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Targeting purine metabolism as the next generation of cancer therapeutic strategies



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Highlights:

- Purine metabolism is aberrantly reprogrammed across multiple cancers.
- Purine metabolic enzymes connect nucleotide synthesis with tumour progression and therapy resistance.
- Selective targeting of purine metabolism may enable next-generation anticancer strategies.

Abstract: Purine metabolism, a fundamental metabolic pathway governing nucleic acid synthesis, energy supply and cellular signaling, is aberrantly reprogrammed in tumor cells and acts as a critical driver of tumorigenesis and malignant progression. This review comprehensively summarizes the expression characteristics, regulatory mechanisms and specific roles of key enzymes involved in purine metabolism, such as phosphoribosyl pyrophosphate synthetase (PRPS), inosine monophosphate dehydrogenase (IMPDH), and adenosine deaminase (ADA), in the occurrence and development of various tumors, as well as recent advances in small-molecule inhibitors targeting these enzymes and evaluating their therapeutic potential and clinical application prospects in cancer treatment. Currently, a series of challenges remain, including diverse reactions, the interaction between tumor cells and the microenvironment, metabolic heterogeneity, and metabolic adaptability. Future research should focus on exploring precise regulatory networks of purine metabolism in tumors and developing novel highly selective inhibitors with low toxicity. This review aims to provide a comprehensive framework for understanding purine metabolic reprogramming and to support the development of novel metabolism-based anticancer strategies.



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Keywords: purine metabolism; cancer; key metabolic enzymes; small-molecule inhibitors; anticancer therapy

1. Introduction

Purine biosynthesis and catabolism, collectively known as the purine metabolism pathway, have attracted increasing attention in cancer research and therapeutic intervention [1,2]. In humans, purine metabolism comprises three major components: *de novo* purine biosynthesis (DNPB), the salvage pathway, and purine catabolism. DNPB begins with ribose-5-phosphate, which is sequentially catalyzed by six enzymes through ten steps to assemble purine nucleotides, with phosphoribosyl pyrophosphate (PRPP) as a key intermediate. Inosine 5'-monophosphate (IMP) serves as a central intermediate in DNPB, which can be readily converted into the final products: adenosine 5'-monophosphate (AMP) or guanosine 5'-monophosphate (GMP) [3]. Rapidly dividing cancer cells exhibit an increased demand for nucleotides to support deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, and consequently upregulate DNPB to sustain intracellular purine nucleotide pools [4]. In parallel, the salvage pathway recycles preformed purine bases and nucleotides to replenish nucleotide pools with lower energetic cost, thereby supporting nucleotide balance and cellular proliferation [5]. Purine catabolism, in contrast, mediates the degradation of purine nucleotides into downstream metabolites such as uric acid, which is ultimately excreted from the body. Together, these three interconnected pathways maintain purine nucleotide availability and metabolic equilibrium under physiological conditions (Figure 1).

Dysregulation of this pathway underpins tumor initiation, progression, and therapeutic resistance across multiple malignancies. Recent mechanistic studies have identified dysregulated enzymes in purine biosynthesis, such as phosphoribosyl pyrophosphate amidotransferase (PPAT) and phosphoribosyl pyrophosphate synthetase 2 (PRPS2), as important drivers of altered purine metabolite profiles in cancer [6]. Thus, components of the purine metabolism pathway have been explored as potential biomarkers for cancer prognosis and treatment response. Monitoring the expression levels or activities of key enzymes in purine metabolism may aid in predicting therapeutic outcomes and patient stratification. Furthermore, inhibitors targeting key enzymes involved in purine biosynthesis, such as inosine monophosphate dehydrogenase (IMPDH), have been developed and evaluated in both preclinical and clinical studies. By impairing nucleotide production, these inhibitors can suppress cancer cell proliferation or induce cell death. Overall, targeting purine biosynthesis and metabolism pathways has shown promise as a therapeutic strategy in cancer treatment. Nevertheless, despite promising advancements, challenges remain in targeting purine metabolism for cancer therapy. Resistance mechanisms and the potential impacts of these inhibitors on normal cell function require further investigation.

In addition to individual metabolic enzymes, increasing attention has been directed toward the purinosome, a dynamic multienzyme complex that facilitates DNPB. By promoting the coordinated organization of biosynthetic enzymes, the purinosome enables efficient nucleotide production in response to cellular proliferative demands and metabolic stress. Emerging evidence further suggests that alterations in purinosome assembly may contribute to metabolic adaptation and tumor progression.

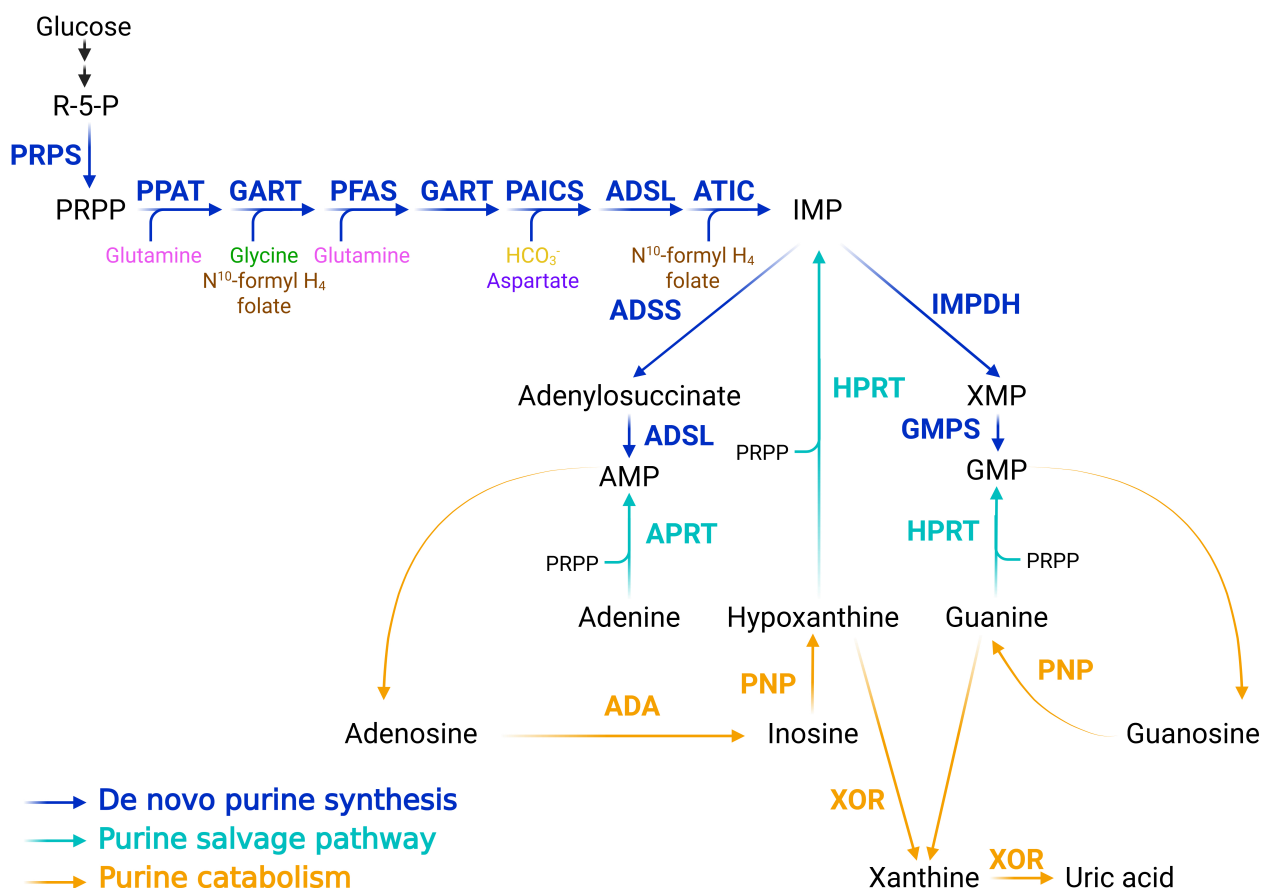


Figure 1. Schematic overview of the purine metabolism network. The purine metabolism network primarily consists of three interconnected pathways: *de novo* purine synthesis (dark blue arrows), the purine salvage pathway (light green arrows), and purine catabolism (yellow arrows). During *de novo* synthesis, PRPP is sequentially converted into IMP through a multi-step enzymatic cascade utilizing amino acids (glutamine, glycine, aspartate) and carbon donors (N [10-]formyl- H_4 folate). IMP subsequently serves as the common precursor for the generation of AMP and GMP. The purine salvage pathway efficiently recycles free purine bases (adenine, hypoxanthine, and guanine) back into their corresponding nucleotides via the enzymes APRT and hypoxanthine-guanine phosphoribosyltransferase (HPRT), utilizing PRPP. Conversely, purine catabolism involves the degradation of purine nucleotides into nucleosides and free bases, which are ultimately oxidized into uric acid by XOR for excretion. This figure was created by Biorender (<https://app.biorender.com/>).

In this review, we summarize recent advances in purine metabolism in cancer, covering the *de novo*, salvage, and catabolic pathways. We focus primarily on DNPB, while also discussing the other two pathways and emphasizing the dysregulation of their key enzymes in cancer. Meanwhile, we summarize the current understanding of how aberrant activation of this pathway contributes to tumor progression and malignancy and discuss representative inhibitors and small-molecule compounds targeting these enzymes as potential therapeutic strategies. Taken together, targeting purine metabolism as an integrated network may provide new opportunities for cancer diagnosis and treatment.

2. Key enzymes in the DNPB pathway in cancer

The DNPB pathway is directly responsible for the *de novo* synthesis of IMP and its downstream products AMP and GMP. It provides critical substrates for sustained proliferation, nucleic acid synthesis, and stress adaptation of tumor cells. Accumulating evidence indicates that most tumors can enhance nucleotide supply capacity by upregulating the expression or activity of enzymes involved in *de novo* biosynthesis, thereby promoting tumor growth, progression, and therapeutic resistance [7]. Consequently, the DNPB pathway constitutes a core component for understanding the link between purine metabolic reprogramming and tumor biology.

