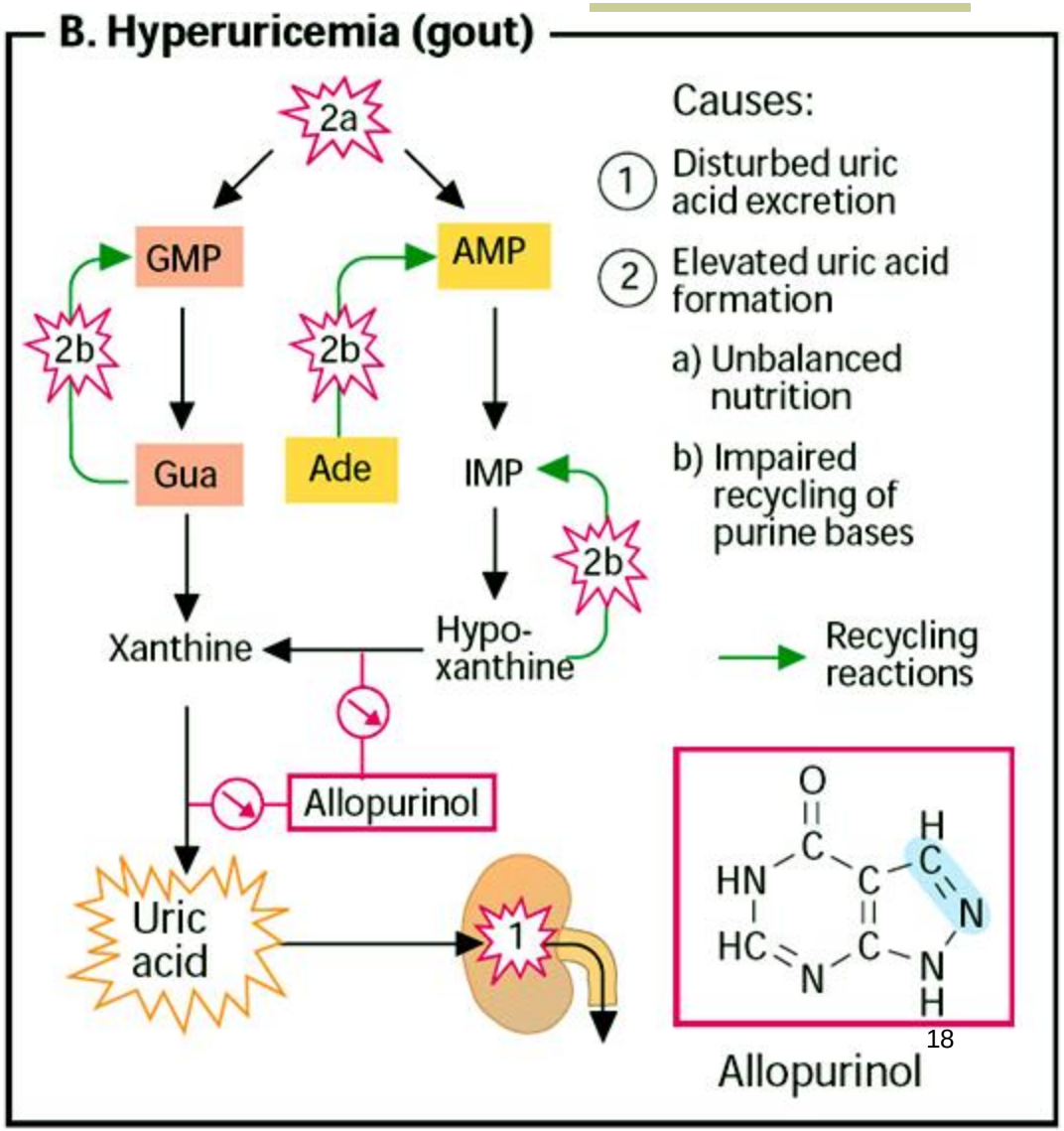
- The **purine nucleotide cycle** serves an important function within exercising muscle. The generation of **fumarate** provides skeletal muscle with its' only source of anapleurotic substrate for the TCA cycle. In order for continued operation of the cycle during exercise, muscle protein must be utilized to supply the amino nitrogen for the generation of aspartate. The generation of asparate occurs by the standard transamination reactions that interconvert amino acids with α-ketoglutarate to form glutamate and glutamate with oxaloacetate to form aspartate. Myoadenylate deaminase is the muscle-specific isoenzyme of AMP deaminase, and deficiencies in myoadenylate deaminase lead to post-exercise fatigue, cramping and myalgias.

Clinical Significances of Purine Metabolism

- Clinical problems associated with nucleotide metabolism in humans are predominantly the result of abnormal catabolism of the purines.
- The clinical consequences of abnormal purine metabolism range from mild to severe and even fatal disorders. Clinical manifestations of abnormal purine catabolism arise from the insolubility of the degradation byproduct, uric acid.

Gout

- Excess accumulation of uric acid leads to hyperuricemia, more commonly known as gout.
  - This condition results from the precipitation of sodium urate crystals in the synovial fluid of the joints, leading to severe inflammation and arthritis.
- Most cases of hyperuricemia are due to disturbed uric acid excretion via the kidneys
  - high-purine diet (e. g., meat).
  - Lesch–Nyhan syndrome, defect in **hypoxanthine phosphoribosyltransferase:** hyperuricemia and severe neurological disorders.
- Hyperuricemia can be treated with allopurinol, a competitive inhibitor of xanthine oxidase.



Lesch-Nyhan syndrome

- Two severe disorders, both quite well described, are associated with defects in purine metabolism: **Lesch-Nyhan syndrome** and **severe combined immunodeficiency disease (SCID)**.
- **Lesch-Nyhan syndrome** results from the loss of a functional HGPRT gene. The disorder is inherited as a sex-linked trait, with the HGPRT gene on the X chromosome (Xq26-q27.2). Patients with this defect exhibit not only severe symptoms of gout but also a severe malfunction of the nervous system. In the most serious cases, patients resort to self-mutilation. Death usually occurs before patients reach their 20th year.

