Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2026.66.010310

Purine and Pyrimidine Nucleotide Metabolism: Molecular Pathways, Regulatory Mechanisms, Cellular Functions, and Their Contributions to Human Diseases

Alber Fares*

Professor of Medical Biochemistry and Genetics, Orlando, Florida, USA

***Corresponding author:** Alber Fares, Professor of Medical Biochemistry and Genetics, Orlando, Florida, USA

ARTICLE INFO

Received: June 26, 2026

Published: July 16, 2026

Citation: Alber Fares. Purine and Pyrimidine Nucleotide Metabolism: Molecular Pathways, Regulatory Mechanisms, Cellular Functions, and Their Contributions to Human Diseases. Biomed J Sci & Tech Res 66(2)-2026. BJSTR. MS.ID.010310.

ABSTRACT

Purine and pyrimidine nucleotide metabolism comprises a highly coordinated network of biochemical pathways essential for cellular growth, energy transfer, signal transduction, and the synthesis, repair, and maintenance of genetic material. As the fundamental building blocks of DNA and RNA, nucleotides play indispensable roles in preserving genomic integrity and regulating numerous cellular processes. Dysregulation of nucleotide metabolism has been implicated in a wide range of inherited, metabolic, immunological, and neoplastic disorders, underscoring its significance in human health and disease. This review examines the molecular mechanisms underlying purine and pyrimidine nucleotide metabolism, focusing on de novo biosynthesis, salvage pathways, and catabolic processes. Key enzymes, intermediates, and regulatory networks involved in maintaining nucleotide homeostasis are discussed. The clinical consequences of disruptions in nucleotide metabolism are explored through selected disorders. Additionally, emerging evidence highlights the role of altered nucleotide metabolism in cancer development and progression, particularly through metabolic reprogramming that supports rapid cellular proliferation and immune evasion. Advances in molecular biology have further identified several enzymes within purine and pyrimidine pathways as promising therapeutic targets for anticancer, antiviral, and immunomodulatory interventions. By integrating biochemical, molecular, genetic, and clinical perspectives, this review provides a comprehensive overview of nucleotide metabolism and its central role in cellular physiology and disease pathogenesis. A deeper understanding of these pathways offers valuable insights for developing precision medicine strategies and novel therapeutic approaches to restore metabolic balance and improve patient outcomes.

Keywords: Purines; Pyrimidines; DNA; RNA; Ribose; 2-Deoxyribose

Abbreviations: rNDPs: Ribonucleotides; dNDP: Deoxynucleotides; RR: Ribonucleotide Reductase; RNA: Ribonucleic Acid; DNA: Deoxyribonucleic Acid; I: Inosine; A: Adenine; G: Guanine; U: Uracil; C: Cytosine; T: Thymine; Gly: Glycine; Asp: Aspartate; DNPB : Human De Novo Purine Biosynthesis; IMP : Inosine 5′-Monophosphate; PRPP: Phosphoribosyl Pyrophosphate; AMP: Adenosine 5′- GMP: Guanosine 5′-Monophosphate; UMP: Uridine Monophosphate; CTP: Cytidine Triphosphate; SCID: Severe Combined Immunodeficiency; MTHFD1: Methylenetetrahydrofolate Dehydrogenase 1; 5-PRA: 5-Phosphoribosylamine; GPAT: Glutamine Phosphoribosyl Amidotransferase; GARS: Glycinamide Ribonucleotide Synthase; GAR: Glycinamide Ribonucleotide; GART: Glycinamide Ribonucleotide Transformylase; FGAR: Formylglycinamide Ribonucleotide; AIRS: Aminoimidazole Ribonucleotide Synthase; AIR: Aminoimidazole Ribonucleotide; ADA: Adenosine Deaminase Deficiency; HGPRT: Hypoxanthine-Guanine Phosphoribosyltransferase; miR-128: Microrna Involved in Gene Regulation, PTMs: Post-Translational Modifications; PC: Pancreatic Cancer; PDAC: Pancreatic Ductal Adenocarcinoma; TME: The Tumor Microenvironment; CAFs: Cancer-Associated Fibroblasts; ECs: Endothelial Cells

Introduction

The most pivotal experiment of the 20th century was the clarification of DNA's structure by James D. Watson, Francis H.C. Crick, Maurice Wilkins, and Rosalind Franklin. Watson, Crick, and Wilkins were awarded the Nobel Prize in 1962 for their contributions to the study of nucleic acids, while Franklin was regrettably ineligible due to her passing in 1958. This groundbreaking discovery ignited public fascination and had profound biological and social ramifications. It has been commemorated in various ways, including Salvador Dalí's artwork and a plaque at The Eagle pub in Cambridge, where Watson and Crick first announced their findings in 1953. DNA continues to be at the heart of biological science, with recent developments in microR-

NA and RNA interference further revolutionizing the field. Moreover, nucleotides are vital for cellular energy and signaling. In 1959, Severo Ochoa and Arthur Kornberg were awarded the Nobel Prize for elucidating the mechanisms behind RNA and DNA synthesis. Nucleotides are indispensable for constructing both DNA and RNA, with cells typically containing more RNA than DNA [1]. Both DNA and RNA share the same purine bases: adenine (A) and guanine (G). They also share the pyrimidine base cytosine (C); however, they differ in their second pyrimidine base: DNA includes thymine (T), while RNA features uracil (U). The primary difference between T and U is that only T has a methyl group (-CH3) (Figure 1). Occasionally, modified (unusual) bases can be present in certain DNA and RNA, particularly in viral DNA and transfer RNA. These base modifications may include methylation, glycosylation, acetylation, or reduction. Examples of these atypical bases are shown in Figure 2. The presence of a modified base in a nucleotide sequence can enhance its recognition by specific enzymes or provide protection against nucleolytic degradation [2]. RNA contains a hydroxyl functional group (OH) at the 2' carbon of its pentose sugar, ribose, which is how it gets its name, ribonucleic acid. In contrast, DNA does not have this hydroxyl group (OH) at the same position; instead, it features a hydrogen atom (H), leading to the designation "deoxy" ribonucleic acid (2' deoxyribonucleic acid) (Figure 3) [1].

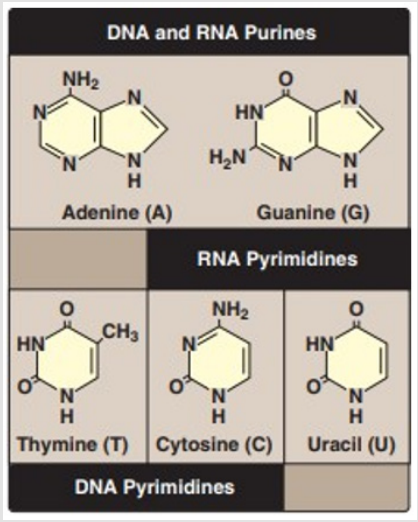

Figure 1: Purines and pyrimidines are essential components commonly present in both DNA and RNA [2].

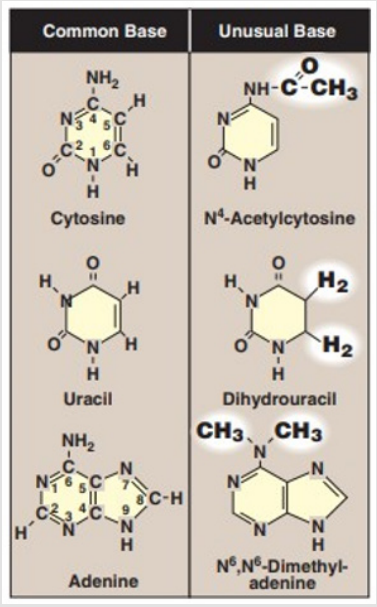

Figure 2: Examples of common and unusual bases [2].

 DOI: 10.26717/BJSTR.2026.66.010310

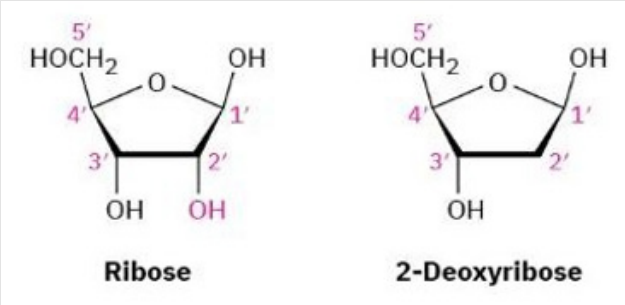

Figure 3: Ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) [103].

Nucleoside tri- and diphosphates, such as ATP and ADP, are essential donors and acceptors of phosphoryl groups (-PO4)3- in metabolism (Figure 4). ATP and ADP play a crucial role in energy transductions linked to metabolic conversions and oxidative phosphorylation [3]. Nucleosides, when connected to sugars or lipids, serve as vital biosynthetic intermediates. UDP-glucose and UDP-galactose participate in sugar interconversions and the synthesis of starch and glycogen. CDP-acylglycerol is a key intermediate in lipid biosynthesis. Deoxynucleotide production begins by reducing ribonucleotides (rNDPs) to deoxynucleotides (dNDPs), a reaction catalyzed by ribonucleotide reductase (RR). RR has a large R1 subunit and a smaller R2 subunit, both of which are crucial for electron transfer during reduction. It is regenerated by thioredoxin or glutaredoxin, which are oxidized and then restored by their respective reductases. NADPH is the electron donor for these reactions [1-3]. Ribonucleotide reductase (RR), also referred to as ribonucleoside diphosphate reductase, is an enzyme responsible for catalyzing the conversion of ribonucleotides into deoxyribonucleotides [4,5]. It achieves this by removing the 2'-hydroxyl group (OH) from the ribose ring of nucleoside diphosphates (or triphosphates, depending on the specific class of RR). This reduction ultimately results in the formation of deoxyribonucleotides [6]. Base + sugar → Nucleoside (Figure 5) nucleosides consist of a nitrogenous base and a five-carbon sugar, typically ribose. Nucleotides are formed when one or more phosphate groups are attached to a nucleoside [7].

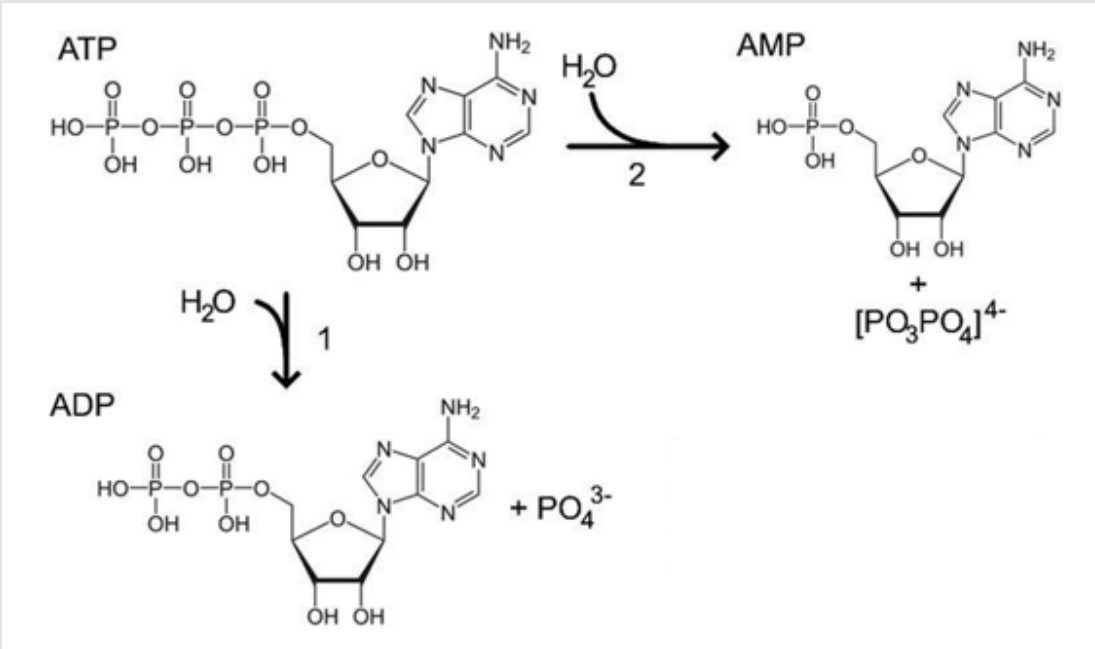

Figure 4: ATP, AMP, and ADP structure [104].

