· CHAPTER · 19 ·

PURINE METABOLISM

Purine Synthesis

Purine Salvage

Deoxynucleotides

Purine Degradation

PURINE SYNTHESIS

Function: To provide purines (A and G) for energy metabolism and for DNA-RNA synthesis.
Location: Cytoplasm of most cells.
Connections: To folate metabolism and one-carbon metabolism in de novo synthesis.
From HMP pathway via ribose and PRPP.
To deoxyribonucleotides through ribonucleotide reductase.
Regulation: Availability of PRPP.
Activity of the enzyme catalyzing the formation of the 5-phosphoribosyl-1-amine from PRPP is inhibited by purines.
Synthesis of GMP requires ATP.
Synthesis of AMP requires GTP.
Equation:

PRPP + glutamine + glycine + formyl-THF + aspartate + some ATP $\longrightarrow$ purines

(See Fig. 19-1.)

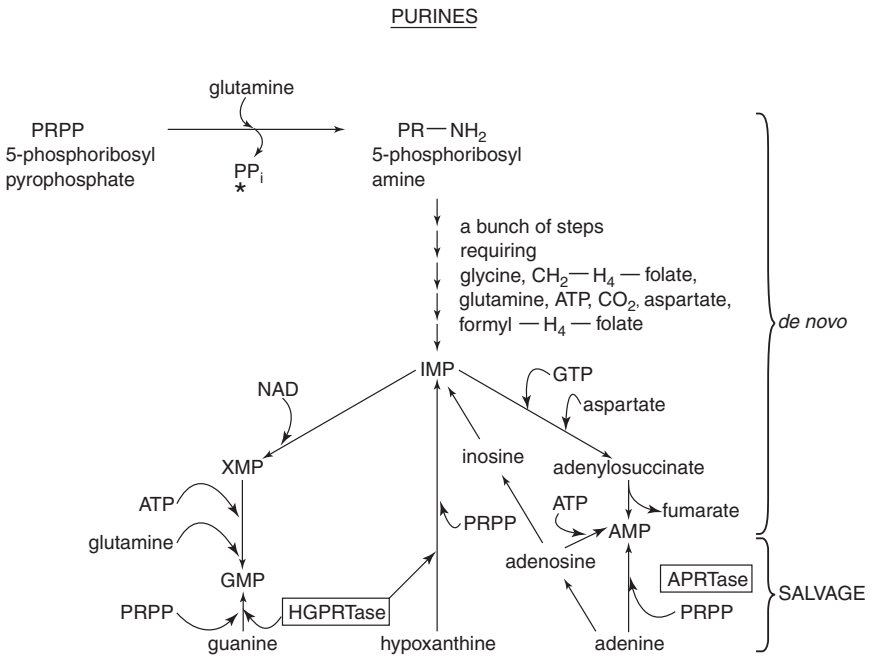

Figure 19-1 Purine Synthesis and Salvage

PURINE SALVAGE

HGPRTase: Hypoxanthine or Guanine + PRPP ⟶ IMP or GMP + PP_i

APRTase: Adenine + PRPP ⟶ AMP + PP_i

The free bases of the purines can be salvaged to spare *de novo* synthesis. The only hard thing is remembering what the names stand for. HGPRTase is hypoxanthine-guanine phosphoribosyltransferase, and it makes both IMP and GMP. A separate enzyme exists for the salvage of adenine. The salvage pathways are included in Fig. 19-1.

DEOXYNUCLEOTIDES

NDP + thioredoxin (SH_2) ⟶ (ribonucleotide reductase) dNDP + thioredoxin (SS)

dTMP made from dUMP with CH_2—THF

Deoxynucleotides for DNA synthesis are made at the nucleoside *diphosphate* level and then have to be phosphorylated up to the triphosphate using a kinase and ATP. The reducing equivalents for the reaction come from a small protein, thioredoxin, that contains an active site with two cysteine residues. Upon reduction of the ribose to the 2′-deoxyribose, the thioredoxin is oxidized to the disulfide. The thioredoxin(SS) made during the reaction is recycled by reduction with NADPH by the enzyme thioredoxin reductase.

Ribonucleotide reductase works on ribo-A, -U, -G, -C diphosphates to give the deoxynucleotide. The deoxyuridine, which is useless for RNA synthesis, is converted to deoxythymidine by the enzyme thymidylate synthase, which uses methylene tetrahydrofolate as a one-carbon donor. The odd thing here is that ribonucleotide reductase uses the UDP as a substrate to give the dUDP. This must then be hydrolyzed to the dUMP before thymidylate synthase will use it to make dTMP. Then the dTMP has to be kinased (phosphorylated) up to dTTP before DNA can be made.

Regulation of ribonucleotide reductase is a bear. There appear to be two regulatory sites, one that affects the overall activity and another that changes the relative specificity for the various purine and pyrimidine substrates. ATP binding to the activity regulatory site turns on the activity toward all substrates, while dATP binding to the same site turns it off. A complex pattern of specificity changes is observed when one of the deoxynucleotides binds to the second regulatory site. The general idea is to keep the levels of the various deoxynucleotides at the proper levels and ratios for DNA synthesis. ATP binding to the specificity site activates the formation of dCDP, while dTTP binding to the site activates dGDP formation and inhibits dCDP formation. The dGTP activates the formation of dADP but inhibits the formation of dCDP and dGDP. Simple . . .? Don't put this one too high on your trivia list.

PURINE DEGRADATION

GMP → guanosine → guanine → xanthine → urate
AMP → adenosine → inosine → hypoxanthine → xanthine → urate
AMP → IMP → inosine → → → urate

Name changes may be confusing here; when AMP loses the phosphate to become adenosine and adenosine loses the ribose to become adenine, it's still easy to tell who came from where. When IMP loses the phosphate, it becomes inosine, but when inosine loses the ribose it becomes hypoxanthine. It may be a little confusing, but it's still better than trying to pronounce *inonine*.