Severe Combined Immunodeficiency Disease (SCID).

- **SCID (severe combined immunodeficiency disease)** is caused by a deficiency in the enzyme **adenosine deaminase (ADA)**. This is the enzyme responsible for converting adenosine to inosine in the catabolism of the purines.
- This deficiency selectively leads to a destruction of B and T lymphocytes, the cells that mount immune responses.
- In the absence of ADA, deoxyadenosine is phosphorylated to yield levels of dATP that are 50-fold higher than normal. The levels are especially high in lymphocytes, which have abundant amounts of the **salvage enzymes**, including nucleoside kinases.
- High concentrations of dATP inhibit ribonucleotide reductase (see below), thereby preventing other dNTPs from being produced. The net effect is to inhibit DNA synthesis.
- Since lymphocytes must be able to proliferate dramatically in response to antigenic challenge, the inability to synthesize DNA seriously impairs the immune responses, and the disease is usually fatal in infancy unless special protective measures are taken.
- A less severe immunodeficiency results when there is a lack of **purine nucleoside phosphorylase (PNP)**, another purine-degradative enzyme.

Glycogenoses

- **von Gierke's disease** (glycogen storage diseases) leads to excessive uric acid production.
  - result of low glucose 6-phosphatase activity.
  - ↑ glucose-6-phosphate → ↑ pentose phosphate pathway (PPP), → ↑ ribose-5-phosphate and ↑ PRPP → ↑ purine biosynthesis.

Other Disorders of Purine Metabolism

Disorder	Defect	Nature of Defect	Comments
Gout	PRPP synthetase	increased enzyme activity due to elevated Vmax	hyperuricemia
Gout	PRPP synthetase	enzyme is resistant to feed-back inhibition	hyperuricemia
Gout	PRPP synthetase	enzyme has increased affinity for ribose-5-phosphate (lowered K_m)	hyperuricemia
Gout	PRPP amidotransferase	loss of feed-back inhibition of enzyme	hyperuricemia
Gout	HGPRT[a]	partially defective enzyme	hyperuricemia
Lesch-Nyhan syndrome	HGPRT	lack of enzyme	see above

Other Disorders of Purine Metabolism (cont'd)

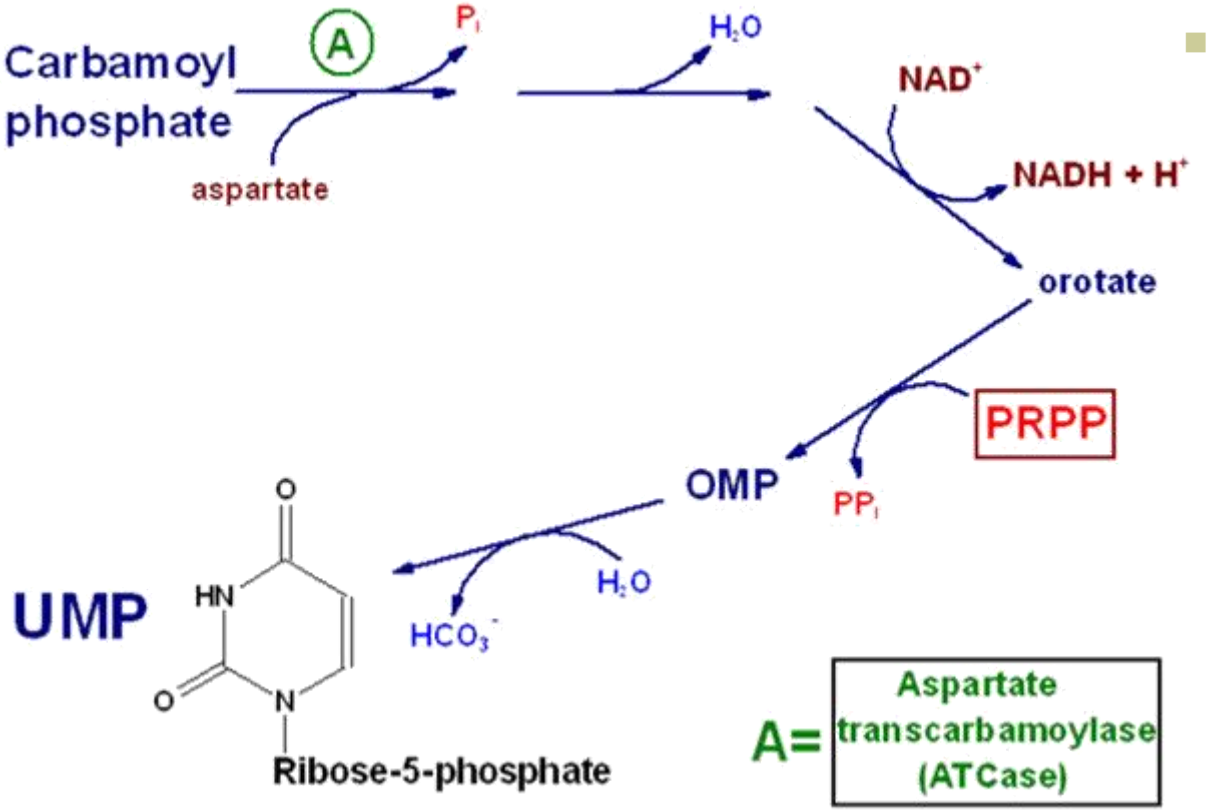
Disorder	Defect	Nature of Defect	Comments
SCID	ADA[b]	lack of enzyme	see above
Immuno-deficiency	PNP[c]	lack of enzyme	see above
Renal lithiasis	APRT[d]	lack of enzyme	2,8-dihydroxyadenine renal lithiasis
Xanthinuria	Xanthine oxidase	lack of enzyme	hypouricemia and xanthine renal lithiasis
von Gierke's disease	Glucose-6-phosphatase	enzyme deficiency	see above