 DOI: 10.26717/BJSTR.2026.66.010310

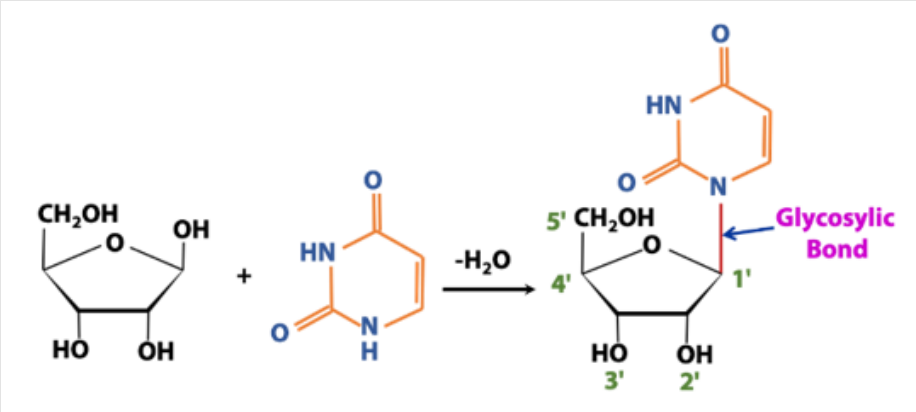

Figure 5: A nucleoside is a unique form of glycoside comprised of sugar and a base [8].

Nucleosides, when connected to sugars or lipids, serve as vital biosynthetic intermediates. UDP-glucose and UDP-galactose participate in sugar interconversions and the synthesis of starch and glycogen. CDP-acylglycerol is a key intermediate in lipid biosynthesis. Deoxynucleotide production begins by reducing ribonucleotides (rNDPs) to deoxynucleotides (dNDPs), a reaction catalyzed by ribonucleotide reductase (RR). RR has a large R1 subunit and a smaller R2 subunit, both of which are crucial for electron transfer during reduction. It is regenerated by thioredoxin or glutaredoxin, which are oxidized and then restored by their respective reductases. NADPH is the electron donor for these reactions [1,2,3]. Ribonucleotide reductase (RR), also referred to as ribonucleoside diphosphate reductase, is an enzyme responsible for catalyzing the conversion of ribonucleotides into deoxyribonucleotides [4,5]. It achieves this by removing the 2'-hydroxyl group (OH) from the ribose ring of nucleoside diphosphates (or triphosphates, depending on the specific class of RR). This reduction ultimately results in the formation of deoxyribonucleotides [6]. Base + sugar → Nucleoside (Figure 5) nucleosides consist of a nitrogenous base and a five-carbon sugar, typically ribose. Nucleotides are formed when one or more phosphate groups are attached to a nucleoside [7]. Base + Sugar + Phosphate → Nucleotide (Figure 6) nucleotides serve various roles in metabolism, extending beyond their function as the building blocks of nucleic acids. Both purine and pyrimidine nucleotides play crucial roles in a broad array of metabolic processes, including energy metabolism, protein synthesis, enzyme activity regulation, and signal transduction. When combined with vitamins or their derivatives, nucleotides contribute to the formation of various coenzymes [1]. Nucleotides also facilitate metabolic regulation through various mechanisms, including ATP-dependent phosphorylation of essential metabolic enzymes, Allosteric regulation of enzymes by ATP, ADP, AMP, and CTP, ADP's control over the rate of oxidative phosphorylation. Cyclic nucleotides such as cAMP and cGMP act as second messengers in hormone-regulated processes, while GTP and GDP are pivotal in the signaling cascades that underlie signal transduction pathways. In addition to their fundamental roles in metabolism, nucleotides have significant medical applications. Synthetic purine and pyrimidine analogs containing halogens, thiols, or extra nitrogen atoms are utilized in the chemotherapy of cancer and AIDS, as well as in suppressing immune responses during organ transplantation. Errors or deficiencies in their synthesis can often result in fatal outcomes. Conversely, excessive production or insufficient elimination of nucleic acid derivatives can lead to specific medical conditions [3].

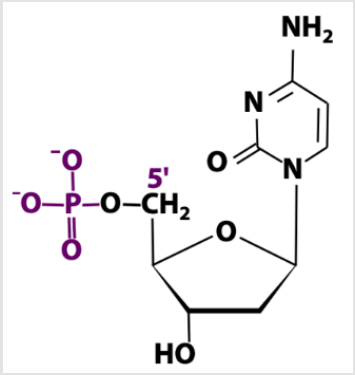

Figure 6: A nucleoside combined with a phosphate forms a nucleotide [8].

Components of Nucleosides and Nucleotides

Nucleic acids are linear polymers composed of nucleotides connected by phosphodiester bonds. Each nucleotide consists of three components: a carbohydrate (sugar), a nitrogenous base, and a phosphate group, similar to how proteins are formed from amino acids via peptide bonds (Figure 7) [8].

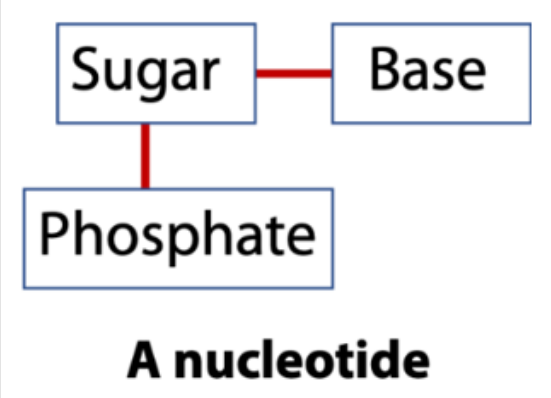

Figure 7: A nucleotide consists of sugar, a base, and a phosphate group [8].

Carbohydrates (Sugar)

The carbohydrate component of nucleosides and nucleotides is sugar ribose. When the hydroxyl group (OH) is removed from carbon 2 (typically after the nitrogenous base has been added to the carbohydrate), the resulting sugar is deoxyribose, which is found in DNA (Figure 8) [3].

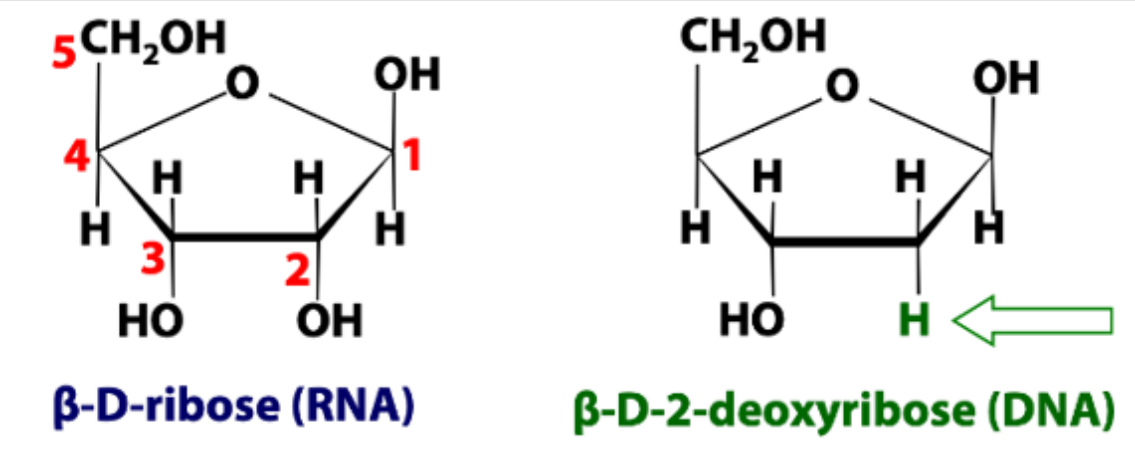

Figure 8: D-ribose is present in RNA, whereas D-2-deoxyribose is a component of DNA [8].

Nitrogenous Base

The nitrogenous base of a nucleoside or nucleotide (named for the nitrogen atoms (N) in its structure) can be classified as either a purine or a pyrimidine (Figure 9) [7].

- Purines, which include inosine (I), adenine (A), and guanine (G), are characterized by their two-ring structures.
- Pyrimidines, such as uracil (U), cytosine (C), and thymine (T), consist of a single ring.
- Both types of nitrogenous bases are partially derived from amino acids.

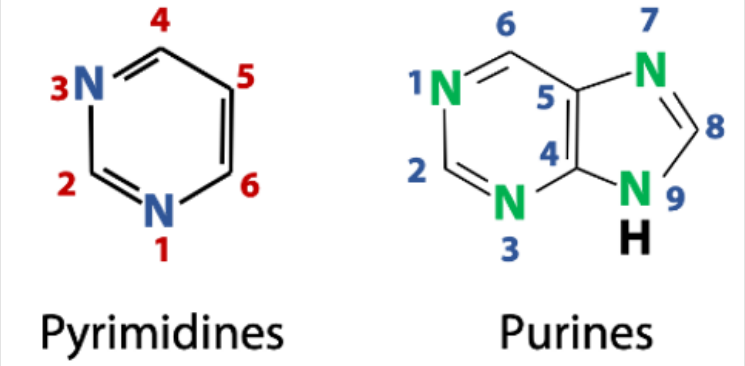

Figure 9: The nitrogenous bases in nucleic acids and their numbering conventions [8].

Phosphate Group

One or more phosphate groups (-PO4)3- can be attached to the carbon 5' of the carbohydrate molecule. These phosphate groups play a crucial role in energy storage and signaling functions of nucleosides and nucleotides (Figure 6) [7].

Nucleotide Metabolism Fundamental Pathway

The biosynthesis of purine nucleotides, beginning with phosphoribosyl pyrophosphate (PRPP) and culminating in the formation of inosine monophosphate (IMP), adenosine monophosphate (AMP), and guanosine monophosphate (GMP), is explored alongside the pyrimidine biosynthetic pathway leading to the production of uridine monophosphate (UMP), cytidine triphosphate (CTP), and thymidine nucleotides. Nucleotide metabolism is an essential metabolic pathway that plays a crucial role in homeostasis and cell physiology across all three domains of life [9-14]. All nucleotides share a common chemical structure, where the base is connected via a β-N-glycosidic bond to the hydroxyl group at C′1 of the sugar, and the phosphate is attached to the hydroxyl group at C′5 of the sugar (see Figure 6). Nucleotides serve not only as the building blocks that polymerases use to synthesize nucleic acids but also as integral components of various cellular processes, including as enzyme cofactors, metabolic precursors, and signal transducers [15,16]. Due to their significant role in metabolism, nucleotide pools must be continuously replenished, especially during high-demand situations, such as cell division. The pools of purine and pyrimidine nucleotides are maintained through two conserved pathways (illustrated in Figure 10A) the salvage pathway, which recycles free nitrogenous bases and is less energy-intensive, occurs solely in the cytoplasm [17] and the de novo biosynthesis pathway (illustrated in Figure 10B), which produces nucleotides from carbon and nitrogen precursors, is energy-consuming and can take place in the cytoplasm and possibly in the mitochondria/chloroplasts. This is relevant to purine synthesis in plants and to pyrimidine synthesis in both animals and plants [18].

