SECTION 9
Nucleic Acid Metabolism

CONTACT INFORMATION

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OBJECTIVES

- Describe the difference between a pyrimidine and a purine base, discern a nucleoside from a nucleotide, and name the sugars found in nucleotides.

- List the names of the common purine and pyrimidine bases and nucleosides.

- Explain why deficiency of glucose 6-phosphate dehydrogenase (G6PD) can result in hemolytic anemia.

- Describe the roles of vitamin B12 and the folate coenzymes in nucleotide metabolism, and name the processes that these play.

- Compare and contrast deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

- Describe the structure of nucleic acids.

- Name the functions of DNA and RNA.

- Explain the relationship between nucleic acid metabolism and gout.

ANTI-OBJECTIONS

- Chemical and metabolic deficiencies (see the strategies for treating these)

- Ansatz for understanding the role of nucleic acid metabolism in disease
Some of the material in this chapter provides important foundation for content in future blocks, but will not be covered on the Immunology exam. You may wish to return to this chapter in I-3 Micro to address anti-folate antibacterial drugs and the risks of use of antimalarial drugs in individuals with G6PD deficiency. Both of these topics will come up again in M3 with regard to hematology and cancer treatment. So this is a good time to establish a basic foundation!

**KEY WORDS**

- **ADENOSINE DEAMINASE (ADA)**
- **LESCH-NYHAN SYNDROME**
- **ALLOPURINOL**
- **NUCLEOSIDE**
- **ANEMIA**
- **NUCLEOTIDE**
- **COBALAMIN (VITAMIN B12)**
- **ONE-CARBON GROUPS**
- **DIHYDROFOLATE REDUCTASE (DHFR)**
- **PENTOSE PHOSPHATE PATHWAY**
- **FOLATE**
- **PRPP (5-PHOSPHORIBOSYL-1-PYROPHOSPHATE)**
- **FOLIC ACID**

**I. OVERVIEW**

Nucleotide metabolism plays a crucial role in cellular energetics and serves as a primary source of reducing equivalents. The pathways of nucleotide metabolism are complex and multifaceted, involving a variety of enzymes and intermediators. This chapter will provide an overview of the key processes and mechanisms involved in nucleotide metabolism, including the synthesis, degradation, and salvage of nucleotides, as well as their role in energy production and cellular signaling. Each section will be detailed with an explanation of the biological context and functional significance of the processes discussed. The emphasis will be placed on understanding the regulatory mechanisms that govern nucleotide metabolism, including allosteric effects of substrate concentrations and co-factors on enzyme activity.
NUCLEIC ACID METABOLISM

Nucleotide metabolism involves several interconnected pathways (Figure 2.8). Nucleotides can be synthesized de novo, or from components “salvaged” from the degradation products of nucleic acids. When in excess, nucleotides are degraded to products that can either be consumed by other pathways or excreted. Defects in the pathways for de novo synthesis, salvage, and degradation of nucleotides result in clinical disorders, and many drugs target these pathways.

FIGURE 2.8 Overview of Nucleotide Metabolism

REVIEW

A nucleotide consists of a pentose sugar (ribose or deoxyribose), a phosphate group, and a purine or pyrimidine base (Figure 2.10). A nucleoside is a nucleotide that contains a pentose sugar and a base, but is not phosphorylated.

FIGURE 2.10 Structure of a nucleotide.
phosphate group at the 5' position either a nucleotide or a nucleoside 5'-monophosphate. The 8 major species of nucleoside triphosphates are listed in Table 1.

![Diagram of nucleotide structures](image)

**Figure 2.10** Component sugars and bases of the common nucleotides.

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Table 1: Common nucleoside triphosphates.