[a]Hypoxanthine-guanine phosphoribosyltransferase; [b]adenosine deaminase; [c]purine nucleotide phosphorylase; [d]adenosine phosphoribosyltransferase

Pyrimidine Nucleotide Biosynthesis

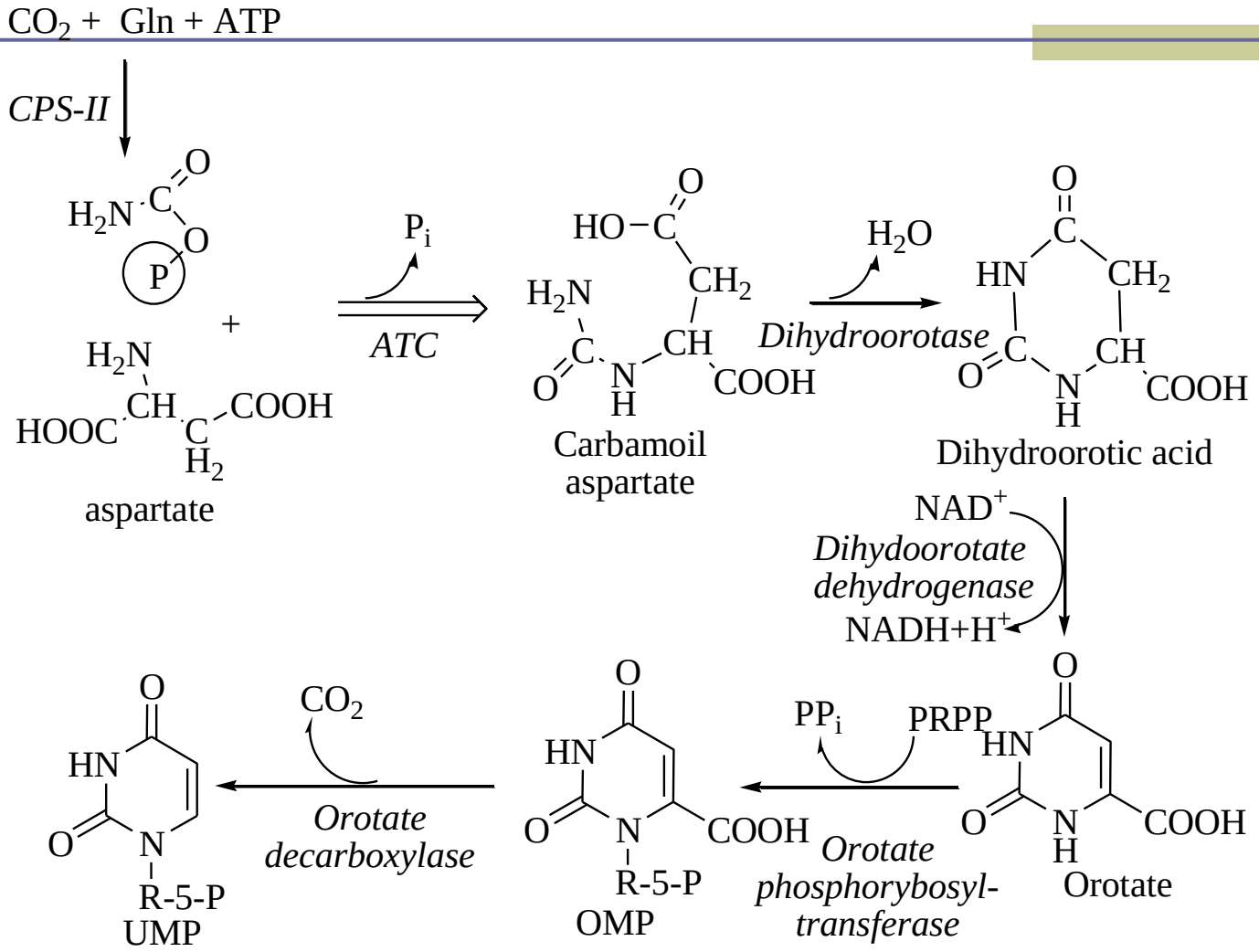
- Synthesis of the pyrimidines is less complex than that of the purines, since the base is much simpler. The first completed base is derived from 1 mole of glutamine, one mole of ATP and one mole of CO_2 (which form **carbamoyl phosphate**) and one mole of aspartate. An additional mole of glutamine and ATP are required in the conversion of UTP to CTP. The pathway of pyrimidine biosynthesis is diagrammed below.
- The carbamoyl phosphate used for pyrimidine nucleotide synthesis is derived from glutamine and bicarbonate, within the cytosol, as opposed to the urea cycle carbamoyl phosphate derived from ammonia and bicarbonate in the mitochondrion. The urea cycle reaction is catalyzed by carbamoyl phosphate synthetase I (CPS-I) whereas the pyrimidine nucleotide precursor is synthesized by **CPS-II**. Carbamoyl phosphate is then condensed with aspartate in a reaction catalyzed by the rate limiting enzyme of pyrimidine nucleotide biosynthesis, aspartate transcarbamoylase (ATCase).
- The synthesis of pyrimidines differs in two significant ways from that of purines. First, the ring structure is assembled as a free base, not built upon PRPP. PRPP is added to the first fully formed pyrimidine base (**orotic acid**), forming **orotate monophosphate (OMP)**, which is subsequently decarboxylated to UMP. Second, there is no branch in the pyrimidine synthesis pathway. UMP is phosphorylated twice to yield UTP (ATP is the phosphate donor). The first phosphorylation is catalyzed by uridylate kinase and the second by ubiquitous nucleoside diphosphate kinase. Finally UTP is aminated by the action of CTP synthase, generating CTP. The thymine nucleotides are in turn derived by de novo synthesis from dUMP or by salvage pathways from deoxyuridine or deoxythymidine.