Human De Novo Purine Biosynthesis (DNPB)

In humans, the de novo synthesis of inosine 5′-monophosphate (IMP) is carried out by six enzymes that sequentially add a purine base to phosphoribosyl pyrophosphate (PRPP) over 10 steps (see Figure 10A). This entire process is known as DNPB. IMP serves as a crucial branch-point purine intermediate that can be readily converted into either adenosine 5′-monophosphate (AMP) or guanosine 5′-monophosphate (GMP) by four specific enzymes. Notably, these enzymes are not exclusive to the DNPB pathway; they also play a role in the salvage synthesis of purine mononucleotides [19,20]. Figure 10A illustrates that purines are regenerated through salvage from hypoxanthine, guanine, and adenine, or synthesized de novo from PRPP, using substrates from glucose metabolism. Key metabolites include glucose-6-phosphate (generating PRPP via the pentose phosphate pathway), 3-phosphoglycerate (leading to serine production), and pyruvate (fueling the TCA cycle "citric acid cycle" for aspartic acid). The conversion of serine to glycine and formate occurs in mitochondria and involves one-carbon metabolism enzymes [19].

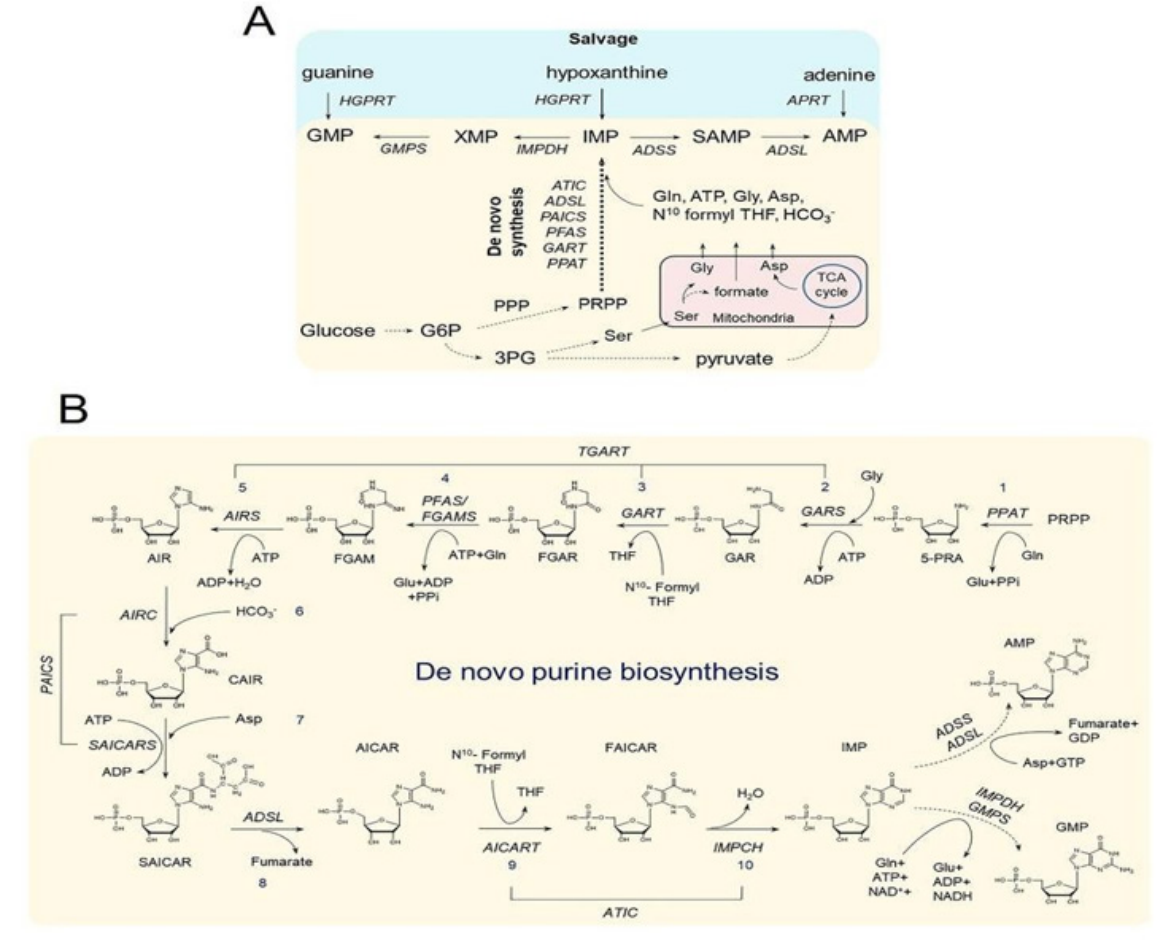

Figure 10: The salvage pathways and de novo purine biosynthesis [19].

Additionally, the DNPB pathway converts phosphoribosyl pyrophosphate (PRPP) to AMP and GMP through a series of 10 reactions catalyzed by six enzymes, producing IMP, which can further convert to AMP or GMP. This energy-intensive pathway requires three amino acids (glycine, aspartic acid, and glutamine) and the cofactor N10-formyltetrahydrofolate [19]. DNPB is an energy-demanding process that requires many substrates and cofactors to be produced from various metabolic pathways, including the glycolytic and pentose phosphate pathways (PRPP), serine biosynthesis (glycine), one-carbon metabolism (formate), and the tricarboxylic acid cycle in conjunction with amino acid metabolism (aspartate, glutamine) [19,20]. For glycine (Gly), aspartate (Asp), and formate (CHO -), the primary production occurs in the mitochondria. Their use in the DNPB pathway requires their transport into the cytoplasm, where the DNPB process occurs [21-25]. The shuttling of these essential biomolecules from the mitochondria is supported by several mitochondrial transporters [26,27]. A recent study shows that anion channels in the mitochondrial inner membrane may mediate formate transport [28]. Once in the cytoplasm, formate is converted into N10-formyltetrahydrofolate by methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) and subsequently utilized as a cofactor in DNPB.

The Initial Steps of DNPB

In the first committed step of de novo purine biosynthesis (DNPB), 5-phosphoribosylamine (5-PRA) is generated by adding a glutamine (Gln)-derived amine group to PRPP [29-31]. This reaction is facilitated by the enzyme glutamine phosphoribosyl amidotransferase (GPAT), which features two significant domains:

- A glutaminase domain, where Gln is hydrolyzed to produce ammonia (NH3).
- A phosphoribosyl transferase domain, where ammonia is transferred to PRPP.

Based on bacterial enzyme behavior, substrate binding to the first domain induces conformational changes that prepare the second domain for PRPP binding, thereby forming 5-PRA [32-35]. Given the

sequence and structural similarities between human PPAT and the Bacillus subtilis enzyme, a similar mechanism is expected [30,36]. Phosphoribosyl pyrophosphate amidotransferase (PPAT) exists in a dynamic equilibrium between dimeric and tetrameric states, and it is subject to feedback inhibition by AMP in its presumed active tetrameric form [37,38]. For mammalian PPAT to achieve and maintain its active structure, two processes are necessary: cleavage of an N-terminal propeptide and the formation of an iron-sulfur cluster [4Fe-4S] [35,39]. The impact of prolonged oxidative stress on the stability of PPAT's iron-sulfur cluster was demonstrated in the human neuroblastoma cell line SH-SY5Y, where inhibition of mitochondrial complex I by rotenone significantly diminished the fraction of the mature enzyme [40].

The second enzyme in the DNPB pathway is trifunctional GART (TGART), which has three main activities:

- Glycinamide ribonucleotide synthase (GARS) catalyzes the ATP-dependent conversion of 5-PRA and Gly to glycinamide ribonucleotide (GAR).
- Glycinamide ribonucleotide transformylase (GART) transfers a formyl group from N10-formyltetrahydrofolate to GAR, forming formylglycinamide ribonucleotide (FGAR).
- Aminoimidazole ribonucleotide synthase (AIRS) converts FGAM to aminoimidazole ribonucleotide (AIR) also in an ATP-dependent manner.

The first two reactions produce FGAR, which is further processed by the next enzyme, formylglycinamidine synthase (PFAS/FGAMS) [36]. FGAMS contains a glutaminase domain, which is believed to create a channel for direct transfer of ammonia to the amidotransferase domain, based on its structure and similarity to bacterial enzymes [41]. The ammonia produced by the glutaminase domain remains available for the subsequent reaction, which converts FGAR to FGAM. FGAM is then transformed into AIR by the AIRS domain of TGART, leading to a five-membered ring closure. Steps 6 and 7 (Figure 10 A) involve the carboxylation of AIR to CAIR and the ATP-dependent ligation of CAIR with an amid group from Asp, forming SAICAR. These reactions are catalyzed by the bifunctional enzyme PAICS, which have N-terminal SAICARS and C-terminal AIRC domains, and forms homo-octamers as shown by gel filtration and X-ray crystallography [42,43]. Crystal structure analysis has unveiled a tunnel system within the octamer, suggesting that it may facilitate the transport of CAIR from the AIRC domain to the SAICARS domain while limiting its diffusion into the surrounding cytosol [42]. Recent studies have confirmed these structural insights through a pair of substrate-bound octameric structures of the human enzyme [43]. The eighth step (Figure 10A) in the DNPB pathway is facilitated by adenylosuccinate lyase (ADSL) and involves a β-elimination reaction on SAICAR, resulting in the release of fumarate and aminoimidazole-4-carboxamide ribonucleotide (AICAR). ADSL can also catalyze the reverse reaction. The active site of this homotetrameric enzyme is formed by residues from the other three subunits [44]. The final two steps (Figure 10A) of the pathway are mediated by the bifunctional AICAR transformylase/IMP cyclohydrolase (ATIC). The transformylase domain first converts AICAR into formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR) using N10- formyltetrahydrofolate. Subsequently, the cyclohydrolase domain completes the purine ring, producing IMP. While the first reaction is reversible, the activity of the cyclohydrolase domain drives the overall reaction forward [45]. ATIC has been crystallized as a dimer, and a dimer: monomer equilibrium was noted in solution [46,47]. Although the presence of a molecular tunnel for the direct transfer of intermediates between the two domains was expected, kinetic and structural analyses of the isolated enzyme did not demonstrate channeling in vitro [46,48].

Human DNPB Enzymes and Reactions

In conclusion, human DNPB (as previously discussed) consists of the coordinated actions of six enzymes that drive ten sequential reactions, converting PRPP into IMP. Many of these enzymes exhibit multiple functions: TGART is trifunctional, while PAICS and ATIC are bifunctional, and PPAT, FGAMS, and ADSL each catalyze a single step in DNPB. These reactions depend on a variety of substrates and cofactors, which are produced by other metabolic pathways, many of which originate in and are transported from mitochondria [8,29,49-52].

Regulation of the DNPNB Pathway

In conditions with increased demand for purine nucleotides, such as in dividing and tumor cells, the DNPNB pathway is essential for replenishing the purine pool. This pathway is also crucial for bacterial function. Consequently, various levels of regulation have evolved to carefully manage this pathway, allowing it to adapt to environmental changes [20]. In humans, a distinct form of microRNA-mediated translational regulation has been identified for PAICS [53,54]. miR-128 (a microRNA involved in gene regulation) plays a crucial role in negatively regulating PAICS expression by binding to the 3′ untranslated region (3′UTR) of messenger RNAs. In various human cancers, downregulation of miR-128 leads to increased PAICS levels (steps 6 and 7, Figure 10B), a change linked to several cancer types [55-59]. The DNPNB pathway is also controlled at the protein level, either through post-translational modifications (PTMs) or through interactions with different effectors. A comprehensive human study systematically identified PTMs—such as acetylation, methylation, phosphorylation, and ubiquitination—on the six DNPNB enzymes involved in IMP production, uncovering 118 novel PTMs [60]. Notably, differences in PTM patterns were observed between cells grown in purine-supplemented and purine-depleted media. [61] suggested that these PTMs may significantly influence catalytic activity, protein interactions, or oligomerization states, among other roles. Phosphorylation events are likely vital for linking signaling pathways and cell-cycle regulatory mechanisms to the DNPNB pathway, as seen with the RAS-ERK signaling pathway (which is crucial for transmitting signals from cell-surface receptors to the nucleus). This pathway shows no effect

at the transcriptional level or on DNPNB enzyme levels; instead, the stimulation of the DNPNB pathway is facilitated by the direct phosphorylation of the enzyme FGAMS (step 4 Figure 10B) by ERK2, but not by ERK1 (ERK1/2 pathway is part of the MAPK mitogen-activated protein kinase-signaling cascade) [62]. Likewise, in E. coli, lysine acetylations have also been documented in the PurB, PurH, PurT, and IMPDH enzymes [63]. However, the exact molecular implications of all these modifications remain to be fully characterized.