<table>
<thead>
<tr>
<th>Nucleoside Triphosphates</th>
<th>Names of Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bases</td>
</tr>
<tr>
<td>Ribonucleotides</td>
<td></td>
</tr>
<tr>
<td>Adenosine triphosphate (ATP)</td>
<td>Adenine</td>
</tr>
<tr>
<td>Guanosine triphosphate (GTP)</td>
<td>Guanine</td>
</tr>
<tr>
<td>Cytidine triphosphate (CTP)</td>
<td>Cytosine</td>
</tr>
<tr>
<td>Uridine triphosphate (UTP)</td>
<td>Uracil</td>
</tr>
<tr>
<td>Deoxyribonucleotides</td>
<td></td>
</tr>
<tr>
<td>Deoxyadenosine triphosphate (dATP)</td>
<td>Adenine</td>
</tr>
<tr>
<td>Deoxyguanosine triphosphate (dGTP)</td>
<td>Guanine</td>
</tr>
<tr>
<td>Deoxyctydine triphosphate (dCTP)</td>
<td>Cytosine</td>
</tr>
<tr>
<td>Deoxothymidine triphosphate (dTPP)</td>
<td>Thymine</td>
</tr>
</tbody>
</table>

Given that the metabolism of nucleotides has evolved to eight distinct pathways, modular simplicity is understood to characterize each pathway, allowing the overexpression of each enzyme. While we have discussed the metabolism of nucleotides and the concentration of AMP to serve as a relatively stable signal of changes in the energy state, the concentration of AMP decreased in the analysis of purine and pyrimidine bases by the control of pathways. This demonstrates an adaptive system, increasing their concentrations in the construction of new materials.
in is by addressing the synthesis of the 5-carbon sugar ribose.

**FIGURE 2.11 De novo nucleotide synthesis “big picture.”**

B. THE PHASE 1 RESPONSE

1. **OVERVIEW**
   
   Synthesis of ribose 5-phosphate from glucose 6-phosphate (also called the pentose phosphate pathway) is a major component of anabolism, but also indicates that glucose metabolism is the first step in nucleotide synthesis.

   The pentose phosphate pathway of cells. This is used in both anabolic and non-oxidative metabolic pathways, and less independent. It then converts glucose 6-phosphate and produces ribose 5-phosphate. The steps in the pathway are metabolically irreversible and the phosphoribose is a high NAD+ substrate important in enzymes otherwise. Enzymes such as ribulose-5-phosphate (testes, ovary, etc.)
tathione (erythrocytes; a key reaction in protection from oxidative damage). Further utilization of ribulose 5 phosphate occurs via reversible non-oxidative reactions. In cells that have large needs for nucleotides, most of the ribulose 5-phosphate is converted to ribose 5-phosphate and used for nucleotide biosynthesis. In cells that need more NADPH than nucleotides, the excess ribulose 5-phosphate is converted to compounds that enter glycolysis in a series of reversible reactions (not shown).

2. G6PD

Interesting side effects in this pathway arise from an inherited deficiency NADPH in sickle cell disease on exposure to microbiological organisms in the yeast.

The first NADPH produced from phosphates is the phosphate produced (phosphate) by other cells that produces ATP. The phosphate produced by ATP that reduces ribulose 5-phosphate to produce NADPH in the blood cell of the genet deficient in G6PD is exposed to the oxidative oxidant hemoglobin, resulting in anemia. Such...
Nucleic Acid Metabolism

Mia in the setting of G6PD deficiency include infection, use of certain drugs (including sulfa drugs and antimalarial drugs), and consumption of fava beans.

How is NADPH protective? Normally, hydrogen peroxide is eliminated by glutathione. Glutathione is a tripeptide made up of glutamate, cysteine and glycine (Figure 2.13). Its sulfur-containing side chain can reduce hydrogen peroxide to water, and is oxidized in the process. Glutathione reductase restores glutathione to its reduced form using NADPH as the source of reducing power. This decreases G6PD activity, allowing the cell to detoxify hydrogen peroxide.

G6PD deficiency is most common in people who live in Africa, the Middle East, in tropical and subtropical parts of southeast Asia.