Synthesis of UMP from carbamoyl phosphate

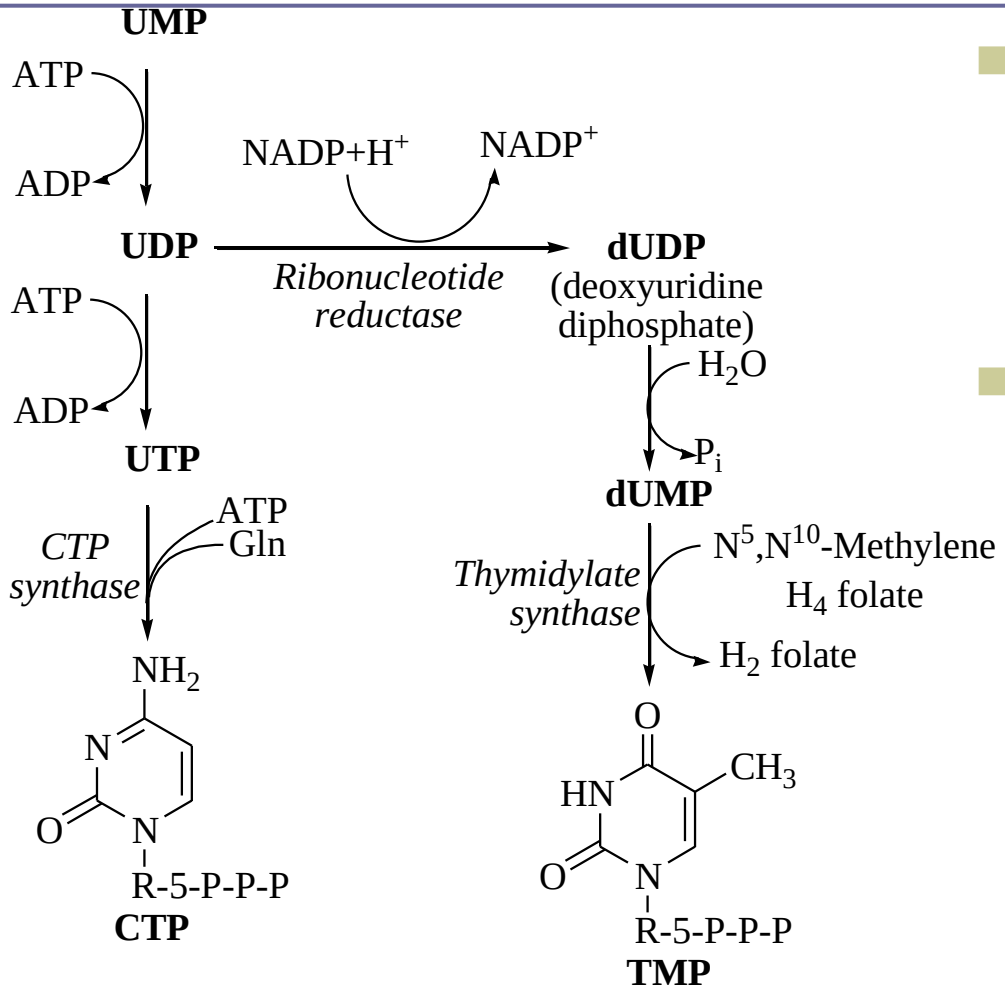


- Carbamoyl phosphate utilized in pyrimidine nucleotide synthesis differs from that synthesized in the urea cycle; it is synthesized from glutamine instead of ammonia and is synthesized in the cytosol. The reaction is catalyzed by carbamoyl phosphate synthetase II (**CPS-II**). Subsequently carbamoyl phosphate is incorporated into the pyrimidine nucleotide biosynthesis pathway through the action of aspartate transcarbamoylase (ATCase) which is the rate limiting step in pyrimidine biosynthesis. Following completion of UMP synthesis it can be phosphorylated to UTP and utilized as a substrate for CTP synthase for the synthesis of CTP. Uridine nucleotides are also the precursors for *de novo* synthesis of the thymine nucleotides.

Synthesis of UMP (reactions)



Synthesis of CTP and TMP



- The de novo pathway to dTTP synthesis first requires the use of dUMP from the metabolism of either UDP or CDP.
- The dUMP is converted to dTMP by the action of ***thymidylate synthase***. The methyl group (recall that thymine is 5-methyl uracil) is donated by tetrahydrofolate, similarly to the donation of methyl groups during the biosynthesis of the purines.

Synthesis of the Thymine Nucleotides

- The salvage pathway to dTTP synthesis involves the enzyme ***thymidine kinase*** which can use either thymidine or deoxyuridine as substrate:

thymidine + ATP <------> TMP + ADP

deoxyuridine + ATP <-------> dUMP + ADP

- The activity of thymidine kinase (one of the various deoxyribonucleotide kinases) is unique in that it fluctuates with the cell cycle, rising to peak activity during the phase of DNA synthesis; it is inhibited by dTTP.