Beyond PTMs, the catalytic activity of DNPNB enzymes is regulated through ligand binding. The primary regulation of the overall DNPNB pathway rate is achieved through product inhibition by purine nucleotides, thereby maintaining appropriate cellular levels [64-66]. Three DNPNB enzymes have been identified to be regulated by feedback inhibition. This begins with the first enzyme in the pathway, PurF, which is negatively regulated by the nucleotides adenine and guanine. The 5′-monophosphates are the most potent inhibitors, with AMP and GMP exhibiting a synergistic effect [67-69]. Finally, the synthesis of the central precursor in the DNPNB pathway, PRPP, is tightly regulated. PRPP synthetase catalyzes the formation of PRPP from R5P and ATP and is inhibited by purine nucleotides [70-74]. Notably, the inhibitory effect of ADP exhibits a complex pattern, acting as either a competitive or allosteric inhibitor depending on R5P concentration [75-77].

Purine Nucleotide Salvage Pathway

Nucleotides can be synthesized from purine and purine nucleosides via a series of steps known as salvage pathways. The process of phosphoribosylation transforms free purine bases—adenine, guanine, and hypoxanthine—into their respective nucleotides. Two crucial transferase enzymes play key roles in purine salvage:

- Adenosine phosphoribosyltransferase (APRT): Converts adenine into AMP.
- Hypoxanthine-guanine phosphoribosyltransferase (HGPRT): Converts hypoxanthine into IMP or guanine into GMP, utilizing PRPP as a substrate (refer to Figure 11) [1,78].

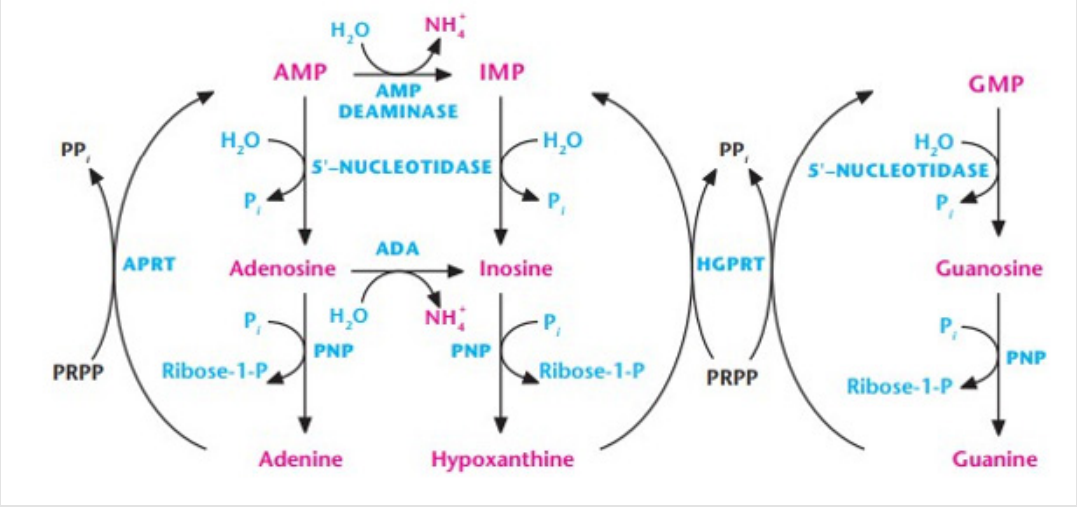

Figure 11: Purine salvage pathway. Two essential transferase enzymes play a critical role in the salvage of purines: adenosine phosphoribosyltransferase (APRT), which transforms adenine into AMP, and hypoxanthine-guanine phosphoribosyltransferase (HGPRT), which converts hypoxanthine into IMP or guanine into GMP, utilizing 5-phosphoribosyl-1-pyrophosphate (PRPP) as a substrate [1].

By using PRPP as a substrate, the salvage pathway reduces PRPP levels, thereby lessening the rate of de novo purine synthesis. The de novo purine synthesis and salvage pathways are intricately linked and depend on PRPP availability. The essential salvage pathway is the purine nucleotide cycle, which produces the TCA-cycle (citric acid cycle) intermediate fumarate, enhancing the TCA cycle's capacity to generate more NADH for ATP production. Increased muscle activity raises the metabolic demand for ATP. Elevated AMP levels signal that energy production via the TCA cycle and electron transport chain is inadequate to meet this demand. This cycle is particularly significant in muscle cells, which lack most of the enzymes required for major anapleurotic reactions (i.e., those that replenish pathway intermediates). Therefore, muscles restore TCA cycle intermediates via fumarate generated by the purine nucleotide cycle. Myoadenylate deaminase serves as the muscle-specific isoenzyme of AMP deaminase; deficiencies in this enzyme can result in post-exercise fatigue and cramping [1,78].

Degradation of Purine Nucleotides

The breakdown of dietary nucleic acids occurs in the small intestine, where a group of pancreatic enzymes hydrolyzes them into nucleotides. Within intestinal mucosal cells, purine nucleotides are progressively degraded by specific enzymes into nucleosides and free bases, culminating in uric acid as the final product. Purine nucleotides formed through de novo synthesis are primarily degraded in the liver, where the free bases are released and salvaged by surrounding tissues [2].

Degradation of Dietary Nucleic Acids in the Small Intestine: The pancreas secretes ribonucleases and deoxyribonucleases to break down dietary RNA and DNA into oligonucleotides, which are further hydrolyzed by pancreatic phosphodiesterases into 3'- and 5'-mononucleotides. Intestinal mucosal cells then use nucleotidases to remove phosphate groups, releasing nucleosides that are broken down into free bases. Dietary purine bases are primarily converted to uric acid, which enters the bloodstream and is excreted in urine. Unlike primates, other mammals produce urate oxidase to convert uric acid to allantoin, and recombinant urate oxidase offers a potential therapy for lowering urate levels [2].

Formation of Uric Acid: This summary outlines the steps involved in uric acid production and highlights genetic disorders associated with deficiencies in specific degradative enzymes, as illustrated in Figure 12. The bracketed numbers correspond to specific reactions in the figure [2].

- An amino group is removed from AMP to create IMP through the action of AMP deaminase, or from adenosine to generate inosine (hypoxanthine ribose) via adenosine deaminase.
- IMP and GMP are transformed into their nucleoside forms—inosine and guanosine—by 5'-nucleotidase.
- Purine nucleoside phosphorylase converts inosine and guanosine into their respective purine bases: hypoxanthine and guanine. Note: A mutase facilitates the interconversion of ribose 1-phosphate and ribose 5-phosphate.
- Guanine undergoes deamination to produce xanthine.
- Hypoxanthine is oxidized by xanthine oxidase into xanthine, which is subsequently oxidized by the same enzyme to yield uric acid, the final product of human purine degradation. Uric acid is primarily excreted in urine.

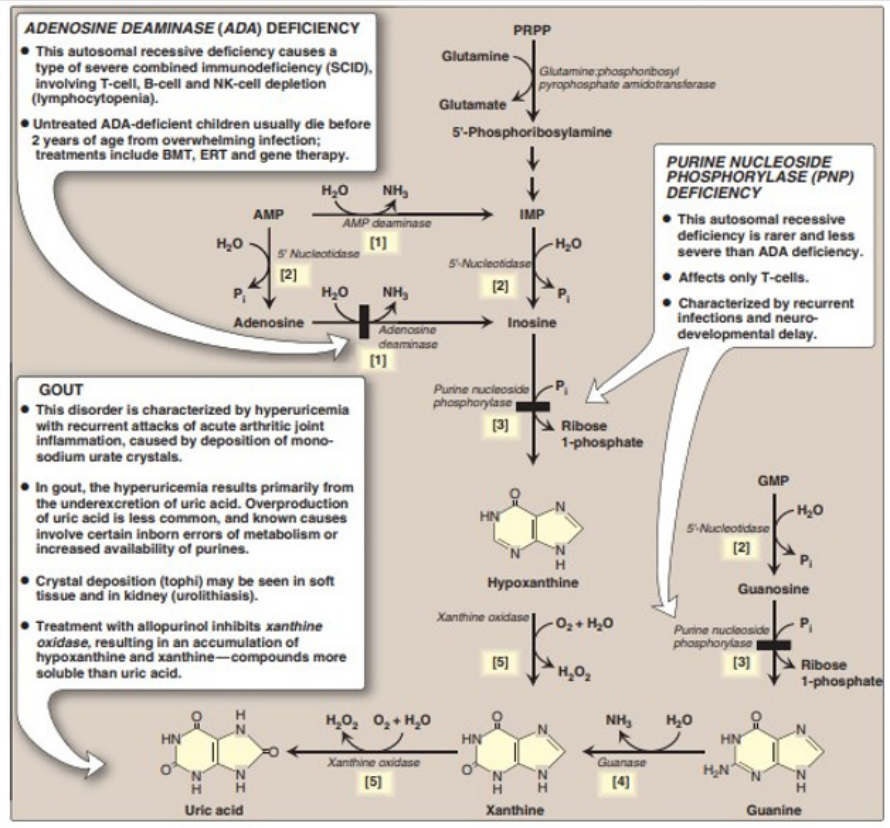

Figure 12: The breakdown of purine nucleotides into uric acid, with a focus on related genetic diseases [2].

Diseases associated with purine degradation: Metabolic disorders in the purine degradation pathway have been strongly linked to various human diseases [79]. The disorders addressed encompassed a range of conditions, including abnormalities in uric acid metabolism, gout, cancer, Lesch-Nyhan disease, immunological disorders, mitochondrial diseases, and various rare inherited metabolic disorders [80].

Lesch-Nyhan Syndrome: Lesch-Nyhan syndrome is a rare, X-linked recessive disorder characterized by a near-complete deficiency of HGPRT. This deficiency prevents the salvage of hypoxanthine or guanine, leading to excessive production of uric acid, the final product of purine degradation. Furthermore, the absence of this salvage pathway leads to elevated PRPP levels and reduced IMP and GMP levels. Consequently, glutamine: phosphoribosyl pyrophosphate amidotransferase (the crucial step in purine synthesis) has abundant substrate and fewer inhibitors, leading to increase de novo purine synthesis. The combination of reduced purine reutilization and heightened purine synthesis leads to greater purine degradation and substantial uric acid production, establishing Lesch-Nyhan syndrome as a hereditary cause of hyperuricemia. In individuals with this syndrome, hyperuricemia often leads to uric acid stones in the kidneys (urolithiasis) and to the accumulation of urate crystals in the joints (gouty arthritis) and soft tissues. Additionally, the syndrome is associated with motor dysfunction, cognitive impairments, and behavioral issues, including self-mutilation behaviors such as lip and finger biting (see Figure 13) [2,81,82].

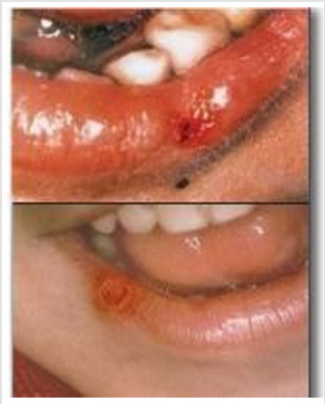

Figure 13: Lesions on the lips of Lesch-Nyhan patients caused by self-mutilation [2].