C. Formation

Let’s return to the structure of the proper structure and the 1’ carbon of the pentose phosphate, 5-phosphoglucono-5-phosphoric acid derivative that is phosphorylated at the phosphate group. (Figure 2.15)}
used to produce nucleotides de novo and via salvage pathways. PRPP synthetase is subject to feedback inhibition by purine and pyrimidine nucleotides.

D. De novo Ribonucleotide Synthesis

Purine and pyrimidine nucleoside 5’-monophosphates can be synthesized de novo from PRPP and various carbon and nitrogen donors. The raw materials for both types of nucleotide have a common origin. However, the pathways by which they are formed are separate and distinct in organization. In the pyrimidine pathway, the ring structure of the base is assembled first and then attached to the pentose sugar PRPP. In contrast, the purine pathway starts with the pentose sugar and builds the ring structure of the base upon it.

Nucleoside 5’-monophosphates are phosphorylated to form the corresponding diphosphates by one of several nucleoside monophosphate kinases, each of which is specific for the base component of the nucleotide (see Figure 2.11 for specifics). Nucleoside diphosphates can be converted to triphosphates by a non-specific nucleoside diphosphate kinase (NDK). ATP is the phosphate donor in all of these phosphorylation reactions.

Now let’s turn our attention to the biosynthesis of purine 5’-monophosphate from its ribose 5’-phosphate precursors.

1. Purine Biosynthesis

a. The Pathway

The pathway for the biosynthesis of purine ribonucleotides begins with the formation of amide precursors. These precursors are synthesized from aspartate and formylmethionine, where the purine nitrogen atoms of the base will be derived from the amide precursors. The amide precursors then are converted into the purine nucleoside 5’-monophosphate precursors.
b. REGULATION

Several inhibitors have been identified, including 5-fluorouracil, which inhibits PRPP synthetase activity. PRPP is an intermediate in the production of many purine and pyrimidine nucleotides. This enzyme is subject to feedback inhibition by the end products of the pathway. Inhibitors of this enzyme can lead to increased purine and pyrimidine nucleotide levels.

c. CLINICAL IMPLICATIONS

A few inhibitors of de novo purine synthesis are clinically useful. Azathioprine (Imuran) and mercaptopurine (Purine) are 6-mercaptopurine analogs that can be used in the treatment of chronic leukemias. Azathioprine is converted to azathio- nate intracellularly, where it is metabolized to 6-mercaptopurine, which inhibits de novo purine synthesis.

IMP dehydrogenase is inhibited by 6-mercaptopurine, and the accumulation of the substrate, IMP, leads to decreased adenosine and guanosine levels, which is the basis for the treatment of chronic leukemias. Azathioprine is converted to azathioprine, which is metabolized to 6-mercaptopurine, which inhibits de novo purine synthesis.
organ transplant rejection. Lymphocytes are unique in being unable to utilize salvage pathways to generate GMP. Their dependence on de novo synthesis for GMP means proliferation of these cells is selectively inhibited by this drug. Note the role of formyl-H$_4$folate, a form of reduced folate carrying a formyl group, in providing a 1-carbon unit to the synthesis of the inosine base. The contribution of folate cofactors and vitamin B12 to nucleotide metabolism and the actions of drugs on these processes will be discussed in more detail below.

2. **Pyrimidine Nucleotide Synthesis**

a. **The Pathway**

*De novo* pyrimidine biosynthesis begins with the formation of carbamoyl phosphate from the amide group of glutamine, CO$_2$, and a phosphoryl group of ATP ([Figure 2.16](#)) via the enzyme carbamoyl phosphate synthase-II (CPSII). Carbamoyl phosphate becomes part of the pyrimidine ring. The remaining atoms of the ring are added as a unit in the form of aspartate. The resulting N-carbamoyl aspartate is converted to a free pyrimidine base, orotate, by ring closure and oxidation. The base is then joined to PRPP to form a nucleoside monophosphate, orotidine.
monophosphate (OMP). Uridine monophosphate (UMP) is derived directly from OMP by decarboxylation. UMP is phosphorylated to produce UTP. CTP arises from an amidation reaction catalyzed by CTP synthase. The synthesis of TTP is described later.