Clinical Relevance of Tetrahydrofolate

- Tetrahydrofolate (THF) is regenerated from the dihydrofolate (DHF) product of the thymidylate synthase reaction by the action of dihydrofolate reductase (DHFR), an enzyme that requires NADPH. Cells that are unable to regenerate THF suffer defective DNA synthesis and eventual death. For this reason, as well as the fact that dTTP is utilized only in DNA, it is possible therapeutically to target rapidly proliferating cells over non-proliferative cells through the inhibition of thymidylate synthase. Many anti-cancer drugs act directly to inhibit thymidylate synthase, or indirectly, by inhibiting DHFR.
- The class of molecules used to inhibit thymidylate synthase is called the **suicide substrates**, because they irreversibly inhibit the enzyme. Molecules of this class include **5-fluorouracil** and **5-fluorodeoxyuridine**.
  - Both are converted within cells to **5-fluorodeoxyuridylate**, **FdUMP**. It is this drug metabolite that inhibits thymidylate synthase.
  - Many DHFR inhibitors have been synthesized, including **methotrexate**, **aminopterin**, and **trimethoprim**. Each of these is an analog of folic acid.

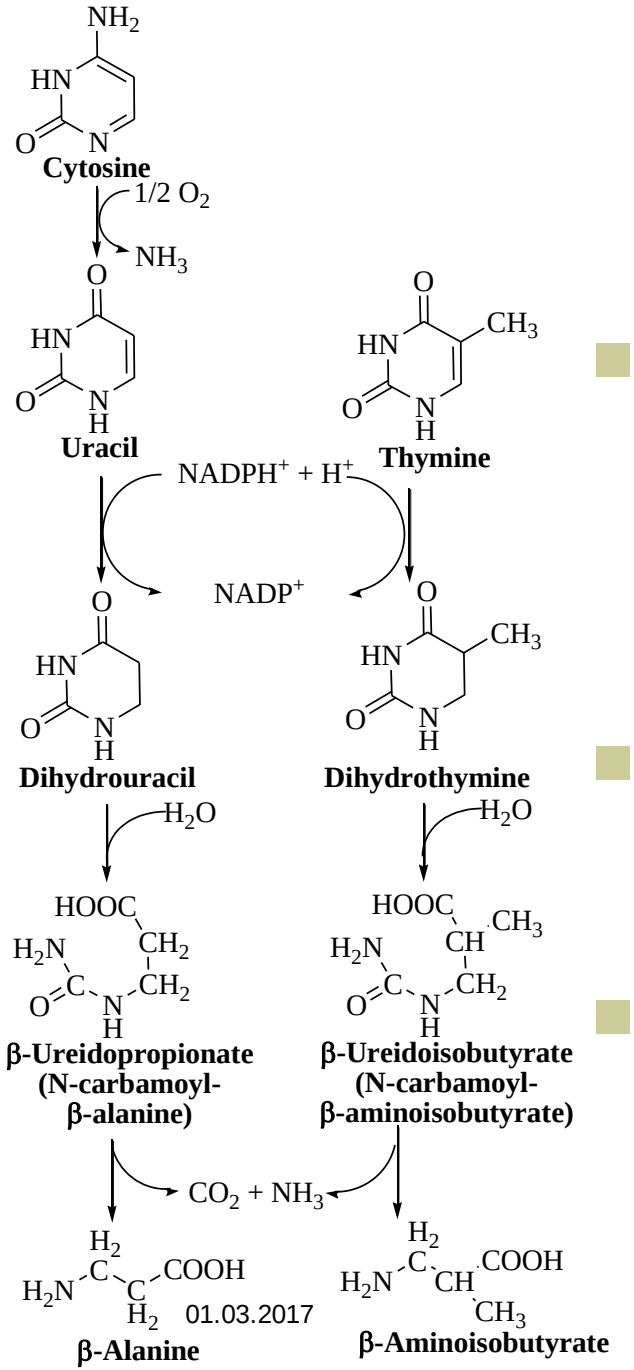
Regulation of Pyrimidine Biosynthesis

- The regulation of pyrimidine synthesis occurs mainly at the first step which is catalyzed by aspartate transcarbamoylase, ATCase. Inhibited by CTP and activated by ATP, ATCase is a multifunctional protein in mammalian cells. It is capable of catalyzing the formation of **carbamoyl phosphate**, **carbamoyl aspartate**, and **dihydroorotate**. The carbamoyl synthetase activity of this complex is termed carbamoyl phosphate synthetase II (CPS-II) as opposed to CPS-I, which is involved in the **urea cycle**. ATCase, and therefore the activity of CPS-II, is localized to the cytoplasm and prefers glutamine as a substrate. CPS-I of the urea cycle is localized in the mitochondria and utilizes ammonia. The CPS-II domain is activated by ATP and inhibited by UDP, UTP, dUTP, and CTP.
- The role of glycine in ATCase regulation is to act as a competitive inhibitor of the glutamine binding site. As in the regulation of purine synthesis, ATP levels also regulate pyrimidine biosynthesis at the level of PRPP formation. An increase in the level of PRPP results in an activation of pyrimidine synthesis.
- There is also regulation of OMP decarboxylase: this enzyme is competitively inhibited by UMP and, to a lesser degree, by CMP. Finally, CTP synthase is feedback-inhibited by CTP and activated by GTP.

Catabolism and Salvage of Pyrimidine Nucleotides

- The end products of pyrimidine catabolism are water-soluble:
  - CO_2,
  - NH_3,
  - β-alanine,
  - β-aminoisobutyrate.
- Excretion of β-aminoisobutyrate increases in leukemia and severe x-ray radiation exposure
  - to increased destruction of DNA.
- Chinese or Japanese people routinely excrete β-aminoisobutyrate.
  - Humans probably transaminate β-aminoisobutyrate to methylmalonate semialdehyde, which then forms succinyl-CoA.
- **Pseudouridine is excreted unchanged**.
  - no human enzyme catalyzes hydrolysis or phosphorolysis of pseudouridine.

Catabolism of Pyrimidine Nucleotides



- **The catabolism** leads to
  - **β-alanine** (when CMP and UMP are degraded) or
  - **β-aminoisobutyrate** (when dTMP is degraded) and NH_3 and CO_2.
- The products then converted to **malonyl-CoA**
  - diverted to fatty acid synthesis
- or **methylmalonyl-CoA**
  - converted to succinyl-CoA
  - can be shunted to the TCA cycle).