3. Phosphoribosyl pyrophosphate synthetase 1/2

Growing evidence indicates that PRPS1/2 are central regulators of tumor progression, metabolic reprogramming, and therapy resistance across multiple cancers. For example, upregulation of PRPS1 or PRPS2 expression promotes malignant progression in prostate cancer (PCa) [8], B-cell acute lymphoblastic leukemia (B-ALL) [9], and breast cancer [10], whereas suppression of PRPS1/2 enhances the sensitivity of breast cancer cells to cisplatin [11]. In T-cell acute lymphoblastic leukemia, ubiquitin protein ligase E3 component N-recognin 7 (UBR7) stabilizes PRPS1/2 and enhances nucleotide synthesis, thereby supporting tumor growth [12]. Notably, although PRPS1 and PRPS2 exhibit a high degree of redundancy in their enzymatic functions, their regulatory patterns and biological roles show marked specificity across different tumor types. PRPS1 is mainly regulated at the transcriptional and post-transcriptional levels. Ketohexokinase-A (KHK-A), MYCN, and nuclear factor erythroid 2-related factor 2 (NRF2) upregulate PRPS1 expression in esophageal squamous cell carcinoma, neuroblastoma, and melanoma, respectively, thereby promoting cell cycle progression and proliferation [13–15]. In colorectal cancer, PRPS1/2 enhance metastatic potential by promoting epithelial–mesenchymal transition (EMT) [16]. PRPS1 is also regulated by non-coding RNAs: miR-124 suppresses PRPS1 and limits colorectal cancer cell proliferation [17], whereas deleted in lymphocytic leukemia 1 (DLEU1) promotes malignant transformation by upregulating PRPS1 through miR-320b [18]. MYC proto-oncogene, bHLH transcription factor (c-Myc) also enhances PRPS1-dependent *de novo* purine biosynthesis, increasing AMP and GMP levels in brain tumor–initiating cells and melanoma [19,20]. In c-Myc-driven lymphomas, PRPS1/2 additionally regulate oxidative pentose phosphate pathway flux in a subtype-specific manner, thereby affecting redox homeostasis, survival, and chemosensitivity [21]. In contrast, the tumor-specific functions of PRPS2 are particularly prominent in lung cancer. PRPS2 stabilizes methionine adenosyltransferase 2A (MAT2A) and promotes the synthesis of S-adenosylmethionine, which enhances RNA m⁶A methylation mediated by the Wilms Tumor 1-Associated Protein (WTAP)/Methyltransferase-Like 3 (METTL3)/Methyltransferase-Like 14 (METTL14) complex. This process drives the proliferation and metastasis of lung adenocarcinoma [22]. It also modulates antitumor immunity by remodeling CCL2-dependent functions of tumor-associated macrophages and myeloid-derived suppressor cells [23]. In Burkitt lymphoma, eukaryotic initiation factor 4E (eIF4E) increases PRPS2 translation to promote DNPB and metabolic activity [11]. Furthermore, genetic mutations in PRPS1/2 have important functional implications for tumor drug resistance and relapse. Chemotherapy, particularly thiopurine treatment, can induce resistance-associated mutations in PRPS1 [24]. Among them, PRPS1 A190T confers thiopurine resistance by escaping feedback inhibition of

purine biosynthesis and is associated with relapsed acute lymphoblastic leukemia [24,25]. Also, the PRPS2 P173R mutation reduces the stability of the PRPS1/2 hexamer while increasing enzymatic activity, further exacerbating therapeutic resistance in relapsed all [26].

Post-translational modifications add another layer of regulation by altering PRPS1/2 oligomerization or stability. OGT-mediated O-GlcNAcylation promotes PRPS1/2 hexamerization and enzymatic activity, driving lung tumorigenesis and resistance to chemoradiotherapy [27]. CLOCK-mediated acetylation at Lys29 stabilizes PRPS1/2 and sustains purine synthesis and tumor growth in hepatocellular carcinoma (HCC) and glioblastoma (GBM) [28,29]. In contrast, AMPK-mediated phosphorylation of PRPS1 at Ser180 and PRPS2 at Ser183 induces hexamer disassembly and suppresses enzymatic activity, thereby limiting tumor proliferation in GBM and melanoma [30,31]. Other kinases, such as KHK-A and cyclin-dependent kinase 1 (CDK1), can also enhance PRPS1 activity through site-specific phosphorylation. This regulation links nucleotide metabolism with redox homeostasis and cell cycle control, thereby promoting malignant progression in HCC and colorectal cancer [32,33].

Together, these findings show that PRPS1/2 are not merely metabolic enzymes but central hubs integrating transcriptional regulation, epigenetic control, metabolic signaling, and therapeutic response (Figure 2). This concept provides an important theoretical basis for targeting PRPS1/2 in cancer metabolic therapy.

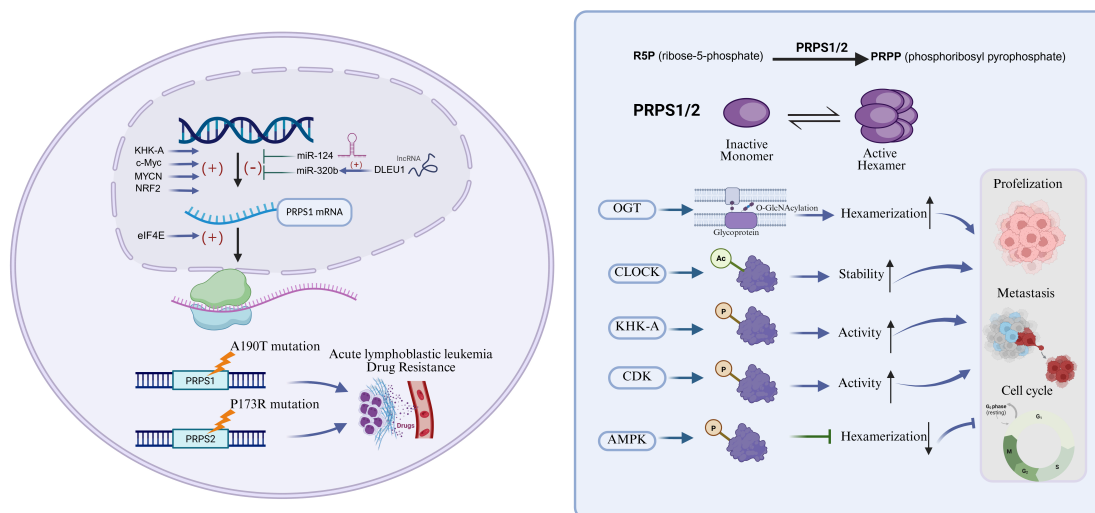


Figure 2. Biology function of PRPS1/2 in cancer. PRPS1/2 catalyzes the conversion of R5P to PRPP, a rate-limiting metabolic step that supports purine nucleotide biosynthesis. PRPS1 expression is regulated at the transcriptional and post-transcriptional levels by KHK-A, c-Myc, MYCN, NRF2, eIF4E, miR-124, miR-320b and lncRNA DLEU1. PRPS1/2 function is further modulated by oligomerization and post-translational modifications, with OGT-mediated O-GlcNAcylation promoting hexamer formation, CLOCK-mediated acetylation enhancing protein stability, KHK-A- and CDK-dependent phosphorylation increasing enzymatic activity, and AMPK-dependent phosphorylation inhibiting hexamerization. These regulatory events collectively drive tumor-promoting phenotypes, including proliferation, metastasis and cell-cycle progression. Moreover, PRPS1 and PRPS2 mutations, such as PRPS1 A190T and PRPS2 P173R, are associated with drug resistance in acute lymphoblastic leukemia. This figure was created by Biorender (<https://app.biorender.com/>).

4. Phosphoribosyl pyrophosphate amidotransferase

PPAT is the rate-limiting enzyme of DNPB. It is frequently upregulated in multiple cancers, including lung adenocarcinoma, small cell lung cancer (SCLC), and HCC. High PPAT expression is associated with poor prognosis [34–36]. Functionally, PPAT promotes tumor cell proliferation, invasion, and metastasis, indicating its critical role in tumor progression.

PPAT acts as a metabolic gatekeeper of DNPB by integrating multiple upstream inputs to maintain nucleotide pool homeostasis. Under hypoxia, hypoxia-inducible factor 1- α (HIF-1 α) directly activates PPAT transcription, promoting melanoma progression [37]. In hormone-driven cancers such as estrogen receptor α (ER α)-positive breast cancer, estrogen enhances one-carbon metabolism and increases substrate flux into the DNPB pathway, rendering tumor cells dependent on PPAT-mediated purine synthesis [38]. PPAT is also tightly linked to amino acid metabolism. Glutamine induces PPAT and phosphoribosylaminoimidazole-succinocarboxamide synthetase (PAICS) expression and promotes purine biosynthesis in lung cancer [35]. In renal cell carcinoma, serine hydroxymethyltransferase 2 (SHMT2) upregulates PPAT, coupling serine metabolism to nucleotide synthesis [39]. Similarly, Kaposi's sarcoma-associated herpesvirus (KSHV)-transformed cells rely on PPAT-driven nucleotide production for glutamine-dependent survival, highlighting its role in metabolic network integration [40]. Beyond metabolism, PPAT contributes to oncogenic signaling. In thyroid cancer, PPAT upregulates pyruvate kinase M2 (PKM2) and activates the STAT3 signaling pathway and MAPK/ERK signaling pathway, thereby promoting proliferation and invasion [41]. In addition, PPAT links metabolism to gene expression. Elevated adenosine triphosphate (ATP) and GTP levels support RNA synthesis and translation, enhancing protein production. Frameshift mutations of PPAT in gastric cancer and microsatellite instability-high (MSI-H) colorectal cancer further suggest its involvement in metabolic reprogramming and genomic instability [42].

From a clinical perspective, PPAT has potential as a prognostic biomarker. This has been reported in cancers such as nasopharyngeal carcinoma (NPC) [43]. Targeting PPAT or the DNPB pathway may deplete nucleotide pools. This can induce replication stress and activate DNA damage responses. As a result, tumor growth is suppressed and sensitivity to therapy is increased. Overall, PPAT is not only a metabolic enzyme but also a key regulator linking metabolism to tumor progression. It represents a promising therapeutic target.

5. Glycinamide ribonucleotide formyltransferase

Glycinamide ribonucleotide formyltransferase (GART) is a trifunctional enzyme that contains glycinamide ribonucleotide synthetase (GARS), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazole ribonucleotide synthetase (AIRS) activities, all of which are essential for DNPB. GART is frequently upregulated in multiple cancers, including invasive breast cancer and malignant pleural mesothelioma (MPM) [44,45], and its elevated expression is associated with tumor proliferation and progression. Its expression is regulated by oncogenic transcriptional programs, such as vestigial-like family member 3 (VGLL3), which promotes purine synthesis and lung cancer growth [44]. In addition, increased activity of the GART enzyme contributes to apoptosis resistance in B-cell chronic lymphocytic leukemia [46]. Mechanistically, GART promotes tumor progression through coordinated metabolic and signaling effects. It enhances cell cycle progression and modulates

sensitivity to temozolomide in hepatocellular carcinoma and glioma [47,48]. And it supports tumor growth under metabolic stress by maintaining UCK2 stability and sustaining pyrimidine salvage synthesis [49]. Moreover, GART activates oncogenic signaling pathways. It promotes proliferation and migration of non-small cell lung cancer (NSCLC) cells via the PAICS–AKT signaling pathway– β -catenin axis, and enhances tumor stemness in multiple myeloma through the HSP90 α /CDK6/ β -catenin pathway [50,51]. Overall, GART integrates purine metabolism with carcinogenic signaling pathways and metabolic adaptation mechanisms, demonstrating significant potential as a therapeutic target.