Gout: Gout is a disorder marked by high uric acid levels (hyperuricemia), resulting from overproduction or underexcretion of uric acid. This leads to the formation of monosodium urate crystals in joints, causing acute and chronic gouty arthritis, and may result in tophi in soft tissues or uric acid stones in the kidneys. While hyperuricemia is often asymptomatic, gout requires diagnosis by examining synovial fluid for needle-shaped crystals under polarized light microscopy. The treatment of gout involves two approaches: managing acute attacks and long-term strategies. Acute gout is treated with anti-inflammatory agents like colchicine, prednisone, and indomethacin. Colchicine reduces neutrophil movement but does not lower uric acid levels. Long-term treatment aims to lower uric acid levels to prevent urate crystal formation. Uricosuric agents like probenecid increase uric acid excretion in "underexcretors," while allopurinol inhibits uric acid synthesis in "overproducers." Allopurinol converts to oxypurinol, which inhibits xanthine oxidase, leading to the accumulation of more soluble compounds. Febuxostat, a non-purine xanthine oxidase inhibitor, is also available. Uric acid typically remains near saturation levels due to its strong antioxidant properties [2,83] (see Figure 14).

Figure 14: Gout is diagnosed by negative-birefringent monosodium urate crystals in aspirated synovial fluid, visible under polarized-light microscopy, often within polymorphonuclear leukocytes [2].

Adenosine Deaminase (ADA) Deficiency: ADA is present in various tissues, but in humans, lymphocytes exhibit the highest activity of this cytoplasmic enzyme. A deficiency in ADA leads to an accumulation of adenosine, which is converted into its ribonucleotide or deoxyribonucleotide forms by cellular kinases. As dATP levels increase, ribonucleotide reductase becomes inhibited, thereby blocking the production of all deoxyribose-containing nucleotides. Consequently, cells are unable to synthesize DNA and divide. The accumulation of dATP and adenosine in ADA deficiency leads to developmental arrest and apoptosis of lymphocytes. In its most severe form, this autosomal recessive disorder results in a type of severe combined immunodeficiency disease (SCID), characterized by a reduction in T cells, B cells, and natural killer (NK) cells. It is estimated that ADA deficiency accounts for approximately 14% of all SCID cases in the United States. Treatment options include either bone marrow transplantation (BMT) or enzyme replacement therapy (ERT). Without proper treatment, children affected by this condition typically do not survive beyond the age of two. Purine nucleoside phosphorylase (PNP) deficiency leads to a less severe immunodeficiency primarily affecting T cells [2,8,51,80].

Human De Novo Pyrimidine Biosynthesis

Pyrimidine synthesis stands apart from purine synthesis in that the pyrimidine ring is fully formed before it attaches to the ribose sugar, while the purine ring is constructed directly on the ribose sugar (PRPP). Overall, pyrimidine synthesis is less complex than that of purines, primarily due to its simple six-membered ring structure (Figure 15). The ring structure is formed with the help of carbamoyl phosphate and aspartate.

- Carbamoyl Phosphate Formation: This compound is derived from:

a) 1 mole of glutamine
b) 2 moles of ATP
c) 1 mole of bicarbonate
d) All occurring within the cytosol.

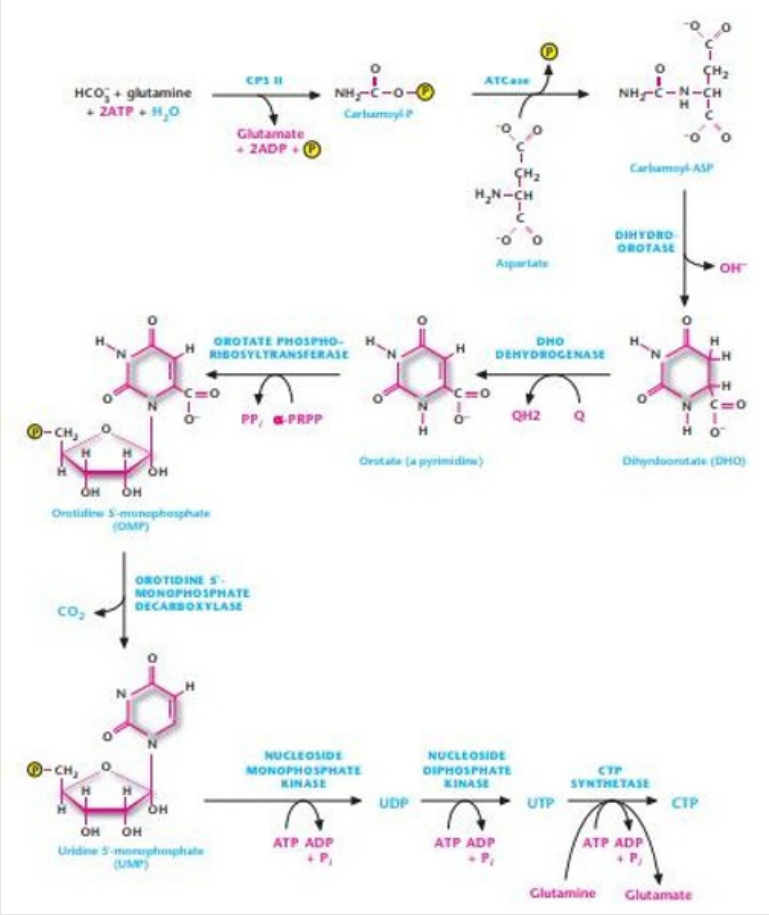

Figure 15: The pyrimidine ring is completely synthesized before being linked to the ribose sugar. The synthesis of pyrimidine nucleotides starts with the reaction of carbamoyl phosphate and aspartate, yielding the pyrimidine base orotate. Following this, the process involves attaching PRPP to orotate to produce orotate monophosphate (OMP), which is then decarboxylated to form UMP. UMP subsequently generates UDP and UTP, which can further produce CTP [1].

It's important to note that the urea cycle also utilizes carbamoyl phosphate, but in that context, it is derived from ammonia and bicarbonate in the mitochondrion. The urea cycle reaction is facilitated by carbamoyl phosphate synthetase I, whereas the precursor for pyrimidine nucleotides is produced by carbamoyl phosphate synthetase II (CPS-II). Following this, carbamoyl phosphate enters the pyrimidine nucleotide biosynthetic pathway via aspartate transcarbamoylase, the rate-limiting step in pyrimidine biosynthesis. The subsequent steps lead to the formation of the first complete pyrimidine base, orotate [1,7].

- Conversion to UMP:

a) PRPP attaches to orotate to form OMP, which is then decarboxylated to yield UMP.

b) UDP is produced from UMP via an ATP-dependent NMP kinase (UMP + ATP → UDP + ADP).

c) UTP is generated by the NDP kinase (UDP + ATP → UTP + ADP).

UTP can then be utilized to produce CTP through the action of ATP and glutamine, a reaction catalyzed by CTP synthetase [1,7].

According to [1], Uridine nucleotides serve as the building blocks for the de novo synthesis of thymine nucleotides. Since thymidine is found exclusively in DNA, the initial step is the conversion of UDP to dUDP, a reaction catalyzed by ribonucleotide reductase (RR), which removes the 2′-hydroxyl group to generate the deoxynucleotide. Following this, dUDP is converted to dUMP, which serves as a precursor to dTMP production (see Figure 16). Any dUDP that gets phosphorylated to form dUTP is swiftly converted to dUMP by UTP diphosphatase, thereby reducing the availability of dUTP and preventing the incorrect incorporation of uracil into DNA. The nitrogen base thymine is essentially 5-methyl uracil; thus, the methylation of dUMP to produce dTMP is catalyzed by thymidylate synthase, which uses N5, N10-methylene THF as the methyl donor. In this reaction, N5, N10-methylene THF is converted to dihydrofolate (DHF). To proceed with the thymidylate synthase reaction, THF is regenerated from DHF by dihydrofolate reductase (DHFR) in conjunction with the conversion of NADPH to NADP+. Subsequently, THF is converted back to N5, N10-methylene THF by serine hydroxymethyltransferase, using serine as the substrate. The crucial role of DHFR in thymidine nucleotide biosynthesis makes it an attractive therapeutic target, as rapidly dividing cancer cells rely on thymidine nucleotides for DNA synthesis. Cells that cannot regenerate THF suffer from impaired DNA synthesis, ultimately leading to cell death. Therefore, it is therapeutically viable to target rapidly proliferating cancer cells with thymidylate synthase inhibitors, such as 5-fluorouracil. This compound is metabolically converted to 5-fluorodeoxyuridine monophosphate, which irreversibly binds to thymidylate synthase. Additionally, the enzyme DHFR can be reversibly inhibited by folate analogs, such as methotrexate, thereby reducing THF availability and limiting both purine synthesis and the methylation of dUMP to dTMP. Degradation of pyrimidine nucleotides, in contrast to purine rings, which remain intact in human cells, the pyrimidine ring is cleaved and broken down into highly soluble byproducts, namely β-alanine and β-aminoisobutyrate. This process also produces NH_3 and CO_2 [1].

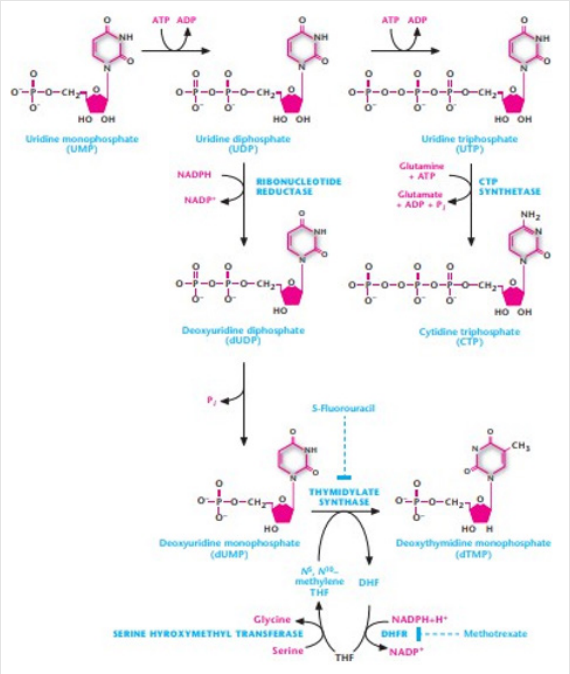

Figure 16: Uridine nucleotides serve as the building blocks for the de novo synthesis of thymine nucleotides. The conversion of UDP to dUDP is facilitated by ribonucleotide reductase. Following this, dUDP is transformed into dUMP. The methylation of dUMP to form dTMP is catalyzed by thymidylate synthase, which utilizes N5, N10-methylene THF as a methyl donor [1].

Coordinated Regulation of Purine and Pyrimidine Nucleotide Biosynthesis

Purine and pyrimidine biosynthesis occur in parallel and in a quantitatively comparable manner, indicating a coordinated regulation of their synthesis. Several points of cross-regulation are identified within the pathways that produce purine and pyrimidine nucleotides. One key enzyme, PRPP synthase, generates a crucial precursor for both pathways and is feedback-inhibited by purine and pyrimidine nucleotides. Humans metabolize adenosine and guanosine into uric acid, beginning with the conversion of adenosine to inosine by the enzyme adenosine deaminase (EC 3.5.4.4) (see Figure 17). In mammals other than higher primates, the enzyme uricase (EC 1.7.3.3) further transforms uric acid into the water-soluble compound allantoin. However, since humans lack uricase, the final product of purine catabolism in our bodies is uric acid [3].