The Salvage of Pyrimidine Bases

- Less clinical significance than that of the purines,
  - the solubility of the by-products.
- The salvage pathway to thymidine nucleotide synthesis is important for cell division.
- Uracil can be salvaged to form UMP by the action of **uridine phosphorylase** and **uridine kinase**:

uracil + ribose-1-phosphate <---------> uridine + P_i

uridine + ATP ----------> UMP + ADP

Deoxyuridine and Deoxycytidine Salvage

- Deoxyuridine is also a substrate for uridine phosphorylase. Formation of dTMP, by salvage of dTMP requires thymine phosphorylase and the previously encountered thymidine kinase:

thymine + deoxyribose-1-phosphate <---------> thymidine + P_i

thymidine + ATP ---------> dTMP + ADP

- The salvage of deoxycytidine is catalyzed by deoxycytidine kinase:

deoxycytidine + ATP <--------> dCMP + ADP

Clinical Significances of Pyrimidine Metabolism

- Few disorders
- In pyrimidine biosynthesis:
  - deficiencies in the bifunctional enzyme (orotate phosphoribosyl transferase + OMP decarboxylase).
  - Result: **orotic aciduria:**
    - retarded growth,
    - severe anemia.
    - leukopenia.
  - Treatment:
    - uridine and/or cytidine ➔ ↑UMP ➔ ↓CPS-II ➔ ↓orotic acid production.

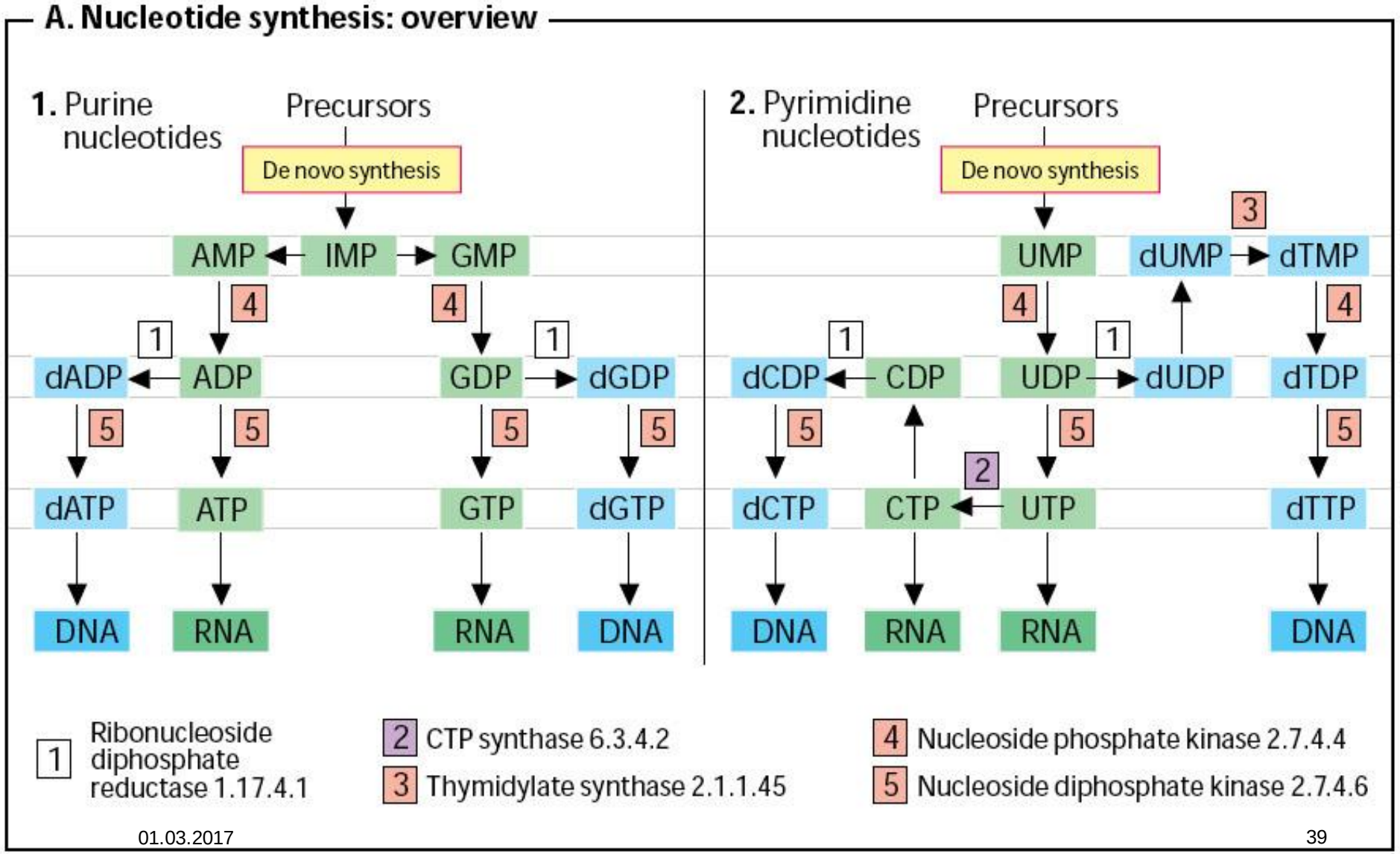
Disorders of Pyrimidine Metabolism

Disorder	Defective Enzyme	Comments
Orotic aciduria, Type I	orotate phosphoribosyl transferase and OMP decarboxylase	see above
Orotic aciduria, Type II	OMP decarboxylase	see above
Orotic aciduria (mild, no hematologic component)	the urea cycle enzyme, ornithine transcarbamoylase, is deficient	increased mitochondrial carbamoyl phosphate exits and augments pyrimidine biosynthesis; hepatic encephalopathy
β-aminoisobutyric aciduria	Transaminase, affects urea cycle function during deamination of α-amino acids to of α-keto acids	benign, frequent in Orientals
Drug induced orotic aciduria	OMP decarboxylase	Allopurinol and 6-azauridine treatments cause orotic acidurias without a hematologic component; their catabolic by-products inhibit OMP decarboxylase

