De Novo Purine Synthesis

Purines, essential building blocks of DNA and RNA, are synthesized via the de novo pathway. This complex biochemical process begins with Ribose-5-Phosphate, derived from the pentose phosphate pathway, which is converted to PRPP (Phosphoribosyl Pyrophosphate) by PRPP synthase. PRPP serves as the starting point for purine nucleotide biosynthesis. The rate-limiting step involves the enzyme Glutamine PRPP Amidotransferase, which transfers an amino group from glutamine to PRPP, forming Phosphoribosylamine, an essential intermediate in this pathway. This is followed by a series of reactions that utilize folate cofactors to build the inosine monophosphate (IMP) skeleton. Folate contributes critical carbon groups, highlighting its importance in purine synthesis. Deficiency in folate can impair this process, leading to conditions such as megaloblastic anemia. IMP, the central precursor for purines, undergoes distinct modifications to form Adenosine Monophosphate (AMP) and Guanosine Monophosphate (GMP). The conversion of IMP to AMP requires GTP and involves the intermediate adenylosuccinate, while the synthesis of GMP requires ATP and proceeds through the intermediate xanthosine monophosphate (XMP). Both pathways are tightly regulated by feedback inhibition, ensuring balance in purine synthesis. Dysregulation of enzymes such as PRPP synthase or Glutamine PRPP Amidotransferase can lead to increased purine production and uric acid accumulation, contributing to hyperuricemia and gout. Similarly, inhibitors of IMP dehydrogenase, like mycophenolate mofetil, are used therapeutically to suppress immune responses in transplant patients.

PLAY PICMONIC

PRPP Synthesis

Ribose-5-Phosphate

Rib-O (5) Hand Phosphate-P

De novo purine synthesis starts with ribose-5-phosphate, which is the starting material. It is formed during RBCs' pentose phosphate pathway (HMP shunt) and is an integral component of nucleic acids. DNA contains deoxyribose sugar, and RNA contains ribose sugar. A nucleoside contains a base and sugar (ribose or deoxyribose) linked by an N-glycosidic bond, whereas a nucleotide contains a nucleoside linked by a 3'-5' phosphodiester bond.

PRPP (Phosphoribosyl Pyrophosphate)

PRePPy-boy

The first step in purine synthesis is creating PRPP (Phosphoribosyl Pyrophosphate) from ribose-5-phosphate. PRPP synthase synthesizes PRPP by combining ribose 5-phosphate with ATP. AMP is a by-product of this reaction. PRPP synthase is allosterically inhibited by purine nucleotides (AMP, GMP) and activated by inorganic phosphate. Here is a visual representation of this reaction:
Ribose-5-Phosphate (R5P) + ATP ? PRPP + AMP

IMP Synthesis

Glutamine PRPP Amidotransferase

Glued-a-mean-ol' PRePPy-boy A-mean-ol' Transformer

After creating PRPP, the next step is synthesizing IMP (Inositol Mono-phosphate), the first fully formed purine nucleotide produced during de novo purine synthesis. Reaction which makes IMP takes 10 steps. The first enzyme in this 10-step process is glutamine PRPP amidotransferase, which adds an amino group from glutamine to PRPP, previously synthesized from ribose-5 phosphate, to form phosphoribosylamine. This step is the rate-limiting step. This enzyme is highly regulated and is inhibited by the products of purine synthesis: AMP, IMP, and GMP, as part of negative feedback. Overactivity or mutations in this enzyme can increase purine synthesis and uric acid production, contributing to gout.

Phosphoribosylamine

Rib-O Phosphate-P A-mean-ol'

PRPP is then converted to phosphoribosylamine, which serves as the starting framework for sequentially adding carbon and nitrogen atoms to build the purine ring. The enzyme glutamine PRPP amidotransferase catalyzes this conversion, adding an amino group from glutamine to PRPP. The phosphoribosylamine molecule acts as a key intermediate in the purine synthesis pathway. During this process, a series of nine steps adds carbon and nitrogen groups to eventually form the purine ring, an essential part of DNA and RNA.
Here is a visual representation of the reaction:
PRPP + Glutamine ? Phosphoribosylamine + Glutamate + Pyrophosphate (PPi).