6. Phosphoribosylformylglycinamidine synthetase

Phosphoribosylformylglycinamidine synthetase (PFAS), also known as FGAMS, catalyzes the conversion of N-formylglycinamide ribonucleotide (FGAR) to FGAM and is therefore a key enzyme in DNPB. Emerging evidence indicates that PFAS is subject to oncogenic regulation and contributes to tumor progression through both metabolic and signaling mechanisms. At the metabolic level, ERK2-mediated phosphorylation of PFAS at Tyr619 enhances DNPB flux and tumor growth [52]. Furthermore, NOP2/Sun RNA methyltransferase 2 (NSUN2)/ALYREF-mediated m⁵C methylation can stabilize PFAS to maintain intracellular purine synthesis, elevate AMP and GMP production, and promote retinoblastoma progression [53]. Beyond nucleotide biosynthesis, PFAS also regulates protumorigenic signaling. It has been identified as a negative regulator of autophagy, acting through the tuberous sclerosis complex–Ras homolog enriched in brain–mechanistic target of rapamycin complex 1 (TSC–RHEB–mTORC1) axis [54]. In colorectal cancer, PFAS further promotes proliferation and invasion by targeting retinoic acid-inducible gene I (RIG-I) and suppressing RLR–NF- κ B signaling [55]. Together, these findings identify PFAS as a metabolic enzyme that links nucleotide biosynthesis with oncogenic signaling and autophagy, supporting PFAS-targeted therapy, particularly in combination with autophagy inhibitors.

7. Phosphoribosylaminoimidazole succinocarboxamide synthetase

PAICS is a bifunctional enzyme that catalyzes the sixth and seventh steps of DNPB. It is frequently overexpressed in multiple cancers, including lung cancer, breast cancer, glioblastoma, acute myeloid leukemia (AML), and gastric cancer (GC), and is associated with tumor progression and poor prognosis [56–60]. In lung adenocarcinoma, PAICS often exhibits copy number amplification together with PPAT and correlates with patient survival [61]. Functionally, PAICS promotes tumor proliferation, migration, and metastasis, and contributes to therapy resistance. For example, PAICS depletion enhances cisplatin sensitivity in GC by inducing DNA damage and impairing DNA repair [60], and suppresses glioma growth through downregulation of nucleotide excision repair genes [62]. PAICS is tightly controlled by oncogenic regulatory networks. Members of the MYC family are key upstream drivers. c-MYC and MYCN upregulate PAICS expression. They also couple one-carbon metabolism to purine biosynthesis, thereby supporting nucleotide production [63–66]. Non-coding RNAs further regulate *PAICS*. The COX10-AS1/miR-142-5p/*PAICS* axis promotes non-small cell lung cancer progression [67]. In contrast, miR-128 suppresses *PAICS* and inhibits epithelial–mesenchymal transition in bladder cancer [68,69]. The

transcription factor forkhead box K2; forkhead box O3 (FOXO3), forkhead box K2 (FOXK2) represses *PAICS* expression and disrupts purine metabolism [70].

At the mechanistic level, *PAICS* promotes tumor progression through both metabolic and signaling pathways. It activates the AKT signaling pathway– β -catenin axis to enhance cell proliferation and migration [51]. In ER α -positive breast cancer, *PAICS* regulates estrogen receptor activity through metabolic signaling [71]. Increased purine nucleotide levels elevate ATP and cyclic adenosine monophosphate (cAMP), activating protein kinase A (PKA) and promoting phosphorylation of ER α and CREB1. Meanwhile, *PAICS* activates the mechanistic target of rapamycin (mTOR) signaling pathway, enhancing S6 phosphorylation and reducing eIF2 α phosphorylation. These effects lead to ER α activation, tamoxifen resistance, and sustained tumor growth [71].

The *PAICS*-derived metabolite succinylaminoimidazolecarboxamide ribonucleotide (SAICAR) mediates an additional mechanism. SAICAR binds to and activates PKM2. This induces ERK phosphorylation and activates the MAPK signaling pathway. A positive feedback loop is formed, which further promotes tumor cell growth [72]. Under metabolic stress, SAICAR accumulates. It enhances PKM2-dependent metabolic adaptation. This supports cancer cell survival under nutrient-limited conditions [73]. Together, these studies establish *PAICS* as a key metabolic hub that links oncogenic transcriptional regulation, purine nucleotide synthesis, and downstream signaling activation. In addition to sustaining purine biosynthesis, *PAICS* and its metabolite SAICAR jointly promote adaptive proliferation, therapy resistance, and cell survival across diverse cancer types.

8. Adenylosuccinate lyase

Adenylosuccinate lyase (ADSL) is a key enzyme in the DNPB pathway. It catalyzes the cleavage of SAICAR and adenylosuccinate (S-AMP) to produce 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and AMP, respectively, with the concomitant generation of fumarate. Thus, ADSL links nucleotide metabolism to the tricarboxylic acid (TCA) cycle. ADSL is aberrantly overexpressed in a variety of cancers and promotes cell proliferation and migration [74,75]. Conversely, low ADSL expression is associated with better survival, particularly in HCC [76,77].

Mechanistically, ADSL enhances purine flux to support DNA replication, repair, and cell-cycle progression. Its overexpression also disrupts mitochondrial function and activates the mTORC1–cMYC and Kelch-like ECH-associated protein 1 (KEAP1)–NRF2 signaling pathways, enhancing cellular adaptation to oxidative stress [75]. In HCC, ADSL sustains tumor growth by maintaining AMP synthesis and mitochondrial ATP production⁷⁶. In triple-negative breast cancer, its activity is regulated by egl-9 family hypoxia-inducible factor 2 (EglN2)-mediated hydroxylation [78]. Elevated ADSL activity has also been linked to precancerous tubulovillous adenomas [79]. In endometrial cancer and glioma stem cells, ADSL-associated succinate accumulation promotes invasiveness, therapy resistance, and adaptation to acidic or stem-like states [80–83]. ADSL also contributes to drug resistance, including tyrosine kinase inhibitor (TKI) tolerance in epidermal growth factor receptor (EGFR)-mutant lung cancer [84]. and gemcitabine resistance in pancreatic cancer [85]. In addition, post-translational modifications further diversify its function. Protein kinase R-like endoplasmic reticulum kinase (PERK)-mediated phosphorylation at S140 enhances autophagy and supports hepatocellular tumor growth [86], whereas hypoxia-induced inhibitor of nuclear factor kappa-B kinase subunit beta (IKK β)-mediated phosphorylation enables fumarate-dependent

suppression of stimulator of interferon genes (STING) signaling and antitumor immunity in breast cancer [87]. However, in colorectal cancer, low ADSL expression is associated with poor prognosis, especially in advanced-stage disease [88]. This finding implies that the function of ADSL might be contingent upon the tumor type and the specific context.

9. 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/inosine monophosphate cyclohydrolase (ATIC)

ATIC is a bifunctional enzyme that catalyzes the last two steps of DNPB pathway, and many studies have demonstrated that it is associated with multiple types of tumors. Specifically, in lung adenocarcinoma tissues and cells, the expression of ATIC is significantly upregulated, which is strongly correlated with poorer survival advanced clinical stages in lung adenocarcinoma patients [89]. ATIC is tightly regulated by oncogenic networks at multiple levels. It can form oncogenic fusion proteins with anaplastic lymphoma kinase (ALK) [90], and NPM-ALK-mediated phosphorylation of ATIC (p-ATIC) enhances its enzymatic activity, promotes cellular transformation, and reduces sensitivity to methotrexate [91]. Non-coding RNAs also contribute to ATIC regulation. For example, lncRNA ZFAS1 upregulates ATIC expression and activates the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway, thereby promoting HCC progression [92]. In contrast, lncRNA TPT1-AS1 interacts with CBP to suppress ATIC-associated purine metabolism and inhibit breast cancer development [93].

At the mechanistic level, ATIC promotes tumor progression through coordinated metabolic and signaling effects. In colorectal cancer, the p53–VDR complex and lysine acetyltransferase 2B (KAT2B)-mediated acetylation of ATIC at Lys226 suppress tumor growth by inhibiting purine metabolism [94]. In HCC, ATIC activates the PI3K/AKT/FOXO3 axis, leading to reduced caspase-3 cleavage and LC3-II levels, thereby suppressing apoptosis and autophagy [95]. At the same time, ATIC inhibits AMPK and activates the mTOR-S6K1-S6 signaling cascade, further supporting tumor growth [96]. Notably, inhibition of ATIC induces 5-aminoimidazole-4-carboxamide ribonucleotide (ZMP) accumulation and activates AMPK, which enhances radiosensitivity [97]. Activated AMPK can, in turn, suppress purine biosynthesis by promoting PFAS dissociation, forming a negative feedback loop [98]. From a clinical perspective, ATIC has both diagnostic and therapeutic potential. Serum ATIC serves as a novel diagnostic and prognostic biomarker for multiple myeloma [99]. Moreover, it serves as a target antigen of the tumor-associated autoantibody XC154 in HCC, and combined detection of anti-ATIC autoantibodies and alpha-fetoprotein (AFP) improves diagnostic accuracy [100]. In addition, pharmacological inhibition of ATIC, such as by shikonin, suppresses tumor growth by downregulating purine biosynthetic enzymes [101].

Overall, accumulating evidence suggests that ATIC functions as an important regulator linking purine metabolism, oncogenic signaling, and therapeutic response. These features highlight its potential as both a biomarker and a therapeutic target in cancer.

10. Inosine monophosphate dehydrogenase 1/2

IMPDH, the rate-limiting enzyme in guanine nucleotide synthesis, as a key driver of tumor metabolic reprogramming. IMPDH has two isoforms: IMPDH1, broadly expressed in normal tissues, and IMPDH2, which is preferentially upregulated in malignant cells and correlates with aggressive tumor phenotypes [102]. Elevated IMPDH expression has been documented in brain tumors and lymphoid leukemias, where increased *IMPDH2* mRNA supports cancer cell proliferation and maintenance of an undifferentiated state [103–105]. Accordingly, pharmacological inhibition of IMPDH consistently suppresses tumor growth in multiple preclinical models [106,107]. In solid tumors, IMPDH2 overexpression has been reported in NPC [108], osteosarcoma [109], ovarian cancer [110], colorectal cancer [111], renal, prostate and bladder cancer (BLCA) [112], HCC [113,114], and triple-negative breast cancer (TNBC) [115]; notably, this overexpression is generally linked to increased invasiveness and poor patient prognosis [111,116]. No significant difference in IMPDH expression is observed in testicular cancer [112], likely due to the intrinsically high purine demand of this malignancy [117]. The IMPDH1/2 expression ratio also holds prognostic value in glioma [118].