Formation of Deoxyribonucleotides

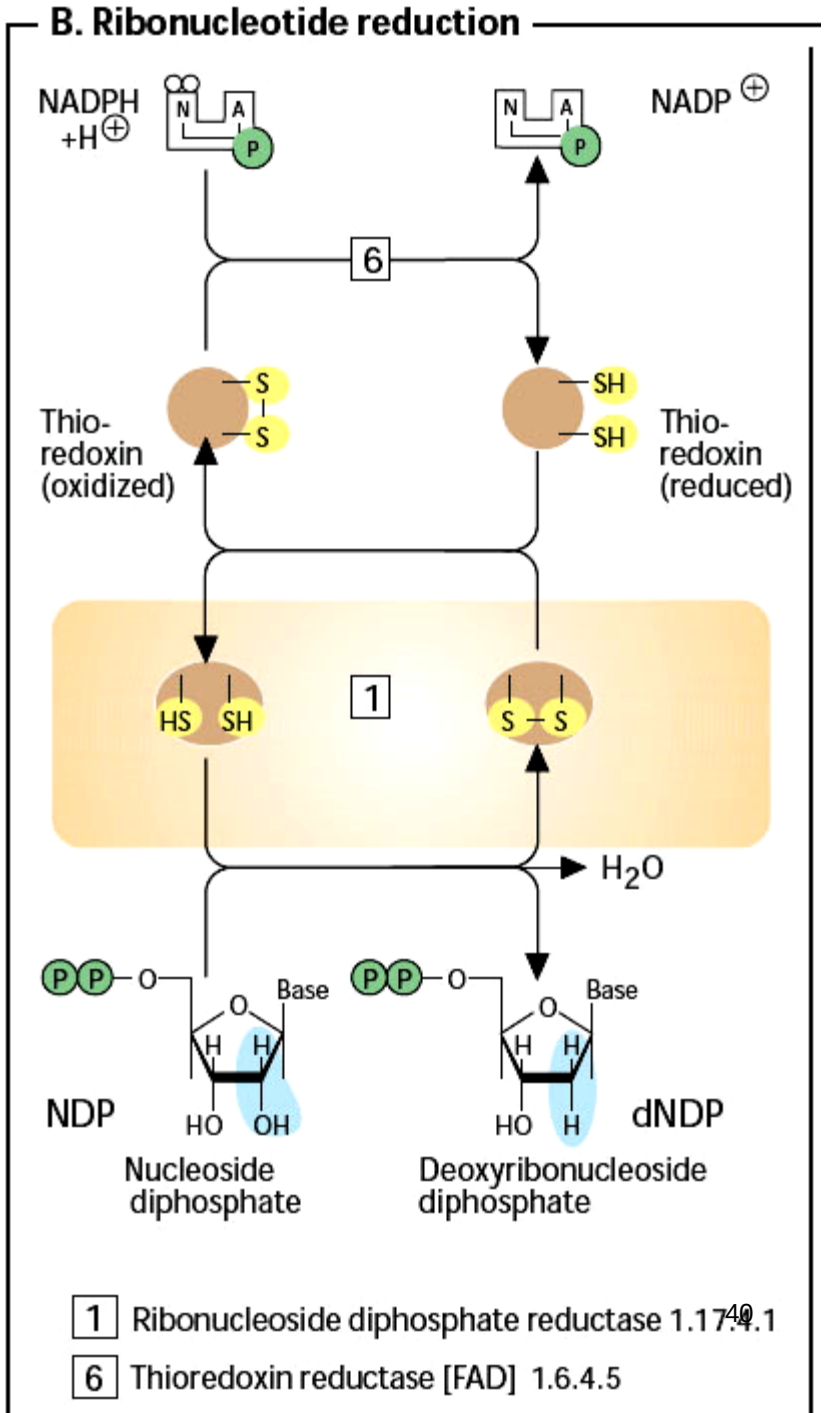
- The typical cell contains 5-10 times as much RNA (mRNAs, rRNAs and tRNAs) as DNA.
- For cells proliferation the production of dNTPs is also necessary.
  - the reduction of rNDPs,
  - phosphorylation to yield the dNTPs.
    - The phosphorylation of dNDPs to dNTPs is catalyzed by the same nucleoside diphosphate kinases that phosphorylates rNDPs to rNTPs, using ATP as the phosphate donor.

Nucleotide Synthesis



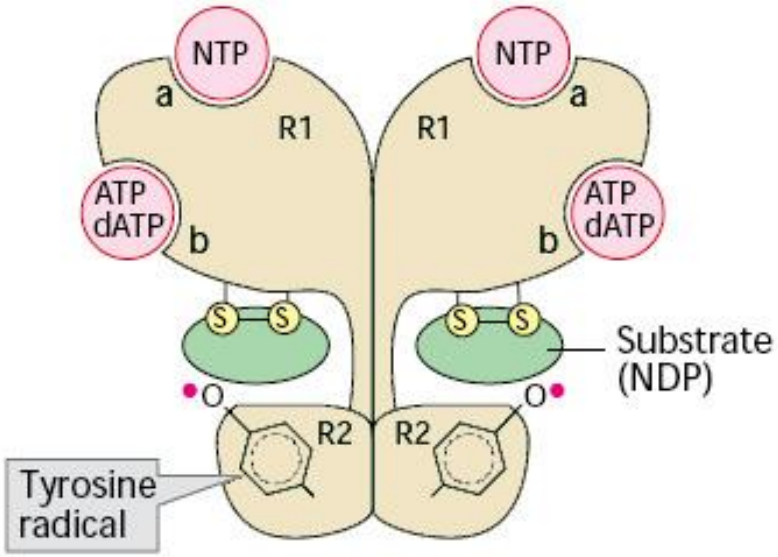
Ribonucleotide Reductase

- **Ribonucleotide reductase** (RR):
  - multifunctional enzyme
  - contains redox-active **thiol** groups for the transfer of electrons.
  - RR becomes oxidized.
  - RR is reduced, by either thioredoxin or glutaredoxin.
  - The ultimate source of the electrons is NADPH.
  - The complex series of steps involves enzymes that regenerate the reduced forms of ***thioredoxin*** or ***glutaredoxin*** by **thioredoxin reductase** and **glutathione reductase** respectively.