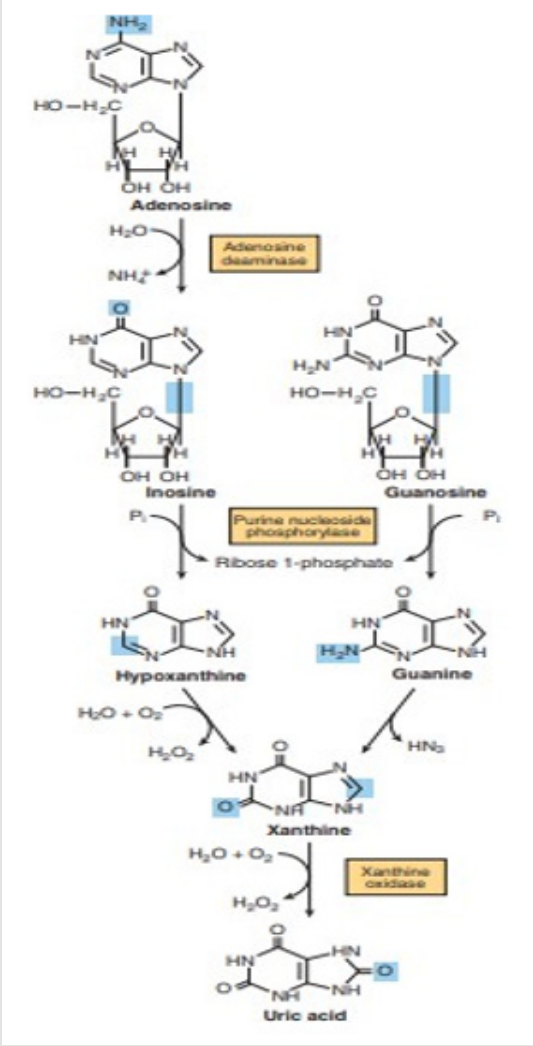

Figure 17: The process of uric acid formation occurs from purine nucleosides through the purine bases hypoxanthine, xanthine, and guanine. Purine deoxyribonucleosides undergo degradation via the same catabolic pathway and enzymes, all of which are present in the mucosa of the mammalian gastrointestinal tract [4].

Precancerous Lesions

According to [77], Precancerous Lesions, also known as pre-malignant cells, are abnormal cells that exhibit changes in their appearance or growth patterns. The cells are not cancerous, but they show changes that increase the risk of developing cancer over time. The pathogenesis of Pancreatic cancer (PC) is a prolonged, multifactorial process that entails a series of genetic and cellular changes. It is characterized by various pathological alterations and progresses through several precursor lesions, including pancreatic acinar cell transformation (ADM), pancreatic intraepithelial neoplasia (PanIN), and intraductal pancreatic mucinous neoplasms (IPMN). ADM is defined as the reversible trans differentiation of pancreatic acinar cells into duct-like cells. However, due to the influence of carcinogenic factors and chronic inflammation, ADM can evolve into more advanced lesions such as PanIN [84]. Typically, PanIN lesions are small (< 5mm) and present as flat or papillary formations within the intralobular pancreatic ducts [85]. They are classified into three grades based on nuclear atypia: PanIN-1 (low-grade), PanIN-2 (moderate-grade), and PanIN-3 (high-grade). Conversely, IPMN is characterized by cystic lesions arising from the pancreatic ductal system that produce mucin. These lesions are divided into three subtypes: main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), and mixed-type IPMN (MT-IPMN) [86]. Importantly, metabolic reprogramming occurs in these precursor lesions, suggesting that early pancreatic carcinogenesis involves metabolic adaptations to satisfy the demands of nucleotide metabolism. Additionally, metabolic changes observed at the PanIN/IPMN stage seem to persist in the pancreatic ductal adenocarcinoma (PDAC) stage. A metabolomic analysis of a PanIN mouse model showed that intermediates in the purine synthesis pathway did not increase as carcinogenesis progressed. In fact, the levels of dAMP, GMP, and dGMP decreased [87]. Conversely, there was a significant rise in ADP and ATP levels, indicating increased cellular energy metabolism. This shift may suggest either an enhancement or a subtle alteration of the purine synthesis pathway, which requires further exploration. In contrast, the pyrimidine synthesis pathway exhibited more notable upregulation during carcinogenesis, with levels of UDP and CMP increasing, while the concentration of carbamoylaspartate, an early byproduct of pyrimidine synthesis, decreased [88].

Mechanisms of Pancreatic Carcinogenesis

Pancreatic cancer (PC) is an extremely aggressive malignancy that can be divided into two main categories based on its cellular origin: pancreatic epithelial-derived and non-pancreatic epithelial-derived cancer. Most PC cases fall under the category of pancreatic epithelial-derived cancers, with pancreatic ductal adenocarcinoma (PDAC) making up over 90% of these cases. This category also encompasses adenosquamous carcinoma, colloid carcinoma, and undifferentiated carcinoma [88]. The tumorigenesis of PDAC is driven by genomic instability, including somatic mutations, chromosomal rearrangements, copy-number changes, and epigenetic modifications. There are two primary molecular models of PDAC pathogenesis that offer different perspectives on tumor progression: one suggests a gradual, stepwise evolution, while the other proposes a punctuated evolutionary pattern [89]. In addition to genetic alterations, mechanisms of nucleotide metabolism are crucial to the progression of PDAC. These mechanisms, operating through a complex regulatory network, influence PDAC progression either directly or indirectly. Figure 18 illustrates the mechanisms associated with nucleotide metabolism in pancreatic cancer cells. Angiogenesis, as seen in other solid tumors, is a critical factor in PC, serving as a key rate-limiting step in both tumor growth and metastasis. In the context of PC, angiogenesis is often triggered by hypoxic conditions within the tumor. Tumor cells react by producing and releasing various growth factors, such as vascular endothelial growth factor receptor (VEGFR) and neuropilin (NRP), which are instrumental in mediating and promoting angiogenesis [90]. Moreover, PC cells display a distinctive pathological feature known as basal microvillus supply, which supports elevated metabolic activity. These structures facilitate glucose transport into tumor cells and exhibit endocytic characteristics similar to those of normal microvessels, thereby promoting nutrient exchange within the tumor microvasculature. This interaction may also enhance the activity of phagocytes and macrophages in PDAC [91]. The tumor microenvironment (TME) of PDAC is primarily composed of diverse non-tumor cells, including cancer-associated fibroblasts (CAFs), endothelial cells (ECs), nerve cells, and immune cells, mainly of the myeloid lineage. The TME is also abundant in extracellular matrix (ECM) components, including growth factors, cytokines, hyaluronic acid (HA), and collagen. Notably, the TME of PDAC exhibits significant immunosuppression, characterized by a pronounced absence of highly active infiltrating CD8+ T cells [92]. This specific immunosuppressive environment is instrumental in facilitating PDAC proliferation, migration, and drug resistance. PC cells accommodate their rapid proliferation needs by regulating purine and pyrimidine synthesis pathways. Furthermore, the metabolites released can influence the activity of immune cells [93,94]. Within the TME, tumor-associated macrophages (TAMs) undergo metabolic reprogramming from an M1 phenotype, which is pro-inflammatory, to an M2 phenotype, which is immunosuppressive. This transition impairs effector T cell function, thereby fostering tumor immune escape and progression. Elevated levels of metabolites like adenosine suppress T cell proliferation and cytotoxic functions by binding to adenosine receptors on T cell surfaces [95,96]. Additionally, regulatory T cells (Tregs) accumulate within the PC microenvironment, further depleting essential metabolites like ATP, thereby impairing the antitumor responses of effector T cells and contributing to tumor immune evasion [97-99]. Metabolic reprogramming within the TME alters how immune cells utilize metabolites, diminishing their antitumor effectiveness and ultimately aiding tumor growth and metastasis.

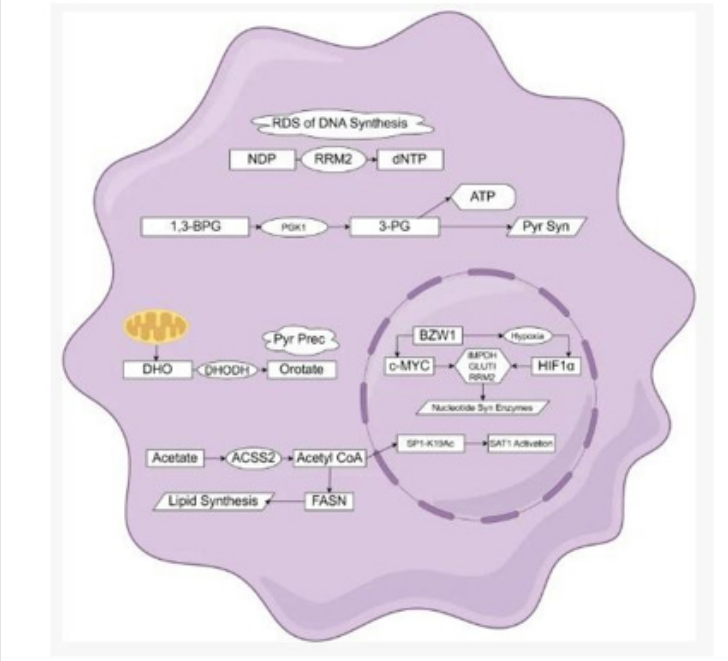

Figure 18: The mechanisms of nucleotide metabolism in pancreatic cancer cells, including DNA synthesis, pyrimidine precursor production, and gene regulation. Key factors such as RRM2, PGK1, and DHODH is crucial for these processes. It outlines changes in metabolic pathways and identifies potential drug targets and regulatory mechanisms. Key terms include RDS (rate-determining step), 1,3-BPG (1,3-Bisphosphoglycerate), and Pyrimidine Synthesis [82].

Current research also highlights the role of purinergic signaling in the crosstalk between CAFs and PDAC. In PDAC, the CD39/CD73 pathway (the ATP-AMP-adenosine axis) is significantly upregulated, leading to elevated extracellular adenosine levels that suppress CD8+ T-cell and NK-cell activity while promoting Tregs and myeloid-derived suppressor cells (MDSCs) [100]. Notably, CAFs and tumor cells are primary contributors to this pathway [99, 100]. CAFs express CD73 (NT5E) and other ectonucleotidases, producing adenosine and reinforcing local immune evasion [100,101]. For instance, multiscale profiling in PDAC revealed that CD73+ CAFs cluster near tumor cells, facilitating metabolic crosstalk and immunosuppression within the dense stroma [101]. Single-cell analysis and spatial data demonstrate that PDAC cells and CAFs are associated with higher purine metabolism scores. Co-culture experiments indicate that silencing NT5E (CD73) in PDAC cells diminished their invasion and proliferation; however, this effect was largely countered by co-culturing with CAFs [102-103]. Collectively, these findings suggest that CAF- derived purine metabolites and enzymes drive PDAC progression and immune suppression through metabolic reprogramming of the tumor microenvironment (e.g., the conversion of ATP/AMP to adenosine). Targeting this CAF-purine axis may present a strategic approach to disrupt tumor-promoting metabolic symbiosis and restore antitumor immunity in PDAC.

Summary

This study provides a comprehensive review of the molecular pathways involved in purine and pyrimidine metabolism, including de novo synthesis, salvage pathways, and degradation mechanisms. The research examines the key enzymes, intermediates, and regulatory networks that coordinate nucleotide production and utilization. Special emphasis is placed on the mechanisms that maintain nucleotide homeostasis. The review highlights the biological significance of nucleotide metabolism in health and disease. Disruptions in purine and pyrimidine pathways can lead to severe metabolic and genetic disorders, including Lesch–Nyhan syndrome, adenosine deaminase deficiency, severe combined immunodeficiency, hyperuricemia, and gout. Furthermore, emerging evidence demonstrates that altered nucleotide metabolism contributes to cancer development and progression by supporting enhanced DNA synthesis, metabolic reprogramming, and tumor cell proliferation. Recent advances in molecular biology have identified several enzymes within nucleotide metabolic pathways as promising therapeutic targets. Additionally, growing research on the role of nucleotide metabolism in the tumor microenvironment has revealed new opportunities for precision medicine and targeted therapies. Overall, this study emphasizes the central role of purine and pyrimidine metabolism in maintaining cellular homeostasis and human health. A deeper understanding of these pathways provides important insights into disease pathogenesis and supports the development of innovative diagnostic tools and therapeutic strategies to improve patient outcomes.