b. REGULATION

CPSII catalyzes the key regulated step in pyrimidine synthesis. The enzyme is inhibited by UTP and activated by PRPP. Thus, as pyrimidine concentrations decrease (as indicated by UTP concentration), CPSII activity increases and more pyrimidines are produced. CTP synthase is inhibited by its product, CTP.

c. CLINICAL CONNECTIONS

A few important clinical connections are worth mentioning. First, do you remember that carbamoyl phosphate is an intermediate in another key metabolic pathway? Carbamoyl phosphate is utilized as a substrate in the urea cycle by the enzyme or-nithine transcarbamoylase. Inherited deficiency of this enzyme (the most common urea cycle defect) is associated with hyperammonemia and associated problems, but is also marked by elevated blood and urinary orotate, because excess carba-

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Regulation of ribonucleotide reductase activity is effected mainly through an allosteric site, to which ATP binds and activates the enzyme, and dATP binds and inhibits the enzyme. A chemotherapeutic drug, hydroxyurea, acts by inhibiting ribonucleotide reductase and reducing the dNTP pool available to rapidly dividing cells.

![Figure 2.17 Synthesis of the Deoxyribonucleotides](image)

Synthesis of the deoxyribonucleotides is catalyzed by ribonucleotide reductase. Reproduced with permission from Colby, Biochemistry, a Synopsis, Lange, 1985.

2. **Production of dTTP**

Thymine-containing nucleotides must be generated from uracil-containing nucleotides. dUMP is the substrate for thymidylate synthase, which methylates uracil, forming dTMP (Figure 2.18). The one-carbon group, donated by methylene-\(\text{H}_4\)folate, is transferred to dUMP by the enzyme thymidylate synthase. The end product is dTMP, which is then incorporated into DNA.

In this process, the product \(\text{H}_4\)folate is oxidized to \(\text{H}_2\)folate, which is then recycled by the enzyme dihydrofolate reductase. This reaction also utilizes NADPH as a cofactor, which is then oxidized to NADP⁺.
F. FOLATE AND VITAMIN B12 IN DE NOVO NUCLEOTIDE SYNTHESIS

1. ROLES AND METABOLISM

Having seen folate cofactors utilized as 1-carbon carriers in two parts of nucleotide biosynthesis, now is a good time to delve more deeply into this water-soluble vitamin’s metabolism, along with that of another important water-soluble vitamin, vitamin B12 (cobalamin), which plays a key role in the formation of active folate.

The generic term “folate” refers to a group of compounds that include folic acid in their structures (Figure 2.19). The biologically active form of folate is a reduced derivative of folic acid, tetrahydrofolate (H₄folate). Polyglutamation (addition of glutamate residues to the existing glutamate in the structure of folic acid) is required for retention and utilization of folate intracellularly, but only monoglutamated folates can be transported across cell membranes. These are important considerations in the pharmacokinetic parameters of drugs that are folate analogues.

The type of “folate” contained in vitamin and dietary supplements is folic acid. When folic acid is con-
Figure 2.20 Dihydrofolate reductase converts folic acid to $H_4$folate in two steps.

Reproduced with permission from Colby, Biochemistry, a Synopsis. Lange, 1985.
The resulting $\text{H}_4\text{folate}$ can then pick up a formyl (HCO) or methylene (CH$_2$) group and take part in nucleotide synthesis. Homocysteine methyltransferase requires a vitamin B$_{12}$ derivative (methylcobalamin) as its coenzyme. In individuals who lack homocysteine methyltransferase or its coenzyme, dietary folate is trapped as methyl-$\text{H}_4\text{folate}$, and nucleotide synthesis is impaired. Because methyl-$\text{H}_4\text{folate}$ is a poor substrate for the enzyme that attaches glutamate residues, the folate is not retained by cells and is excreted from the body.