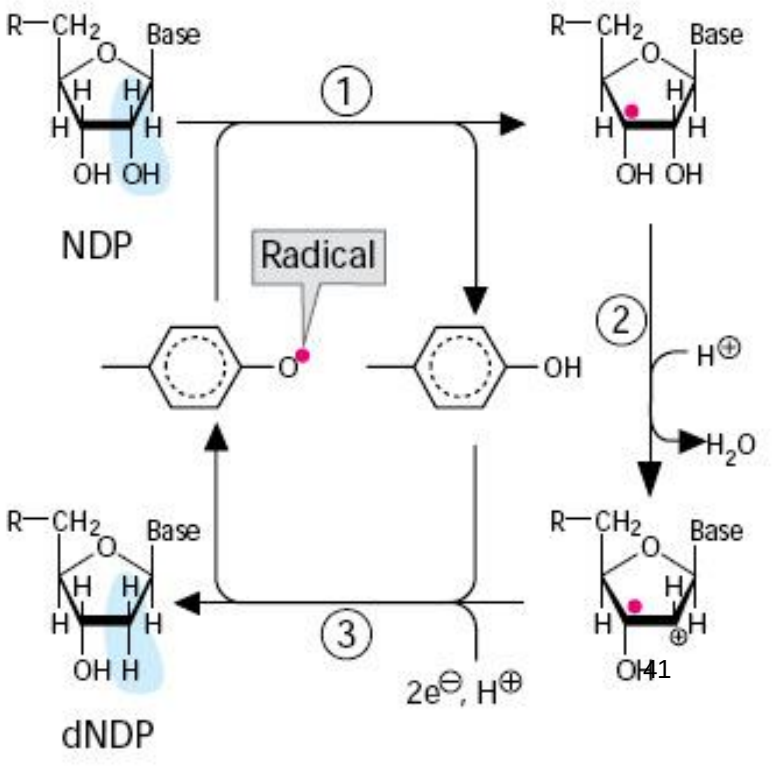


Ribonucleotide Reductase (Mechanism)

- In eukaryotes, ribonucleotide reductase is a tetramer consisting of two R1 and two R2 subunits.
- **Tyrosine radical** in the enzyme also participates in the reaction (**2**).
  - initially produces a substrate radical (**3**).
  - This cleaves a water molecule and thereby becomes **radical cation**.
  - Finally, the **deoxyribose** residue is produced by reduction, and the tyrosine radical is regenerated.



2. Ribonucleotide reductase



Regulation of dNTP Formation

- **Ribonucleotide reductase** is the only enzyme used in the generation of all the deoxyribonucleotides. Therefore, its activity and substrate specificity must be tightly regulated to ensure balanced production of all four of the dNTPs required for DNA replication.
- Such regulation occurs by binding of nucleoside triphosphate effectors to either the activity sites or the specificity sites of the enzyme complex.
- The activity sites bind either ATP or dATP with low affinity, whereas the specificity sites bind ATP, dATP, dGTP, or dTTP with high affinity. The binding of ATP at activity sites leads to increased enzyme activity, while the binding of dATP inhibits the enzyme.
- The binding of nucleotides at specificity sites effectively allows the enzyme to detect the relative abundance of the four dNTPs and to adjust its affinity for the less abundant dNTPs, in order to achieve a balance of production. thioredoxin reductase and glutathione reductase respectively.

Interconversion of the Nucleotides

- During the catabolism of nucleic acids, nucleoside mono- and diphosphates are released.
- The nucleosides do not accumulate to any significant degree, owing to the action of nucleoside kinases.
- These include both nucleoside monophosphate (NMP) kinases and nucleoside diphosphate (NDP) kinases.
- The NMP kinases catalyze ATP-dependent reactions of the type:

(d)NMP + ATP <---------> (d)NDP + ADP

NMP Kinases

- There are four classes of NMP kinases that catalyze, respectively, the phosphorylation of:
  1. AMP and dAMP; this kinase is known as **adenylate kinase**.
  2. GMP and dGMP.
  3. CMP, UMP and dCMP.
  4. dTMP.
- The enzyme **adenylate kinase** is important for ensuring adequate levels of energy in cells such as liver and muscle. The predominant reaction catalyzed by adenylate kinase is:

2ADP <-------> AMP + ATP

NDP Kinases Reactions

- The **NDP kinases** catalyze reaction of the type:

$$N_1TP + N_2DP \leftrightarrow N_1DP + N_2TP$$

  - N_1 can represent a purine ribo- or deoxyribonucleotide; N_2 a pyrimidine ribo- or deoxyribonucleotide.
  - The activity of the NDP kinases can range from 10 to 100 times higher than that of the NMP kinases.
  - This difference in activity maintains a relatively high intracellular level of (d)NTPs relative to that of (d)NDPs.
  - Unlike the substrate specificity seen for the NMP kinases, the NDP kinases recognize a wide spectrum of (d)NDPs and (d)NTPs.


Thank you
for your attention