Mechanistically, IMPDH sustains intracellular GTP pools to coordinate oncogenic signaling, ribosome biogenesis, and cell cycle progression. Specifically, IMPDH2 activates Wnt/ β -catenin signaling and EMT [119], forms a positive feedback loop with Wnt signaling to promote oxaliplatin resistance in colorectal cancer [120], and drives G1/S phase transition through PI3K/AKT-associated pathways [121]. In cooperation with guanosine monophosphate synthetase (GMPS), IMPDH2 enhances RNA polymerase I activity and rRNA synthesis [122]; conversely, IMPDH inhibition reduces rRNA production, induces nucleolar stress, and stabilizes p53 [122–124]. Nuclear-localized IMPDH2 also regulates poly(ADP-ribose) polymerase 1 (PARP1) and participates in DNA damage response pathways [125].

IMPDH expression and enzymatic activity are tightly regulated at multiple levels. Myc directly promotes *IMPDH1/2* transcription [123,126] and elevates intracellular GTP pools, thereby enhancing rRNA synthesis and chemoresistance in small cell lung cancer [126,127]; in contrast, p53-induced miR-34a represses *IMPDH* transcription [128]. Additional regulators, including lnc-UCA1, FANCI, Rac family small GTPase 1 (RAC1), proteasome 26S subunit, non-ATPase 14 (PSMD14), and ubiquitin-specific peptidase 5 (USP5), enhance IMPDH2 expression or stability, supporting cancer cell proliferation and invasiveness across diverse tumor types [129–133]. Post-translational modifications further fine-tune IMPDH activity, including CDK1-dependent phosphorylation, fibroblast growth factor receptor (FGFR)–protein phosphatase 2A (PP2A)-mediated dephosphorylation [134], sirtuin 5 (SIRT5)-dependent desuccinylation [135], and inositol binding [136]. Functionally, IMPDH2 contributes to therapeutic resistance against cisplatin, radiotherapy, and temozolomide [137–140]. In KRAS-mutant pancreatic ductal adenocarcinoma (PDAC), guanine nucleotide depletion via IMPDH2 targeting enhances sensitivity to KRAS inhibition [141]; meanwhile, extracellular matrix (ECM) remodeling-induced IMPDH1/2 upregulation promotes nucleotide excision repair and oxaliplatin resistance [142]. Guanine depletion through IMPDH inhibition stabilizes TP53, suppresses MYC, impairs leukemia stem cell self-renewal [143], and represents a critical metabolic dependency in mixed-lineage leukemia (MLL)-rearranged AML stem cells [144].

As an isoform of IMPDH, IMPDH1 does not exhibit widespread overexpression in cancer cells as observed for IMPDH2, and the underlying molecular mechanism remains unelucidated. Consequently, most current cancer research predominantly focuses on IMPDH2. As stated in the latest review, the IMPDH system in cancers presents diverse mechanisms and intricate regulatory patterns [145]. Accumulating studies have linked IMPDH-mediated guanine nucleotide biosynthesis to oncogenic signaling, ribosomal activity, DNA repair and therapeutic resistance, highlighting its promising translational application potential in various malignant tumors (Figure 3).

11. Guanine monophosphate synthase

GMPS catalyzes the conversion of xanthosine monophosphate (XMP) to GMP and is essential for GTP biosynthesis in *de novo* purine metabolism. GMPS is frequently upregulated in multiple cancers, including esophageal and prostate cancers, and its elevated expression correlates with poor prognosis [146,147]. It also promotes melanoma invasion and metastasis and has been proposed as a prognostic biomarker in ovarian cancer [148,149]. Mechanistically, GMPS is closely linked to the p53 axis. Wild-type p53 suppresses GMPS expression and nucleotide synthesis, thereby inducing cellular senescence [150], whereas mutant p53 enhances GTP production and tumor invasion [151]; inhibition of GMPS partially reverses this effect. GMPS is also regulated post-translationally. SERPINB5 recruits GMPS to tripartite motif-containing 21 (TRIM21) for ubiquitin-mediated degradation, reducing GMPS and TP53 levels and contributing to radioresistance [152]. In addition, GMPS modulates tumor progression through multiple signaling pathways. It activates the STAT3 signaling pathway–p53 axis and regulates serpin family B member 2 (SERPINB2)-associated pathways to influence cell migration [153,154]. Moreover, GMPS promotes immune evasion by facilitating STT3A-dependent programmed death-ligand 1 (PD-L1) glycosylation [155]. Collectively, GMPS links GTP biosynthesis with oncogenic signaling and immune regulation, highlighting its potential as both a prognostic biomarker and a therapeutic target.

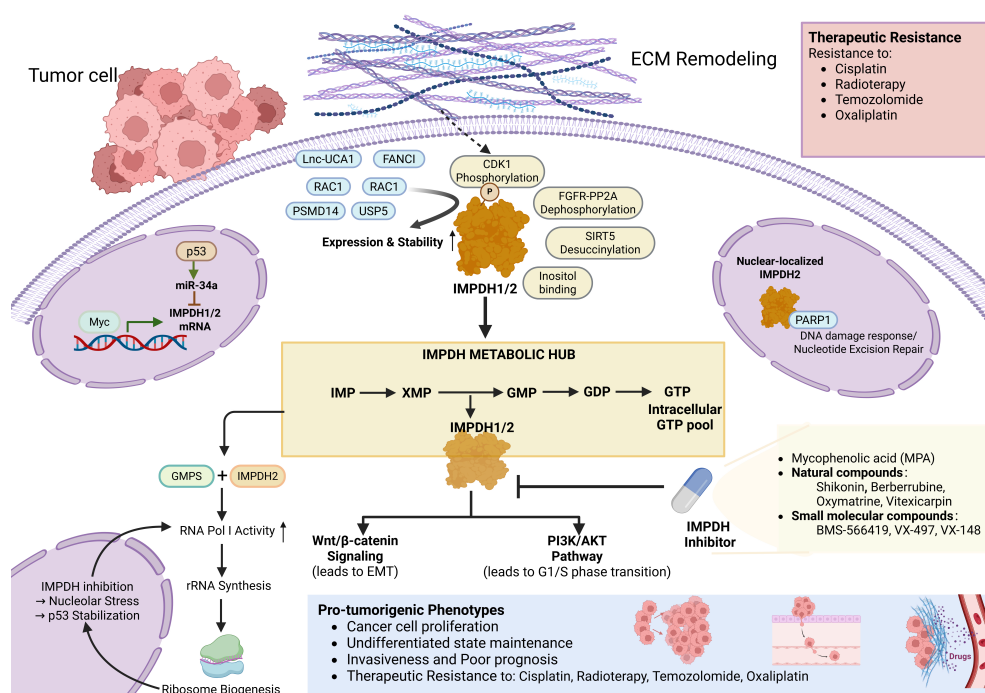


Figure 3. Biology function of IMPDH1/2 in cancer. IMPDH1/2 catalyzes the conversion of IMP to XMP, a rate-limiting step in guanine nucleotide biosynthesis that sustains the intracellular GTP

pool. IMPDH1/2 expression is positively regulated by MYC, but restrained by the p53–miR-34a axis, whereas lnc-UCA1, FANCI, RAC1, PSMD14 and USP5 enhance its expression and/or stability. Its activity is further modulated by CDK1-dependent phosphorylation, FGFR-PP2A-mediated dephosphorylation, SIRT5-dependent desuccinylation and inositol binding. Beyond its metabolic role, nuclear IMPDH2 cooperates with PARP1 in the DNA damage response and nucleotide excision repair, and the IMPDH2–GMPS axis promotes RNA polymerase I activity, rRNA synthesis and ribosome biogenesis. Increased IMPDH1/2 activity also engages Wnt/ β -catenin and PI3K/AKT signaling, thereby driving epithelial–mesenchymal transition, G1/S progression, extracellular matrix remodeling and other pro-tumorigenic phenotypes, including proliferation, maintenance of an undifferentiated state, invasiveness, poor prognosis and therapeutic resistance. This figure was created by Biorender (<https://app.biorender.com/>).

12. Purinosome

The purinosome is a dynamic multienzyme complex composed of six core enzymes (PPAT, GART, PFAS, PAICS, ADSL, and ATIC) that catalyze the conversion of phosphoribosyl pyrophosphate to inosine monophosphate (IMP) in *de novo* purine biosynthesis [156]. In cancer, its assembly is closely linked to the cell cycle and proliferative demand, enabling tumor cells to efficiently sustain nucleotide supply [157]. Notably, purinosome formation is reversible and responsive to intracellular purine levels, allowing flexible regulation of metabolic flux [158,159], and thereby supporting nucleotide homeostasis and tumor growth [160]. Purinosome assembly is tightly regulated by oncogenic signaling and tumor microenvironmental stress. Hypoxia, a hallmark of solid tumors, induces its formation through HIF-1–mediated metabolic reprogramming, facilitating adaptation to nutrient and oxygen limitation [161]. In parallel, Hsp70/Hsp90 chaperones, GPCR signaling, and Akt-independent 3-phosphoinositide-dependent protein kinase 1 (PDK1) and AMPK pathways coordinate its assembly and spatial dynamics [162–165], while mTOR signaling and microtubule networks further regulate its localization and function [166,167]. Additionally, lysosome-mediated purine recycling cooperates with *de novo* synthesis to maintain purine pools in cancer cells [168].

Post-translational modifications also contribute to purinosome regulation. PAICS ubiquitination recruits ubiquitin-associated protein 2 (UBAP2) to promote phase separation and assembly, a process linked to epigenetic regulation via ankyrin repeat and SOCS box containing 11 (ASB11) and implicated in tumor progression [169]. Conversely, the nudix hydrolase 5 (NUDT5)–PPAT interaction promotes purinosome disassembly, indicating dynamic control of its activity [170]. Functionally, cancer cells exploit purinosome assembly to maintain purine biosynthesis under metabolic stress, and purinosome-associated genes are strongly correlated with proliferation, survival, and therapeutic response [171,172]. In cancer, purinosome assembly supports sustained purine biosynthesis under metabolic stress, and purinosome-related genes are associated with cell proliferation, survival, and therapeutic response [171,172]. In a word, targeting purinosome assembly has emerged as a promising area of investigation in cancer therapy; however, current evidence remains largely preclinical and requires further validation [173].

13. Key enzymes in the purine salvage pathway in cancer

Compared with the *de novo* biosynthesis pathway, research on the purine salvage pathway in cancer is relatively limited, yet its role in maintaining nucleotide homeostasis is equally noteworthy. This pathway recycles purine bases such as adenine, hypoxanthine, and guanine to regenerate AMP, IMP and GMP, thereby providing crucial compensation when exogenous substrates are available, metabolic stress is increased, or *de novo* biosynthesis is impaired. Classic studies have indicated that adenine phosphoribosyltransferase (APRT) and HPRT exhibit high affinity for PRPP, and their enzymatic capacity can exceed the rate-limiting steps of *de novo* biosynthesis in certain tumor tissues. This suggests that the salvage pathway is not merely a recycling branch but may be involved in tumor cells' maintenance of purine supply and adaptation to the inhibition of *de novo* biosynthesis [174]. Consequently, the salvage reactions mediated by APRT and HPRT should be incorporated into the overall discussion of purine metabolic reprogramming.