$\text{H}_4\text{folate}$ picks up the one-carbon groups needed for nucleotide synthesis from several sources, and the formyl, methenyl, and methylene derivatives can be interconverted by freely reversible reactions (Figure 2.22). Recall that the formyl derivative is required for purine synthesis, while the methylene derivative is needed for synthesis of thymine. Methylene-$\text{H}_4\text{folate}$ can be reduced to methyl-$\text{H}_4\text{folate}$, via an irreversible reaction. This step removes folate from the pool that can participate in nucleotide synthesis. The folate can return to the active pool only by transferring its methyl group to homocysteine.

2. **Clinical Connections**

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**FIGURE 2.22**

a. **FOLATE DERIVATIVES**

Folate derivatives are interconverted within cells. The methylene group is a minimum requirement of folate for cells, but the formyl group is not. The test for megaloblastic anemia (a disorder characterized by large red blood cells) involves determining the amount of folate. Methyl-$\text{H}_4\text{folate}$ is a common folate derivative, but it cannot enter mammalian cells because it is not a coenzyme. Folates that are not coenzymes are converted to coenzymes by the reaction that involves transfer of a methyl group from $\text{H}_4\text{folate}$ to homocysteine.
circulation. This anemia will be discussed further in the M3 block.

In addition to anemia, vitamin B12 deficiency causes neurologic disturbances, including peripheral neuropathy. Unlike other cells in the body, cells in the nervous system are dependent on B12 for generation of methionine, the direct precursor to an important methyl donor called S-adenosylmethionine. The neurological problems seen in B12 deficiency are believed to be caused by hypomethylation within the nervous system.

Major sources of vitamin B12 are meat, eggs, dairy products, fish, and seafood. As you recall from M&N, absorption of B12 is a complex process. It will not be reviewed here, except to say that B12 must be bound to intrinsic factor (IF) in order to be absorbed in the distal ileum. It has been estimated that 10 – 15% of people over the age of 60 are vitamin B12 deficient. Among the causes are decreased gastric acidity, autoimmune destruction of the parietal cells of the stomach, and autoantibodies against intrinsic factor. Failure to produce intrinsic factor due to autoimmune destruction of intrinsic factor or...
III. NUCLEOTIDE CATABOLISM AND SALVAGE

A. OVERVIEW

Nucleotide turnover occurs continuously in cells. Breakdown of DNA and RNA releases nucleoside 5'-monophosphates, which can be hydrolyzed by 5'-nucleotidases to yield nucleosides. Although both purine and pyrimidine nucleosides can be degraded to waste products that are excreted, the catabolic pathways have branch points in most cells at which the components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) catabolism are diverted (Fig. 2.23). Unless the cells are able to salvage nucleotides, catabolism of DNA and RNA can generate more complex compounds that are more toxic (Intestinal nucleotidase is an example of this, and complications can be severe). Nucleotide degradation may be particularly costly because the degradation process uses energy.

As with most metabolic pathways, the enzymes for nucleotide degradation are enzymes that synthesize (de novo) nucleotides. Nucleotides are synthesized by other tissues to catabolize salvaged nucleosides and by the liver. (Note that salvaged nucleotides are recycled and are not available for de novo synthesis.) Nucleotides are salvaged by cells under certain conditions, especially for the types containing adenine and uracil.
NUCLEIC ACID METABOLISM

can be converted by adenosine deaminase.

Adenosine deaminase can be converted into inosine, which can then be converted to base. The salvage of inosine into nucleoside (inosine monophosphate, IMP) and guanosine (guanosine monophosphate, GMP) and adenosine (adenosine monophosphate, AMP) is facilitated by the base salvage/adenosine deaminase pathway (HGPRT). The salvage of xanthine (xanthine oxidase) and hypoxanthine (HGPRT) using PRPP produces hypoxanthine (HGPRT) which can be converted to base.