Conclusion

This study has highlighted the molecular mechanisms governing nucleotide metabolism, emphasizing the complex regulatory systems that coordinate nucleotide biosynthesis and utilization. Key enzymes and intermediates within purine and pyrimidine pathways function in concert to ensure adequate nucleotide availability for DNA replication, RNA transcription, cellular repair, and proliferation. Disruptions in these pathways can have profound biological consequences, leading to metabolic disorders, immunodeficiencies, neurological abnormalities, and cancer development. Clinical conditions such as Lesch–Nyhan syndrome and gout demonstrate the critical importance of maintaining nucleotide homeostasis. Furthermore, emerging evidence indicates that alterations in nucleotide metabolism significantly contribute to tumor initiation, progression, immune evasion, and therapeutic resistance. These findings have established nucleotide metabolic pathways as attractive targets for pharmacological intervention. Advances in molecular biology, genomics, and metabolic research continue to expand our understanding of nucleotide metabolism and its role in human disease. Therapeutic agents targeting key enzymes involved in purine and pyrimidine biosynthesis have already proven successful in treating cancer, autoimmune disorders, and metabolic diseases, while newer precision-medicine approaches offer promising opportunities for more selective and effective interventions. In conclusion, nucleotide metabolism remains a cornerstone of cellular physiology and human health. Continued investigation of the molecular, genetic, and regulatory aspects of purine and pyrimidine pathways will deepen our understanding of disease pathogenesis and facilitate the development of innovative diagnostic, preventive, and therapeutic strategies. Such advances hold significant potential to improve clinical outcomes and advance personalized medicine.

References

1. Chandel N S (2021) Nucleotide Metabolism. Cold Spring Harb Perspect Biol J 13(7): a040592.
2. Harvey R, Ferrier D (2008) Lippincott's Illustrated Reviews: Biochemistry.
3. Rodwell V W (2015) McGraw-Hill Education, Harper's Illustrated Biochemistry, (30th Edn.)., Ch, p. 32.
4. Hofer A, Crona M, Logan D T, Sjöberg B M (2012) DNA building blocks: keeping control of manufacture. Cri Rev Biochem Molecu Bio 47(1): 50-63.
5. Stubbe J, Nocera D G, Yee C S, Chang M C (2003) Radical Initiation in the Class I Ribonucleotide Reductase: Long-Range Proton-Coupled Electron Transfer?. Chem Rev 103(6): 2167-2201.
6. Sneeden J L, Loeb L A (2004) Mutations in the R2 subunit of ribonucleotide reductase that confer resistance to hydroxyurea. J Bio Chem 279(39): 40723-40728.
7. Janson L W, Tischler, M E (2024) McGraw-Hill, The Big Picture: Medical Biochemistry, Ch, p. 4.
8. Dawson J (2021) Introduction to Biochemistry. Ch, p. 14.
9. Armenta-Medina D, Segovia L, Perez-Rueda E (2014) Comparative genomics of nucleotide metabolism: a tour to the past of the three cellular domains of life. BMC Genomics 15(1): 800.
10. Neuhard J, Nygaard P (1987) Purines and pyrimidines, in Escherichia coli and Salmonella typhimurium: cellular and molecular biology. Ameri Soci Micro, pp. 445-473.
11. Zalkin H, Nygaard P (1996) Biosynthesis of purine nucleotides, in Escherichia coli and Salmonella: cellular and molecular biology. Ameri Soci Micro, pp. 561-579.
12. Moffatt B A, Ashihara H (2002) Purine and pyrimidine nucleotide synthesis and metabolism. Arab Book 1: e0018.
13. Jensen K F, Dandanell G, Hove-Jensen B, Willemo Es M (2008) Nucleotides, nucleosides, and nucleobases. EcoSal Plus 3(1).
14. Lane A N, Fan T W (2015) Regulation of mammalian nucleotide metabolism and biosynthesis. Nucleic Acids Res 43(4): 2466-2485.
15. Rudolph F B (1994) The biochemistry and physiology of nucleotides. J Nutr 124(1): 124S-127S.
16. Carver J D, Allan Walker W (1995) The role of nucleotides in human nutrition. J Nutr Biochem 6(2): 58-72.
17. Traut T (2014) Nucleotide synthesis de novo, in Encyclopedia of Life Sciences. New York: John Wiley & Sons, Ltd.
18. Atkins C A, Smith P, Storer P J (1997) Reexamination of the intracellular localization of de novo purine synthesis in cowpea nodules. Plant Physiol 113(1): 127-135.
19. Pareek V, Pedley A M, Benkovic S J (2022) Human de novo Purine Biosynthesis. Crit Rev Biochem Mol Biol 56(1): 1-16.
20. Ayoub N, Gedeon A, Munier-Lehmann H (2024) A journey into the regulatory secrets of the de novo purine nucleotide biosynthesis. Front Pharmacol 15: 1329011.
21. Palmieri F (2013) The mitochondrial transporter family SLC25: identification, properties and physiopathology. Mol Aspects Med 34(2-3): 465-84.
22. Vettore L, Westbrook R L, Tennant D A (2020) New aspects of amino acid metabolism in cancer. Br J Cancer 122(2): 150-156.
23. Tibbetts A S, Appling D R (2010) Compartmentalization of Mammalian folate-mediated one-carbon metabolism. Annu Rev Nutr 30: 57-81.
24. Ducker G S, Rabinowitz J D (2017) One-Carbon Metabolism in Health and Disease. Cell Metab 25(1): 27-42.
25. Kory N, Wyant G A, Prakash G, Uit de Bos J, Bottanelli F, et al. (2018) SFXN1 is a mitochondrial serine transporter required for one-carbon metabolism. Science 362(6416): eaat9528.
26. Amoedo N D, Punzi G, Obre E, Lacombe D, De Grassi A, et al. (2016) AGC1/2, the mitochondrial aspartate-glutamate carriers. Biochim Biophys Acta 1863(10): 2394-2412.
27. Lunetti P, Damiano F, De Benedetto G, Siculella L, Pennetta A, et al. (2016) Characterization of Human and Yeast Mitochondrial Glycine Carriers with Implications for Heme Biosynthesis and Anemia. J Biol Chem 291(38): 19746-19759.
28. Misak A, Grman M, Malekova L, Novotova M, Markova J, et al. (2013) Mitochondrial chloride channels: electrophysiological characterization and pH induction of channel pore dilation. Eur Biophys J 42(9): 709-720.
29. Zalkin H, Dixon J E (1992) De novo purine nucleotide biosynthesis. Prog Nucleic Acid Res. Mol Biol 42: 259-287.
30. Zhang Y, Morar M, Ealick S E (2008) Structural biology of the purine biosynthetic pathway. Cell Mol Life Sci 65(23): 3699-3724.
31. Hove-Jensen B, Andersen K R, Kilstrup M, Martinussen J, Switzer R L, et al. (2017) Phosphoribosyl Diphosphate (PRPP): Biosynthesis, Enzymology, Utilization, and Metabolic Significance. Microbiol Mol Biol Rev 81(1): e00040-16.

32. Kim J H, Krahn J M, Tomchick D R, Smith J L, Zalkin H (1996) Structure and function of the glutamine phosphoribosylpyrophosphate amidotransferase glutamine site and communication with the phosphoribosylpyrophosphate site. J Biol Chem 271(26): 15549-15557.

33. Bera A K, Chen S, Smith J L, Zalkin H (1999) Interdomain signaling in glutamine phosphoribosylpyrophosphate amidotransferase. J Biol Chem 274(51): 36498-36504.

34. Bera A K, Smith J L, Zalkin H (2000) Dual role for the glutamine phosphoribosylpyrophosphate amidotransferase ammonia channel. Interdomain signaling and intermediate channeling. J Biol Chem 275(11): 7975-7979.

35. Krahn J M, Kim J H, Burns M R, Parry R J, Zalkin H, et al. (1997) Coupled formation of an amidotransferase interdomain ammonia channel and a phosphoribosyltransferase active site. Biochemistry 36(37): 11061-11068.

36. Batool S, Nawaz M S, Kamal M A (2013) In silico analysis of the amido phosphoribosyltransferase inhibition by PY873, PY899 and a derivative of isophthalic acid. Invest New Drugs 31(5): 1355-1363.

37. Smith J L, Zaluzec E J, Wery J P, Niu L, Switzer R L, et al. (1994) Structure of the allosteric regulatory enzyme of purine biosynthesis. Science 264(5164): 1427-1433.

38. Wong J Y, Bernlohr D A, Turnbough C L, Switzer R L (1981) Purification and properties of glutamine phosphoribosylpyrophosphate amidotransferase from Bacillus subtilis. Biochemistry 20(20): 5669-5674.

39. Zhou G, Broyles S S, Dixon J E, Zalkin H (1992) Avian glutamine phosphoribosylpyrophosphate amidotransferase propeptide processing and activity are dependent upon essential cysteine residues. J Biol Chem 267(11): 7936-7942.

40. Mena N P, Bulteau A L, Salazar J, Hirsch E C, Nunez M T (2011) Effect of mitochondrial complex I inhibition on Fe-S cluster protein activity. Biochem Biophys Res Commun 409(2): 241-246.

41. Sharma N, Ahalawat N, Sandhu P, Strauss E, Mondal J, et al. (2020) Role of allosteric switches and adaptor domains in long-distance crosstalk and transient tunnel formation. Sci Adv 6(14): eaay7919.

42. Li S X, Tong Y P, Xie X C, Wang Q H, Zhou H N, et al. (2007) Octameric structure of the human bifunctional enzyme PAICS in purine biosynthesis. J Mol Biol 366(5): 1603-1614.

43. Skerlova J, Unterlass J, Gottmann M, Marttila P, Homan E, et al. (2020) Crystal structures of human PAICS reveal substrate and product binding of an emerging cancer target. J Biol Chem 295(33): 11656-11668.

44. Ray S P, Deaton M K, Capodagli G C, Calkins L A, Sawle L, (2012) Structural and biochemical characterization of human adenylosuccinate lyase (ADSL) and the R303C ADSL deficiency-associated mutation. Biochemistry 51(33): 6701-6713.

45. Wall M, Shim J H, Benkovic S J (2000) Human AICAR transformylase: role of the 4-carboxamide of AICAR in binding and catalysis. Biochemistry 39(37): 11303-11311.

46. Greasley S E, Horton P, Ramcharan J, Beardsley G P, Benkovic S J, et al. (2001) Crystal structure of a bifunctional transformylase and cyclohydrolase enzyme in purine biosynthesis. Nat Struct Biol 8(5): 402-406.

47. Vergis J M, Bulock K G, Fleming K G, Beardsley G P (2001) Human 5-aminoimidazole-4-carboxamide ribonucleotide transformylase/inosine 5'-monophosphate cyclohydrolase. A bifunctional protein requiring dimerization for transformylase activity but not for cyclohydrolase activity. J Biol Chem 276(11): 7727-7733.

48. Bulock K G, Beardsley G P, Anderson K S (2002) The kinetic mechanism of the human bifunctional enzyme ATIC (5-amino-4-imidazolecarboxamide ribonucleotide transformylase/inosine 5'-monophosphate cyclohydrolase). A surprising lack of substrate channeling. J Biol Chem 277(15): 22168-22174.