14. Adenine phosphoribosyltransferase

APRT, a key enzyme in the purine salvage pathway, converts adenine to AMP and helps maintain intracellular purine nucleotide homeostasis. Current studies suggest that APRT is more closely associated with metabolic reprogramming, subtype-specific phenotypes, and clinical outcomes than established as an autonomous oncogenic driver. In solid tumors, APRT dysregulation has been associated with poor prognosis in colorectal cancer [88], aggressive metabolic programs in high-risk breast cancer subtypes [175], progression-related molecular signatures in prostate cancer [176], and adverse outcome-associated signatures in head and neck squamous cell carcinoma [177]. Pan-cancer analyses further implicate APRT in broader purine metabolism- and uricogenesis-related transcriptional remodeling, although it appears to function mainly as part of a larger metabolic network rather than a dominant driver gene [178].

More direct functional evidence has mainly come from hematologic malignancies, where APRT has been identified as a context-dependent metabolic vulnerability required for proliferation in a subset of acute leukemia cell lines [179]. APRT has been most extensively investigated in the context of APRT deficiency, an autosomal recessive purine metabolism disorder. In the field of cancer research, current evidence supports APRT as a context-dependent metabolic regulator with potential value as a biomarker and therapeutic target in specific tumor types. However, the available literature remains limited and is still largely dominated by correlative multi-omics and prognostic studies, rather than definitive mechanistic investigations.

15. Hypoxanthine-guanine phosphoribosyltransferase

HPRT, encoded by the *HPRT1* gene, is a key enzyme in the purine salvage pathway that catalyzes the conversion of hypoxanthine and guanine into IMP and GMP, thereby maintaining intracellular nucleotide homeostasis. Elevated HPRT protein and transcript levels have been frequently observed across multiple diverse tumor types [180–182]. In particular, this consistent overexpression pattern has been prominently highlighted in specific malignancies such as B-cell lymphoma and head and neck squamous cell carcinoma (HNSCC) [183–185]. Its dysregulation supports metabolic adaptation by

sustaining nucleotide supply under conditions of high proliferative demand and metabolic stress [4,186]. Notably, aberrant localization of HPRT on the plasma membrane has been reported in certain cancer cell lines, suggesting a potential noncanonical role in tumor biology [180].

Mechanistically, HPRT contributes to tumor progression through metabolic and signaling regulation. In EGFR-mutant lung adenocarcinoma, mutant EGFR stabilizes HIF-1 α , which transcriptionally upregulates HPRT to enhance purine metabolism and sustain rapid proliferation; inhibition of HPRT increases sensitivity to EGFR-targeted therapy [187]. Under metabolic stress, such as glutamine deprivation, HPRT promotes cell survival by enhancing salvage pathway flux [188]. In addition, HPRT has been implicated in promoting tumorigenesis through modulation of DNA damage repair and recruitment of immune cells such as neutrophils [189]. Its expression is also regulated by noncoding RNAs, including the miR-125b-5p/*HPRT* axis, which contributes to malignant progression in HNSCC [190].

Beyond its metabolic role, HPRT is increasingly linked to tumor immunity and therapeutic response. Elevated HPRT expression is associated with an immunosuppressive tumor microenvironment and may facilitate immune evasion [191]. Its surface localization in cancer cells further suggests potential as a tumor-associated antigen, enabling antibody-mediated targeting strategies [180,192]. Moreover, HPRT contributes to chemoresistance; for example, it metabolizes temozolomide and activates AMPK signaling in glioblastoma [193]. Collectively, these findings identify HPRT as a multifunctional regulator that integrates purine salvage, oncogenic signaling, and immune modulation, highlighting its potential as both a biomarker and a therapeutic target in cancer [194].

16. Key enzymes in the purine catabolic pathway in cancer

The purine catabolic pathway not only undertakes the terminal degradation of nucleotides but also participates in regulating the fate of purine substrates in tumor cells. AMP and GMP are progressively degraded via intermediate metabolites such as adenosine, inosine, guanosine, hypoxanthine, and xanthine to ultimately generate uric acid. This process interfaces with the salvage pathway at multiple nodes, collectively influencing the fate distribution of purine bases and nucleosides. In this cascade, adenosine deaminase (ADA) regulates the conversion of adenosine to inosine, purine nucleoside phosphorylase (PNP) resides at the junction of nucleoside degradation and base reutilization, while xanthine oxidase/xanthine dehydrogenase (XO/XDH) mediates terminal oxidative degradation and modulates the oxidative stress status. Thus, in addition to their roles in metabolic clearance, enzymes involved in the catabolic pathway may participate in tumor biological processes by regulating the tumor microenvironment, inflammatory responses, and therapeutic responses.

17. Adenosine Deaminase

Adenosine deaminase is a key enzyme in purine catabolism that converts adenosine/deoxyadenosine into inosine/deoxyinosine. Current review suggests that the role of ADA in cancer should not be viewed merely as a terminal adenosine-clearing step, but rather in the broader context of an adenosine-rich immunosuppressive tumor microenvironment [195]. Moreover, the distinct origin, localization, and function of ADA1 and ADA2 indicate substantial isoenzyme-specific and context-dependent effects [196]. Recent studies further support the notion that ADA is not simply a

passive executor of adenosine catabolism, but a functional regulator of tumor cell behavior and extracellular purinergic balance. The cancer cell-associated ecto-ADA activity can markedly restrict extracellular adenosine accumulation and, together with the CD73 axis, shape tumor purinergic immunometabolism [197]. In oral carcinogenesis and oral squamous cell carcinoma (OSCC), ADA-mediated adenosine-to-inosine conversion appears to support the survival of premalignant and malignant epithelial cells [198]. In prostate cancer, elevated ADA is associated with higher Gleason score, worse progression-free survival, and a more aggressive phenotype [199]. And in lung adenocarcinoma, ADA knockdown suppresses tumor cell proliferation, migration, and invasion [200]. At the same time, ADA also exerts important immunoregulatory functions within the tumor microenvironment: in non-small cell lung cancer (NSCLC), the ADA/CD26 axis enhances the functionality of intratumoral PD-1+ CD28+ CD8+ T cells and is associated with improved prognosis and better immune checkpoint blockade (ICB) response [201]. Nevertheless, at the clinical level, an elevation in ADA often exhibits a correlation with aggressive disease behavior and unfavorable outcomes, as demonstrated in pediatric non - Hodgkin lymphoma [202]. This duality is also reflected in therapeutic development. On the one hand, multiple preclinical studies have exploited exogenous or engineered ADA to deplete local adenosine and increase inosine generation, thereby enhancing T-cell function and potentiating cancer immunotherapy [203–207]. On the other hand, several studies suggest that ADA inhibition may also be therapeutically beneficial in selected tumor contexts [198,208]. Collectively, current evidence supports ADA as a key regulatory node linking purine catabolism, adenosine-mediated immunosuppression, and tumor metabolic plasticity, rather than a molecule that can be simply defined as uniformly oncogenic or uniformly tumor suppressive. Its true therapeutic value will depend on a clearer understanding of isoenzyme-specific functions, spatial context, and causal mechanisms [195–197].

18. Purine nucleoside phosphorylase

PNP is a key enzyme linking purine degradation and salvage by catalyzing the conversion of inosine and guanosine into hypoxanthine and guanine. It is dysregulated in multiple cancers and acts as a therapeutic target in lymphoproliferative diseases [209]. PNP is overexpressed in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancers, where it correlates with advanced stage and poor prognosis [210]. A reciprocal regulatory loop exists between PNP and HER2, and their combined inhibition markedly reduces tumor cell viability [210]. In EGFR-TKI-resistant lung adenocarcinoma, PNP overexpression enhances drug sensitivity by increasing toxic metabolites and reactive oxygen species (ROS), thereby inducing cell death [211]. PNP also participates in Yes-associated protein (YAP)-mediated metabolic feedback to regulate purine turnover [212]. PNP is negatively regulated by tumor-suppressive miRNAs such as miR-1 and miR-133a4. Clinically, PNP serves as a prognostic and predictive biomarker in muscle-invasive bladder cancer, where high expression indicates poor survival and reduced response to immunotherapy [213].

Emerging evidence suggests that PNP may represent an important node connecting purine metabolism with oncogenic signaling and immune regulation. However, these observations are largely based on recent studies in selected tumor types, and further mechanistic and clinical investigations are required to establish its broader significance as a biomarker and therapeutic target in cancer.

19. Xanthine oxidoreductase

Xanthine oxidoreductase (XOR) is a key terminal enzyme in purine catabolism and exists in two functional states, xanthine dehydrogenase (XDH) and xanthine oxidase (XO). Previous reviews have consistently suggested that XOR plays a distinctly bidirectional and tissue-dependent role in cancer. On the one hand, it contributes to inflammation, oxidative stress, metabolic stress adaptation, and tumor microenvironment remodeling through regulation of uric acid production and ROS/RNS levels. On the other hand, its expression and function vary substantially across tumor types and stress contexts, preventing its classification as either uniformly oncogenic or tumor-suppressive [214,215].

Recent research findings suggest that in numerous types of cancers, XOR/XDH facilitates tumor progression and confers resistance to therapy. For instance, in intrahepatic cholangiocarcinoma, XOR contributes to the maintenance of EGFR signaling and the attenuation of p53-associated DNA damage response [216]. And XOR/XDH is capable of facilitating purine catabolism-driven metabolic adaptation, DNA repair, autophagy, and sustained proliferation in prostate cancer and lung adenocarcinoma [217,218]. Moreover, under chemotherapy conditions, XOR can also induce protective autophagy through the uric acid-TAK1 axis [219]. XOR also participates in immune microenvironment regulation: it can promote immunosuppression via the macrophage urate–NLR family pyrin domain containing 3 (NLRP3)–PD-L1 axis in non-small cell lung cancer [220], and also enhance ROS-dependent tumor killing, NK cell recognition, and CD8⁺ T cell infiltration under conditions of DNA damage or engineered delivery [221,222]. However, in HCC, XOR loss in tumor-associated macrophages enhances M2-like polarization and CD8⁺ T-cell exhaustion [223]. Conversely, in breast cancer, renal cell carcinoma, and selected colorectal cancer models, restoration or activation of XOR/XDH is associated with enhanced ROS damage, apoptosis, and tumor suppression, suggesting that it may also represent an exploitable metabolic vulnerability in specific settings [224–227]. Overall, XOR is better viewed as a highly context-dependent metabolic node linking purine catabolism, uric acid/ROS signaling, tumor immunity, and treatment response rather than as a unidirectional driver enzyme.