2. GENETIC DISORDERS
a. SCID

Several genetic disorders can lead to SCID due to defects in T cell receptor signaling, either due to a mutation in the gene for the phosphatase or due to a mutation in the receptor.
Nucleic Acid Metabolism

hood. Approximately 20% of patients with autosomal recessive Severe Combined Immunodeficiency Disease (SCID) have mutations in their ADA genes.

Because ADA deficiency is much more common than PNP, we will focus on ADA for the remainder of this section. ADA is present in all cell types but is most abundant in lymphoid tissues, brain, and the GI tract. It is important to note that deoxyribonucleotides are substrates for salvage reactions, though they are not necessarily shown in the figures here. In ADA deficiency, the problem does not lie with an inability to generate enough AMP or dAMP via salvage to meet the cell’s needs. In contrast, current thinking is that accumulation of toxic levels of nucleotides and their metabolites result in lymphocyte death. In ADA deficiency, adenosine and deoxyadenosine levels are significantly elevated in plasma and urine.

The most striking hallmark of ADA deficiency is massive accumulation of dATP in lymphocytes, which results from uptake of excessive intermediates from the blood and is hypothesized to be explained by preferential “trapping” of these phosphorylated compounds. Several models have been proposed to explain the observation that PEG-ADA is not effective in ADA deficiency. The most straightforward explanation is that the transport of ADA to the liver is insufficient to meet the metabolic needs of the lymphocytes. However, there is also evidence that the liver is able to take up and process ADA and that the problem lies in the ability of ADA to reach the lymphocyte. It is clear that additional studies are required to fully understand the mechanisms involved.
pensive and requires life-long adherence. ADA-deficient SCID was the first disorder for which human gene therapy was developed, which is still a treatment under active investigation.

b. LESCH-NYHAN SYNDROME

Mutations in the X-linked HGPRT gene that abolish enzyme activity result in an inability to salvage hypoxanthine or guanine. PRPP levels increase, while IMP and GMP levels decrease, alleviating inhibition of the purine synthesis pathway. Individuals with complete HGPRT deficiency develop Lesch-Nyhan Syndrome (LNS). This remarkable disorder is characterized by choreoathetosis (a movement disorder), spasticity, variable mental retardation, uric acid overproduction and gout (see below), and, most strikingly, self-mutilation (chewing off fingers and biting cheeks and lips). Treatment for LNS is symptomatic. Gout can be treated as described below. There is no standard efficacious treatment for the neurological symptoms of LNS; response to drugs is generally poor. Arm restraints and removal of teeth are usually the only way to prevent self-inflicted wounds.

C. PURINES

A portion of the ornithine, arginine and proline are produced by the action of the organic acid transport enzyme shown to carry proline. There is also the action of the enzyme arginase and ornithine transcarbamylase, an arginase and another metabolite. The proline is metabolized in the endoplasmic reticulum and the only specific 1,2-oxo-amino acid is used to form diluted proline. In this case, the level of the (uric acid) is increased but the uric acid is excreted through the liver. Upon ingestion, the LND is consumed and an inflammatory reaction is known to occur.

In the LND, the ingestion of LND is associated with the development of the lesion. In an LND, the lesion is characterized by severe pain, edema and induration. In a LND, the lesion is characterized by a decrease in the excretion of the lesion. The lesion is characterized by a decrease in the excretion of the lesion. For example, in
Uric acid is the end product of purine catabolism. Reproduced with permission from Colby, *Biochemistry, a Synopsis*, Lange, 1985.

Diseases, treatment of cancer with chemotherapeutic agents). Various genetic defects result in overproduction of purine catabolites, including mutations in PRPP synthetase (e.g. an elevated Vmax, increased affinity for substrate, or resistance to feedback inhibition), and Lesch-Nyhan syndrome.