49. Hartman S C, Buchanan J M (1959) Nucleic acids, purines, pyrimidines (nucleotide synthesis). Annu Rev Biochem 28: 365-410.

50. Villa E, Ali E S, Sahu U, Ben-Sahra I (2019) Cancer Cells Tune the Signaling Pathways to Empower de Novo Synthesis of Nucleotides. Cancers (Basel) 11(5): 688.

51. AsilbekAkbarjono'g'li M, Akbarovna J D (2023) Causes of Purine and Pyrimidine Metabolism Disorders. International Multidisciplinary Journal for Research & Development 10(11): 499-502.

52. Seegmiller J E (1979) Disorders of Purine and Pyrimidine Metabolism. In: Freinkel, N. (Edt.)., Contemporary Metabolism.

53. HeL Hannon G J (2004) MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 5(7): 522-531.

54. Ratti M, Lampis A, Ghidini M, Salati M, Mirchev M B, et al. (2020) MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside. Target Oncol 15(3): 261-278.

55. Goswami M T, Chen G, Chakravarthi B V, Pathi S S, Anand S K, et al. (2015) Role and regulation of coordinately expressed de novo purine biosynthetic enzymes PPAT and PAICS in lung cancer. Oncotarget 6(27): 23445-23461.

56. Chakravarthi B V S K, Rodriguez Pena M D C, Agarwal S, Chandrashekar D S, Hodigere Balasubramanya S A, et al. (2018) A Role for De Novo Purine Metabolic Enzyme PAICS in Bladder Cancer Progression. Neoplasia 20(9): 894-904.

57. Hauser B, Zhao Y, Pang X, Ling Z, Myers E, et al. (2015) Functions of MiRNA-128 on the regulation of head and neck squamous cell carcinoma growth and apoptosis. PLoS One. 10(3): e0116321.

58. Agarwal S, Chakravarthi B V S K, Behring M, Kim H G, Chandrashekar D S, et al. (2020) PAICS, a Purine Nucleotide Metabolic Enzyme, is Involved in Tumor Growth and the Metastasis of Colorectal Cancer. Cancers (Basel) 12(4): 772.

59. Agarwal S, Chakravarthi B V S K, Kim H G, Gupta N, Hale K, et al. (2020) PAICS, a De Novo Purine Biosynthetic Enzyme, Is Overexpressed in Pancreatic Cancer and Is Involved in Its Progression. Transl Oncol 13(7): 100776.

60. Liu X, Kimmey J M, Matarazzo L, de Bakker V, Van Maele L, et al. (2021) Exploration of Bacterial Bottlenecks and Streptococcus pneumoniae Pathogenesis by CRISPRi-Seq. Cell Host Microbe 29(1): 107-120.

61. Ali E S, Sahu U, Villa E, O'Hara B P, Gao P, et al. (2020) ERK2 Phosphorylates PFAS to Mediate Posttranslational Control of De Novo Purine Synthesis. Mol Cell 78(6): 1178-1191.

62. Zhang J, Sprung R, Pei J, Tan X, Kim S, et al. (2009) Lysine acetylation is a highly abundant and evolutionarily conserved modification in Escherichia coli. Mol Cell Proteomics 8(2): 215-25.

63. Sharma N, Zhou W, French J B (2026) Structural and molecular basis for allosteric regulation and catalytic coupling of human phosphoribosylformylglycinamidine synthase. Nat Commun 17(1): 2732.

64. Nelson D L, Cox M M (2005) Lehninger principles of biochemistry. (4th Edn.)., New York: W.H. Freeman and Company.

65. Miller R C, Patterson M G, Bhatt N, Pei X, Ando N (2024) Mechanism of Nucleotide-Dependent Allosteric Regulation in Escherichia coli Aspartate Transcarbamoylase. bioRxiv.

66. Holmes E W, McDonald J A, McCord J M, Wyngaarden J B, Kelley W N, et al. (1973) Human glutamine phosphoribosylpyrophosphate amidotransferase: kinetic and regulatory properties. J Biol Chem 248(1): 144-150.

67. Messenger L J, Zalkin H (1979) Glutamine phosphoribosylpyrophosphate amidotransferase from Escherichia coli Purification and properties. J Biol Chem 254(9): 3382-3392.

68. Smith J L (1998) Glutamine PRPP amidotransferase: snapshots of an enzyme in action. Curr Opin Struct Biol 8(6): 686-694.

69. Brosh S, Boer P, Kupfer B, de Vries A, Sperling O (1976) De novo synthesis of purine nucleotides in human peripheral blood leukocytes. Excessive activity of the pathway in hypoxanthine-guanine phosphoribosyltransferase deficiency. J Clin Invest 58(2): 289-297.

70. Gibson K J, Schubert K R, Switzer R L (1982) Binding of the substrates and the allosteric inhibitor adenosine 5′-diphosphate to phosphoribosylpyrophosphate synthetase from Salmonella typhimurium. J Biol Chem 257(5): 2391-2396.

71. Becker M A, Kim M (1987) Regulation of purine synthesis de novo in human fibroblasts by purine nucleotides and phosphoribosylpyrophosphate. J Biol Chem 262(30): 14531-14537.

72. Nosal J M, Switzer R L, Becker M A (1993) Overexpression, purification, and characterization of recombinant human 5-phosphoribosyl-1-pyrophosphate synthetase isozymes I and II. J Biol Chem 268(14): 10168-10175.

73. Eriksen T A, Kadziola A, Bentsen A-K, Harlow K W, Larsen S (2000) Structural basis for the function of Bacillus subtilis phosphoribosyl-pyrophosphate synthetase. Nat Struct Biol 7(4): 303-308.

74. Hove-Jensen B, Harlow K W, King C J, Switzer R L (1986) Phosphoribosylpyrophosphate synthetase of Escherichia coli. Properties of the purified enzyme and primary structure of the prs gene. J Biol Chem 261(15): 6765-6771.

75. Hu H-H, Lu G, Chang C-C, Li Y, Zhong J, et al. (2024) Allosteric inhibition of PRPS is moderated by 2 filamentous polymerizations. bioRxiv preprint.

76. Liu Q, Liu J, Wang S, Bao N, Zhao X, et al. (2025) Roles of nucleotide metabolism in pancreatic cancer. Front Immunol 16: 1637768.

77. Tran D H, Kim D, Kesavan R, Brown H, Dey T, et al. (2024) De novo and salvage purine synthesis pathways across tissues and tumors. Cell 187(14): 3602-3618.e20.

78. Liu R, Wu Q, Wu C, Qu Y, Fang Y, et al. (2024) Metabolic signatures of metabolites of the purine degradation pathway in human plasma using HILIC UHPLC-HRMS. J Pharma and Biomed Analysis 251: 116451.

79. Hiranoa M, Petersb G J (2018) Advances in Purine and Pyrimidine Metabolism in Health and Diseases. Nucleo Nucleo Nucle Acids 35(10-12): 495-501.

80. Nanagiri A, Shabbir N (2026) Lesch-Nyhan Syndrome. Treasure Island (FL): StatPearls Publishing.

81. Schretlen D J, Callon W, Ward R E, Fu R, Ho T, et al. (2016) Do clinical features of Lesch-Nyhan disease correlate more closely with hypoxanthine or guanine recycling?. J Inherit Metab Dis 39(1): 85-91.

82. Torres R J, Puig J G, Jinnah H A (2021) Update on the phenotypic spectrum of Lesch-Nyhan disease and its attenuated variants. Curr Rheumatol Rep 14(2): 189-94.

83. Marstrand-Daucé L, Lorenzo D, Chassac A, Nicole P, Couvelard A, et al. (2023) Acinar-to-ductal metaplasia (ADM): on the road to pancreatic intraepithelial neoplasia (PanIN) and pancreatic cancer. Int J Mol Sci 24(12): 9946.

84. Hruban R H, Takaori K, Klimstra D S, Adsay N V, Albores-Saavedra J, et al. (2004) An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 28(8): 977-987.

85. Tanaka M, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, et al. (2017) Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 17(5): 738-753.

86. Vernucci E, Abrego J, Gunda V, Shukla S K, Dasgupta A, et al. (2019) Metabolic Alterations in Pancreatic Cancer Progression. Cancers (Basel) 12(1): 2.

87. Orth M, Metzger P, Gerum S, Mayerle J, Schneider G, et al. (2019) Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol 14(1): 141.

88. Ruff S M, Pawlik T M (2024) Molecular classification and pathogenesis of pancreatic adenocarcinoma and targeted therapies: A review. FBL 29(3): 101.

89. Li S, Xu H X, Wu C T, Wang W Q, Jin W, et al. (2019) Angiogenesis in pancreatic cancer: current research status and clinical implications. Angiogenesis 22(1): 15-36.

90. Hexige S, Ardito-Abraham C M, Wu Y, Wei Y, Fang Y, et al. (2015) Identification of novel vascular projections with cellular trafficking abilities on the microvasculature of pancreatic ductal adenocarcinoma. J Pathol 236(2): 142-154.

91. Falcomatà C, Bärthel S, Schneider G, Rad R, Schmidt-Supprian M, et al. (2023) Context-specific determinants of the immunosuppressive tumor microenvironment in pancreatic cancer. Cancer Discov 13(2): 278-297.

92. Xiang H, Yang R, Tu J, Xi Y, Yang S, et al. (2023) Metabolic reprogramming of immune cells in pancreatic cancer progression. Biomed Pharmacother 157: 113992.

93. Hashimoto A, Hashimoto S (2024) Plasticity and tumor microenvironment in pancreatic cancer: genetic, metabolic, and immune perspectives. Cancers 16(23): 4094.

94. Habtezion A, Edderkaoui M, Pandol S J (2016) Macrophages and pancreatic ductal adenocarcinoma. Cancer Lett 381(1): 211-216.

95. Elebo N, Fru P, Omoshoro−Jones J, Patrick Candy G, Nweke E E (2020) Role of different immune cells and metabolic pathways in modulating the immune response in pancreatic cancer (Review). Mol Med Rep 22(6): 4981-4991.

96. Hartupee C, Nagalo B M, Chabu C Y, Tesfay M Z, Coleman-Barnett J, et al. (2024) Pancreatic cancer tumor microenvironment is a major therapeutic barrier and target. Front Immunol 15: 1287459.

97. Huber M, Brehm C U, Gress T M, Buchholz M, Alashkar Alhamwe B, et al. (2020) The Immune Microenvironment in Pancreatic Cancer. Int J Mol Sci 21(19): 7307.

98. Zhang Y, Lazarus J, Steele N G, Yan W, Lee H J, et al. (2020) Regulatory T-cell Depletion Alters the Tumor Microenvironment and Accelerates Pancreatic Carcinogenesis. Cancer Discov 10(3): 422-439.

99. Liu X, Ding Q, Zhang H, Zhang X, Chen Q, et al. (2025) The CD39-CD73-adenosine axis: Master regulator of immune evasion and therapeutic target in pancreatic ductal adenocarcinoma. Biochim Biophys Acta Rev Cancer 1880: 189443.

100. Zhang E, Ding X, Zhang J, Liu W, Liu G, et al. (2025) Multi-omics analysis of polyamine metabolism implicates NT5E/CD73 in the progression of pancreatic cancer. Cancer Lett 630: 217887.

101. Zhang J, Zhang X, Wu R, Dong C S (2025) Unveiling purine metabolism dysregulation orchestrated immunosuppression in advanced pancreatic cancer and concentrating on the central role of NT5E. Front Immunol, p. 16.

102. Farmer S, Kennepohl D (2025) Nucleotides and Nucleic Acids. The LibreTexts libraries.

103. Thweatt J L, Harman C E, Araújo M N, Marlow J J, Oliver G C, et al. (2024) Chapter 6: The Breadth and Limits of Life on Earth. Astrobiology 24(S1): S124-S142.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2026.66.010310

Alber Fares . Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php