Folate Cofactor

Foliage Crow-flagger

Folate, in the form of 10-formyl Tetrahydrofolate, is required for purine synthesis. It donates two carbons, one in the 5-membered ring and the other in the 6-membered ring of the purine skeleton. The purine ring starts to form by adding atoms (carbon and nitrogen) from other molecules, including glycine, glutamine, aspartate, and tetrahydrofolate. This is a complicated process, but the goal is to create a structure called inosine monophosphate (IMP). Folate

deficiency can impair purine synthesis, leading to megaloblastic anemia, a common finding in conditions like dietary folate deficiency, pregnancy, or methotrexate therapy.

Inosine Monophosphate

N-SYNC with Monkey-phosphate

In the inosine monophosphate skeleton, nitrogen is donated by glutamine (2), glycine (1), and aspartate (1), and carbon is donated by glycine (2), carbon dioxide (1), and 10-formyl-THF (2). Four ATP molecules are required to synthesize IMP from 5-phosphoribosylamine.

AMP Synthesis

Adenosine Monophosphate

A-dentist-singing Monkey-phosphate

IMP is the first purine nucleotide synthesized during de novo purine synthesis. From IMP, AMP is synthesized. The IMP skeleton contains 4 nitrogen and 1 oxygen atom, whereas the AMP skeleton contains 5 nitrogen moieties. Therefore, the conversion of IMP to AMP requires the replacement of an oxygen atom with nitrogen. Aspartate is a nitrogen donor in this reaction, and the enzyme adenylosuccinate synthetase catalyzes the whole conversion.

So step 1 is adenylosuccinate synthetase catalyzes the reaction between IMP and aspartate, with GTP providing the required energy, forming adenylosuccinate.

And during step 2 adenylosuccinate is then converted into AMP by releasing fumarate.

Here is the whole representation of these reactions: IMP + Aspartate + GTP ? Adenylosuccinate + GDP + Pi ? AMP + Fumarate

Requires GTP

Gold-TP wrapped Battery

IMP contains an oxygen atom at a specific position in its purine ring. During the conversion to AMP, this oxygen atom is replaced with a nitrogen atom. This modification is essential to form the characteristic structure of AMP. The conversion of the oxygen moiety (of inosine monophosphate) to the nitrogen moiety (of adenosine monophosphate) requires a high-energy reaction carried out by adenylosuccinate synthetase, with GTP and aspartate as substrates, like ATP, GTP stores and transfers energy. The hydrolysis of its high-energy phosphate bonds releases energy for cellular processes.

GMP Synthesis

Guanosine Monophosphate

G-iguana Monkey-phosphate

IMP has 5 nitrogen atoms and 1 oxygen atom in its purine ring.
The conversion of IMP to GMP involves two main steps:

Step 1: IMP is oxidized to XMP (xanthosine monophosphate) by the enzyme IMP dehydrogenase. This step requires NAD? (which is reduced to NADH) and water. The addition of an oxygen atom turns the structure into XMP, which is more similar to xanthine.
IMP + NAD+ + H2O ? XMP + NADH

Step 2: GMP synthetase converts XMP into GMP (guanosine monophosphate). In this step, the oxygen atom in XMP is replaced by an amino group from glutamine, and ATP is used for energy.
XMP + Glutamine + ATP ? GMP + Glutamate + ADP + Pi

IMP dehydrogenase, the enzyme catalyzing the first step of GMP synthesis, is inhibited by mycophenolate mofetil, an immunosuppressant drug used to prevent organ rejection in transplant patients.

Requires ATP

ATP-battery

The conversion of the Oxygen moiety (of Xanthosine Monophosphate) to Nitrogen moiety (GMP) requires a high-energy reaction carried out by GMP synthetase with ATP and Glutamine as substrates.