To systematically summarize the mechanisms and research progress of key enzymes involved in the *de novo* synthesis, salvage pathway, and catabolic pathway of purine metabolism across different tumor types, this study provides a visual representation of the tumor heterogeneity characteristics exhibited by these critical purine metabolic enzymes in cancer (Table 1, Figure 4).

Mechanism of Purine Metabolizing Enzymes in Cancer

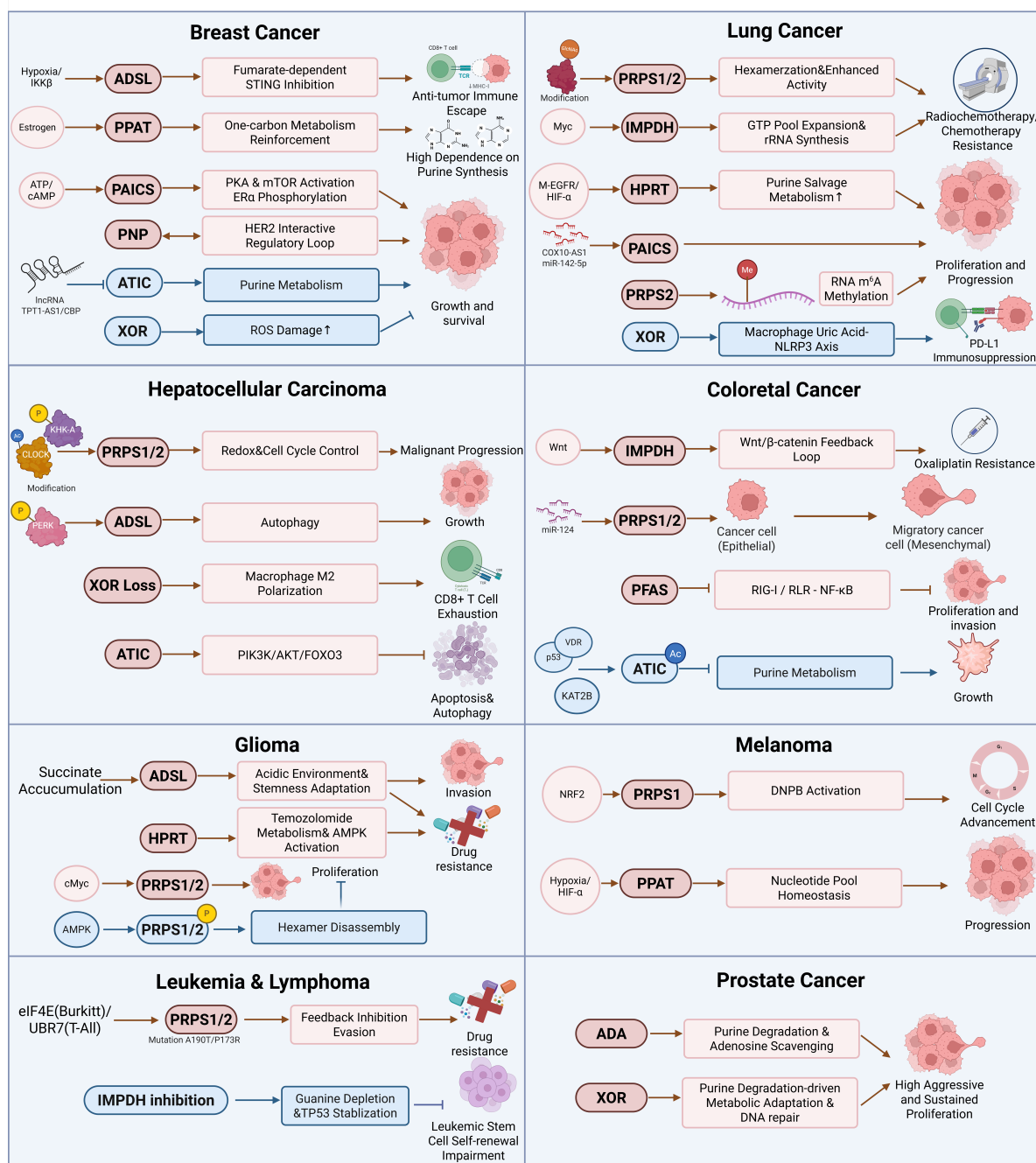


Figure 4. Mechanism of purine metabolizing enzymes in cancer. This comprehensive map delineates both the diverse upstream regulatory signals modulating these enzymes and their complex downstream oncogenic mechanisms across eight distinct cancer types. Rather than exhibiting uniform functions, the dysregulation of these enzymes demonstrates significant tumor heterogeneity. The downstream functional consequences predominantly converge on three crucial hallmarks: sustaining hyperproliferation, orchestrating therapy resistance, and remodeling the tumor microenvironment for immune evasion. Furthermore, the color-coding explicitly indicates their functional impact on cancer: elements and pathways highlighted in red represent processes that promote tumor development, whereas those highlighted in blue indicate tumor-suppressive effects or the inhibition of tumor progression. This figure was created by Biorender (<https://app.biorender.com/>).

Table 1. The role of purine-metabolizing enzymes in different cancer types.

