7.11: Purine de novo Biosynthesis

Synthesis of purine nucleotides differs fundamentally from that of pyrimidine nucleotides in that the bases are built on the ribose ring. The starting material is ribose 5-phosphate, which is phosphorylated by PRPP synthetase to PRPP using two phosphates from ATP. PRPP amidotransferase catalyzes the transfer of an amine group to PRPP, replacing the pyrophosphate on carbon 1. Thus begins the synthesis of the purine ring.

PRPP amidotransferase is regulated partly by GMP and partly by AMP. The presence of either of these can reduce the enzyme's activity. Only when both are present is the enzyme fully inactivated. Subsequent reactions include adding glycine, adding carbon (from N 10-formyltetrahydrofolate), adding amine (from glutamine), closing of the first ring, addition of carboxyl (from \(\text{CO}_2\)), addition of aspartate, loss of fumarate (a net gain of an amine), addition of another carbon (from \(\text{N}_10\)-formyltetrahydrofolate), and closing of the second ring to form inosine monophosphate (IMP).

IMP is a branch point for the synthesis of the adenine and guanine nucleotides. The pathway leading from IMP to AMP
involves addition of amine from aspartate and requires energy from GTP. The pathway from IMP to GMP involves an oxidation and addition of an amine from glutamine. It also requires energy from ATP. The pathway leading to GMP is inhibited by its end product and the pathway to AMP is inhibited by its end product.

Thus, balance of the purine nucleotides is achieved from the IMP branch point forward. It is at this point that the significance of the unusual regulation of PRPP amidotransferase becomes apparent. If there is an imbalance of AMP or GMP, the enzyme is slowed, but not stopped, thus allowing the reactions leading to IMP to proceed, albeit slowly. At IMP, the nucleotide in excess feedback inhibits its own synthesis, thus allowing the partner purine nucleotide to be made and balance to be achieved. When both nucleotides are in abundance, then PRPP amidotransferase is fully inhibited and the production of purines is stopped, thus preventing them from over-accumulating.

![Figure 7.11.2: Synthesis of ATP and GTP](image)

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