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
PRPS1/2	T-ALL	/	Oncogene	PRPS1/2 promoted cell proliferation	NOTCH1 pathway upregulated the expression of UBR7 and maintained the stability of PRPS1/2	[12]
	B-ALL	Upregulated	Oncogene	PRPS1 promoted cell proliferation and inhibited cell apoptosis	PRPS1 increased the expression of Bcl-2	[9]
	Relapsed ALL	/	Oncogene	1. PRPS1 drug-resistant mutations contributed to the recurrence of ALL. 2. 5-FU increased the chemosensitivity of ALL. 3. PRPS2 mutation led to thiopurine resistance and the recurrence of ALL.	1. A190T and S103T mutants of PRPS1 led to the decrease of feedback inhibition of DNFB, inhibiting the transformation of 6-MP into its active metabolites. 2. The mutation of PRPS1 reduced the feedback inhibition of DNFB, promoting the metabolism of 5-FU into FUMP and FUTP. 3. PRPS2 P173R mutation reduced the stability of PRPS1/2 hexamer and decreased feedback inhibition of DNFB.	[24,26,228–230]
	ALL with TEL-AML1 fusion	Downregulated	/	The expression of PRPS2 decreased significantly	/	[231]
	GBM	Upregulated	Oncogene	1. Inhibition of PRPS1/2 inhibited tumor growth 2. CLOCK-driven PRPS1/2 stabilization promoted GBM cell proliferation and migration.	1. Down-regulation of PRPS1/2 inhibited ERN1 and other ER stress signaling enzymes in U87 cells. 2. Energy stress induced AMPK to phosphorylate the Ser180 site of PRPS1 and Ser183 site of PRPS2, thus down-regulating of DNFB in U87 and U251 cells. 3. Cytosolic CLOCK acetylated PRPS1/2 at K29, blocking HSC70-mediated degradation and increasing PRPS1/2 stability and activity	[29,30,232]
	Glioma	Upregulated	Oncogene	PRPS1 promoted proliferation of BTIC 1. PRPS1/2 promoted cell proliferation. 2. PRPS1 reduced ROS level and promoted tumorigenesis	MYC upregulated PRPS1 expression, thus enhancing DNFB 1. Cytoplasmic CLOCK acetylated PRPS1/2 at K29, thus inhibiting PRPS1/2 degradation. 2. KHK-A phosphorylated PRPS1 at Thr225	[19] [28,32]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
					and activated PRPS1, thus promoting DNPB.	
	CRC	Upregulated	Oncogene	1. Inhibition of PRPS1 suppressed cell proliferation. 2. PRPS1 regulated cell cycle. 3. PRPS2 promoted EMT, migration, invasion and tumor metastasis.	1. miR-124 inhibited PPP by targeted reduction of PRPS1 and RIPA mRNA, thus inhibiting DNPB. 2. CDK1 upregulated the activity of PRPS1 by phosphorylating the Ser103 site of PRPS1. 3. PRPS2 degraded extracellular matrix protein, enhanced MMP-9 expression and inhibited CDH1 transcription.	[16,17,33]
	ESCC	Upregulated	Oncogene	KHK-A regulated cell cycle and promoted cell proliferation	KHK-A upregulated the expression of PRPS1	[13]
	Neuroblastoma	Upregulated	Oncogene	1. PRPS1 promoted cell proliferation. 2. PRPS2 promoted cell proliferation and migration.	1. MYCN combined with the promoter region of PRPS1 and upregulated PRPS1 expression. 2. PRPS2 was regulated by MYCN and TFAP4.	[14,233]
	BL	Upregulated	Oncogene	1. PRPS1 A190T mutant improved thiopurine resistance. 2. PRPS2 maintained cell metabolic activity with overexpression of Myc	1. PRPS1 A190T mutant avoided the feedback inhibition of nucleotide synthesis. 2. Myc activated the expression of eIF4E, thus promoting PRPS2 expression and enhancing DNPB.	[25,234]
	BC	Upregulated	Oncogene	1. Inhibition of PRPS1 increased cell apoptosis <i>in vitro</i> , and increased cisplatin sensitivity <i>in vivo</i> . 2. PRPS2 promoted stemness and metastasis.	1. Knocking down PRPS1 induced caspase-3 to activation autonomously in cisplatin-resistant SK-BR-3 and MCF-7 cells. 2. PRPS2 promoted DNPB and activated cGMP/PKG/MAPK signaling pathway.	[10,11]
	Melanoma	/	Oncogene	1. Inhibition of PRPS2 limited tumor proliferation 2. PRPS1 activation increased <i>de novo</i> purine nucleotide synthesis and promoted melanoma proliferation.	1. c-Myc directly bound to IMPDH2 and PRPS2 gene promoters to increased their expression 2. Elevated NDUF3 suppressed AMPK activity, reduced inhibitory PRPS1 S180 phosphorylation, increased PRPS1 enzymatic activity.	[20,31]
	PCa	Upregulated	Oncogene	Inhibition of PRPS2 induced cell apoptosis and G ₁ phase arrest	Knocking down PRPS2 activated Bcl-2/caspase/PARP pathway	[8]
	Myc-driven B cell	/	Oncogene	The loss-of-function of PRPS1	Genetic inactivation of PRPS2 (as opposed	[21]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
PPAT	lymphoma			leads to oxidative stress. Nevertheless, the loss-of-function of PRPS2 results in reductive stress-mediated cell death.	to PRPS1) led to an elevation of NADPH and resulted in reductive-stress-induced cell death.	
	Lung cancer	Upregulated	Oncogene	1. PRPS2 attenuated antitumor immunity. 2. PRPS2 promoted lung tumorigenesis by enhancing RNA m(6)A methylation and SAM supply.	1. PRPS2 promotes tumor immune suppression by upregulating CCL2 to recruit TAMs and MDSCs. 2. PRPS2 stabilizes MAT2A, enhances SAM availability, and thereby promotes elevated m ⁶ A methylation.	[22,23]
	HCC	Upregulated	Oncogene	Related to poor prognosis	/	[34]
	Lung cancer	Upregulated	Oncogene	PPAT and PAICS promoted cell proliferation and invasion	Glutamine induced PPAT expression and upregulated the activity of PK, leading to the increase of DNPB	[35,36]
	Kaposi's sarcoma	/	Oncogene	Knocking down PPAT inhibited cell proliferation	Glutamine-dependent nucleotide synthesis increased	[40]
	Thyroid cancer	Upregulated	Oncogene	PPAT promoted cell proliferation and invasion	PPAT upregulated PKM2 expression and activated STAT3 and ERK pathways	[41]
	BC	Upregulated	Oncogene	PPAT promoted cell proliferation	Estrogen enhanced the metabolism of folate and one carbon to coordinate DNPB	[38]
	RCC	Upregulated	Oncogene	PPAT promoted cell proliferation	SHMT2 upregulated PPAT in RCC, coupling serine metabolism to nucleotide synthesis to promote tumor proliferation.	[39]
	NPC	Upregulated	Oncogene	/	/	[43]
	Lung cancer	Upregulated	Oncogene	GART promoted cell proliferation	1. VGLL3 induced GART expression, thus promoting DNPB in A549 cells 2. GART activated PAICS-Akt-β-catenin pathway	[44,51]
GART	MPM	/	Oncogene	Inhibition of GART induced S phase arrest	/	[45]
	HCC	Upregulated	Oncogene	1. Inhibition of GART blocked cell cycle and inhibited proliferation 2. GART supported HCC growth under glucose deprivation	1. GART inhibition arrested cells in G ₁ phase 2. GART maintained the protein stability of UCK2 and sustained pyrimidine salvage synthesis	[47,49]
	Glioma	Upregulated	Oncogene	GART inhibition suppressed tumor growth	The high expression of GART increased DNPB	[48]
	MM	Upregulated	Oncogene	GART facilitated malignant	GART induced tumor stemness through	[50]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
PFAS				progression in multiple myeloma	activation of the HSP90 α /CDK6/ β -catenin axis	
	PCa	Upregulated	Oncogene	GART inhibition suppressed cell proliferation	Inhibition of GART inhibited DNPB and activated p53 and AMPK-mediated aging signaling pathways	[235]
	Lung cancer	Upregulated	Oncogene	PFAS promoted cell proliferation	ERK2 phosphorylated the Thr619 site of PFAS in A549 cells, which increased DNPB	[52]
	Retinoblastoma	Upregulated	Oncogene	PFAS promoted tumor growth	RB triggered NSUN2/ALYREF/PFAS cascade reaction, upregulated PFAS mRNA methylation level, thus increasing PFAS expression and DNPB	[53]
	Cervical cancer	/	Oncogene	Inhibition of PFAS activated autophagy	Knocking out PFAS inhibited DNPB and induced purine starvation to activate autophagy in HeLa cells	[54]
PAICS	CRC	Upregulated	Oncogene	PFAS promoted CRC cell proliferation and invasion.	PFAS inhibited RIG-I-mediated innate immune signalling by targeting RIG-I, thereby suppressing IFN- β and ISG56 expression.	[55]
	BC	Upregulated	Oncogene	1. PAICS inhibition induced G ₀ /G ₁ phase cell cycle arrest and promoted apoptosis. 2. PAICS increased resistance to tamoxifen.	1. Knocking down PAICS increased the expression of CDK4, Cyclin D1, cleaved-caspase 3 and cleaved-PARP, and decreased the expressions of Bcl-2 and Bcl-xl. 2. PAICS activated cAMP/PKA and mTOR activity, promoted ER α phosphorylation at the Ser305 site and the Ser104/106 site and increased its activity, thus reducing estrogen dependence	[56,57,71]
	AML	/	Oncogene	Inhibition of PAICS inhibited cell proliferation and promoted apoptosis	Knocking down PAICS inhibited DNA synthesis	[58]
	EGFR wild-type NSCLC (including LUAD)	Upregulated	Oncogene	1. PAICS promoted cell proliferation. 2. Inhibition of PAICS induced DNA damage and cell cycle arrest.	1. COX10-AS1/miR-142-5p/PAICS axis alleviated the inhibition of PAICS and increased DNPB. 2. Knocking down PAICS decreased the expression of CDK2, CDK6, Cyclin D1, Cyclin E and p-Rb, and increased the expression of γ H2AX. 3. PAICS regulated the AKT- β -catenin axis	[51,61,67, 236,237]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
	GC	Upregulated	Oncogene	1. Inhibition of PAICS promoted cell apoptosis, blocked cell cycle and increased chemotherapy sensitivity. 2. PAICS promoted invasion.	to promote A549/H1299 cell proliferation and migration 1. Knocking down PAICS increased caspase-3 and γ H2AX, inhibited the activity of HDAC1/2 and decreased the expression of DAD51, Bcl-2, CDC25A, cyclin A2 and CDK2. 2. UNMK1/NCOA3/ATF4 axis promoted ATF4 to bind to the promoter of purine metabolism key enzyme gene, thus promoting DNPB.	[60,70]
	HCC	Upregulated	Oncogene	Inhibition of PAICS suppressed tumor growth and metastasis	Dyrk3/NCOA3/ATF4 axis inhibited ATF4 transcription activity, thus downregulating DNPB	[238]
	CCA	Upregulated	Oncogene	PAICS promoted cell proliferation and invasion	1. CLK3/USP13/c-Myc feedback axis promoted c-Myc to bind to the promoter of purine-related enzyme gene and enhanced its expression 2. c-MYC upregulates C1QBP to regulate PAICS/FAK and drive CCA growth.	[66,239]
	Glioma	Upregulated	Oncogene	Inhibition of PAICS suppressed cell cycle and promoted apoptosis	PAICS downregulated the expression of ERCC1 and XPA	[62]
	PCa	Upregulated	Oncogene	PAICS promoted cell proliferation and invasion	MYC oncogene bound to PAICS promoter to upregulate the expression of PAICS	[63,64]
	PDAC	Upregulated	Oncogene	PAICS promoted cell proliferation, EMT and invasion	PAICS downregulated the expression of E-cadherin, while miR-128 bound to the 3' UTR of PAICS to inhibit the expression of PAICS	[68]
	BLCA	Upregulated	Oncogene	PAICS promoted cell proliferation, EMT and invasion	PAICS downregulated the expression of SNAI1 and E-cadherin and promoted the transcription of SLUG and VIM, while miR-128 combined with the 3' UTR of PAICS to inhibit the expression of PAICS	[69]
	CRC	Upregulated	Oncogene	1. PAICS promoted EMT and invasion. 2. The expression of PAICS decreased with tumor progression in stage III CRC.	1. PAICS decreased the expression of E-cadherin and increased the expression of vimentin, while miR-128 also targeted to inhibit the expression of PAICS. 2. The down-regulation of PAICS	[240,241]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
ADSL	Neuroblastoma	Upregulated	Oncogene	Knocking down MTHFD2 and PAICS blocked cell cycle and inhibited cell proliferation 1. ADSL accelerated cell cycle progression 2. Low expression of ADSL was associated with worse prognosis in CRC subgroups;ADSL predictive particularly in late-stage CRC.	expression was related to the loss of chromosome arm 4q. MYCN targeted to upregulate MTHFD2 and PAICS, thus promoting DNPB	[65,242]
	CRC	Upregulated	Oncogene		Over-expression of ADSL led to mitochondrial dysfunction, and then activated the mTORC1-cMYC axis and KEAP1-NRF2 pathway	[75,88]
	EGFR-mutant lung cancer	Upregulated	Oncogene	Inhibition of ADSL induced DTPCs resistance to TKI	Up-regulated miR-21-3p and miR-21-5p inhibited ADSL, reduced the production of AICAR and inhibited AMPK signaling pathway	[84]
	HCC	Upregulated	Oncogene	1. ADSL promoted cell cycle process 2. Disrupting the ADSL–Beclin1 axis blunted liver tumor growth in mice	1. Knocking out ADSL decreased AMP and ATP levels and led to mitochondrial stress 2. PERK-mediated phosphorylation of ADSL enhances autophagy activation by promoting Beclin1 methylation.	[76,86]
	TNBC	Upregulated	Oncogene	ADSL promoted cell proliferation and invasion	EglN2 hydroxylated the Pro24 site of ADSL, which upregulated cMYC level by inhibiting MIR22HG	[78,243]
	Endometrial cancer	Upregulated	Oncogene	ADSL promoted cell proliferation, migration and invasion	ADSL increased the expression of KLRC3 by upregulating the amount of fumaric acid	[80]
	GBM	Upregulated	Oncogene	ADSL maintained malignancy and drug resistance of GSC	ADSL increased fumaric acid production and promoted the succination of PTEN at cysteine 221, thus reactivating CIA pathway	[81,82]
	Melanoma	Downregulated	Suppressor	Inhibition of ADSL increased DTIC resistance and cancer stemness	Downregulated Dicer inhibited ADSL expression	[83]
	PCa	Upregulated	Oncogene	Inhibition of ADSL blocked cell in G ₀ /G ₁ phase and promoted cell apoptosis	Inhibition of ADSL downregulated the expression of Rb, p21, CDK4, CDC2 and Bcl-2, and upregulated the expression of Bax, Bim and Bid	[74]
	PDAC	/	Suppressor	ADSL knockdown increased gemcitabine resistance.	Nrf2 upregulated ADSL, which suppressed Carma3 expression; loss of ADSL increased	[85]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
ATIC	BC	Upregulated	Oncogene	Disrupting the association between ADSL and STING facilitated STING activation and inhibited tumor growth	Carma3 levels and gemcitabine resistance. IKK β -mediated phosphorylation of ADSL suppresses STING activation and downstream IRF3-dependent cytokine expression.	[87]
	PCa	Upregulated	Oncogene	Inhibition of ATIC induced apoptosis and suppressed proliferation and EMT	Inhibition of ATIC led to AICAR accumulation, which activated AMPK/TSC/mTOR/p70S6K/MYC signal transduction and TGF- β signaling pathway	[244]
	Colorectal cancer	Upregulated	Oncogene	Inhibition of ATIC activated the G ₂ /M cell cycle checkpoint and suppressed tumor growth	1. Inhibition of ATIC led to the depletion of ATP and increased DNA damage responses in HCT116 cells. 2. p53 promoted KAT2B activation and mediated the acetylation of ATIC at the Lys226 site, thus promoting its degradation.	[94,97]
	HCC	Upregulated	Oncogene	ATIC promoted cell proliferation and inhibited autophagy and apoptosis	1. ATIC activated the PI3K/AKT/FOXO3 pathway, inhibited AMPK activity and induced mTOR-S6 K1-S6 signaling pathway 2. LncRNA ZFAS1 regulated ATIC transcription, thereby promoting hepatocellular carcinoma cell proliferation and migration via the PI3K/AKT signaling pathway	[92,95,96]
	ALCL	/	Oncogene	1. ATIC-ALK gene fusion was a subtype of ALCL. 2. p-ATIC contributed to cell transformation.	1. ALK gene and ATIC gene were fused, and ATIC-ALK was activated by homologous dimerization mediated by ATIC. 2. NPM-ALK induced p-ATIC and increased its activity.	[90,91]
	BC	Downregulated	Suppressor	Breast cancer progression is inhibited	LncRNA TPT1-AS1 interacts with CBP to impair ATIC-related purine metabolism and further inhibit breast cancer progression	[93]
IMPDH1/2	B-ALL and T-ALL	Upregulated	Oncogene	1. Inhibition of IMPDH1/2 induced cell differentiation in CEM-2 cells. 2. IMPDH was related to cell proliferation and immature characteristics.	/	[103–106]
	ALL	/	Oncogene	IMPDH1/2 increased	The function-acquired mutation of NT5C2	[245]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
				chemoresistance to 6-MP	led to the increase of purine nucleotide consumption	
	AML	/	/	1. IMPDH1/2 mediates venetoclax resistance, glycolytic reprogramming and leukemia stem cell stemness maintenance in leukemic cells. 2. Inhibiting guanine nucleotide biosynthesis promoted myeloid differentiation and sensitized cells to menin inhibitors.	1. Excess guanine nucleotides suppressed the impaired ribosome biogenesis checkpoint, leading to TP53 destabilization and sustained MYC activation, whereas IMPDH1/2 inhibition restored this checkpoint axis. 2. IMPDH2 inhibition reduces guanine nucleotide availability, thereby impairing LEDGF–menin–MLL complex function and MLL target gene expression	[143,144]
	Melanoma	Upregulated	Oncogene	Inhibition of IMPDH1/2 induced cell differentiation	/	[107]
	PCa	Upregulated	Oncogene	Inhibition of IMPDH2 enabled apoptosis-resistant cells still sensitive to the necrosis signal.	IMPDH2 inhibition exhausted the GTP/GDP levels in cells and induced the necrosis signal pathway transmitted by Cdc42.	[112,116]
	HCC	Upregulated	Oncogene	IMPDH1/2 promoted cell proliferation and tumor progression	1. PI3K/RB/E2F1 signaling allowed E2F1 to combine with the promoter of enzyme gene and promote its expression. 2. Knocking down IMPDH1/2 inhibited MAPK/RAS signal transduction. 3. USP5 deubiquitinated K48-linked chains on IMPDH2, preventing its proteasomal degradation and stabilizing IMPDH2 to promote GTP biosynthesis and HCC progression.	[113,114,133,246]
	BLCA	Upregulated	Oncogene	IMPDH1/2 promoted cell proliferation, migration and invasion	LncRNA UCA1 recruited TWIST1 to combine with IMPDH1/2 promoter, leading to the increase of GTP production and pre-ribosomal RNA expression	[117,129]
	BL	Upregulated	Oncogene	IMPDH1/2 inhibition induced S phase arrest and cell apoptosis	Myc bound to the promoter region of IMPDH1/2 gene and induced its expression	[123]
	CRC	Upregulated	Oncogene	1. IMPDH1/2 promoted tumor growth. 2. IMPDH2 promoted cell proliferation, cell cycle transition and EMT.	1. Myc promoted IMPDH1/2 expression to increase <i>de novo</i> GTP synthesis, and IMPDH2 reduced IMPDH1 ubiquitination level. 2. IMPDH2 regulated the expressions of	[111,120,121,134,139,247]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
				3. Inhibition of IMPDH2 increased the sensitivity of drug-resistant cells to methotrexate. 4. High IMPDH2 increased resistance to oxaliplatin-induced apoptosis.	cyclin D1, p21Cip1 and p27Kip1, and activated PI3K/AKT/mTOR and PI3K/AKT/FOXO1 pathway. 3. Inhibition of IMPDH2 blocked nucleotide synthesis and increased inhibition of DHFR in H129 cells. 4. Wnt/β-catenin signaling formed a positive feedback loop with IMPDH2 in resistant cells, and Wnt/β-catenin inhibition restored drug sensitivity in a GMP-dependent manner. 5. CDK1-mediated phosphorylation of IMPDH2 inhibits its activity, whereas PP2A-dependent dephosphorylation restores IMPDH2 function and promotes guanine nucleotide synthesis.	
	SCLC	Upregulated	Oncogene	IMPDH1/2 promoted proliferation and increased chemotherapy resistance	For SCLC with low expression of ASCL1, Myc bound to the promoter region of ASCL1 to enhance IMPDH expression and then increase synthesize more GTP and rRNA	[126,127]
	NSCLC	Upregulated	Oncogene	1. IMPDH2 promoted cell proliferation, invasion and migration, inhibited apoptosis 2. SIRT5 downregulation decreased IMPDH1 activity and impaired tumor cell proliferation.	1. IMPDH2 reduced GSK3β, activated Wnt/β-catenin signaling pathway. 2. MiR-34a bound to the promoter of IMPDH1/2 gene, down-regulated IMPDH expression and disrupted Ras signaling pathway in H1299 cells. 3. SIRT5 desuccinylated the N-terminus of IMPDH1, enhancing its enzymatic activity and promoting purine biosynthesis and proliferation.	[119,128,135]
	LUAD	Upregulated	Oncogene	Highly expressed FANCI promoted cell migration and invasion	The direct combination of FANCI and IMPDH2 reduced the degradation of IMPDH2, thus activating MEK/ERK/MMPs pathway	[130]
	Neuroblastoma	/	Oncogene	Inhibition of IMPDH1/2 induced cell cycle arrest and promoted cell apoptosis	IMPDH1/2 inhibition induced the upregulation of p53 and p21, increased the expression of Bax and decreased the expression of Bcl-2 and survivin	[248]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
	GBM	Upregulated	Oncogene	1. IMPDH2 promoted cell proliferation. 2. Inhibition of IMPDH1/2 sensitized GBM cells with RT. 3. IMPDH1/2 inhibition enhanced chemotherapy effect of TMZ. 4. Genetic or pharmacologic inhibition of PSMD14 destabilizes IMPDH2, thereby impairing nucleotide metabolism and suppressing malignancy.	1. IMPDH2 enhanced DNPB and activated RNA Pol I for the synthesis of rRNA and tRNA. 2. Inhibition of IMPDH1/2 inhibited the synthesis of rRNA and triggered nucleolar stress response. 3. IMPDH1/2 inhibition increased γ H2AX expression and impaired DNA repair. 4. For recurrent GBM, the interaction between ARL13B and IMPDH2 reduced the incorporation of alkylated purines into salvage synthesis. 5. PSMD14 removed K48-linked polyubiquitin chains from IMPDH2, stabilizing IMPDH2 and supporting <i>de novo</i> purine biosynthesis.	[122,132,140,249]
	Glioma	/	Oncogene	1. Inhibition of IMPDH1/2 decreased the sensitivity to ribavirin-induced apoptosis 2. The expression ratio of IMPDH1 to IMPDH2 modulates chemosensitivity and clinical prognosis in glioma.	1. IMPDH1/2 inhibitors induced cell protective autophagy through down-regulation of Src/Akt/mTORC1 signaling pathway in U251 cells 2. IMPDH1 maintains GTP/GDP homeostasis after DNA damage, and its loss disrupts nucleotide balance, impairs DNA repair, and increases sensitivity to temozolomide.	[118,250]
	Cervical cancer	Upregulated	Oncogene	Inhibition of IMPDH1/2 increased the chemosensitivity of drug-resistant HeLa/DDP cells to cisplatin	IMPDH1/2 inhibition induced mitochondrial-related apoptosis	[251]
	Tuberous sclerosis complex tumor syndrome	/	Oncogene	Inhibition of IMPDH1/2 induced cell apoptosis of TSC2 deficient tumor cells	IMPDH1/2 inhibition increased the level of intracellular AICAR and activated mTORC1, inducing replication stress and DNA damage	[252]
	HNSCC	Upregulated	Oncogene	Inhibition of IMPDH1 increased the proportion of G ₀ /G ₁ phase cells and promoted apoptosis	IMPDH1 inhibitors induced nucleolar stress, resulting in nucleolar atrophy, nucleolar protein degradation and p53 stabilization	[124]
	NPC	Upregulated	Oncogene	Related to tumor invasion characteristics	/	[108]
	Renal cancer	Upregulated	/	/	/	[117]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
GMPS	Erythroleukemia	/	Oncogene	Inhibition of IMPDH2 increased the sensitivity of drug-resistant cells to methotrexate	Inhibition of IMPDH2 blocked nucleotide synthesis and increased inhibition of DHFR in K562 cells	[253]
	Ovarian cancer	Upregulated	Oncogene	Related to prognosis	/	[110]
	Osteosarcoma	Upregulated	Oncogene	Overexpressed IMPDH2 showed chemotherapy and radiotherapy resistance	IMPDH2 induced the inhibition of mitochondrial apoptosis pathway in Saos-2 cells	[109,137,138]
	TNBC	Upregulated	Oncogene	1. Genetic depletion or pharmacologic inhibition of IMPDH2 reduced pro-tumorigenic phenotypes in multiple doxorubicin-resistant TNBC models <i>in vitro</i> and <i>in vivo</i> . 2. IMPDH2 repression led to DNA damage accumulation. IMPDH2, upon binding to and activation by IMPA1-derived inositol, promotes the progression of castration-resistant prostate cancer (CRPC)	1. IMPDH2 contributes to doxorubicin resistance; inhibiting IMPDH2 is proposed as a therapeutic vulnerability to suppress/prevent growth of chemo-resistant lesions. 2. Chromatin-associated IMPDH2 regulated PARP1 activity by maintaining nuclear NAD ⁺ levels to support DNA damage repair.	[115,125]
	CRPC	/	Oncogene	1. Targeting IMPDH2 induced irreversible guanine nucleotide depletion and inhibited PDAC 2. ECM-driven guanylate accumulation alleviated oxaliplatin-induced DNA damage and promoted PDAC proliferation	IMPA1-derived inositol directly bound to and activated IMPDH2, promoting guanylate nucleotide synthesis to sustain AR ^{low/-} PCSC traits and drive CRPC progression and abiraterone resistance, identifying IMPDH2 as an inositol sensor.	[136]
	PDAC	/	Oncogene	GMPS promoted cell proliferation	1. IMPDH2 inhibition induced guanine nucleotide depletion that could not be rescued by mutant KRAS 2. ECM promoted guanylate production through IMPDH and GMPS, and IMPDH1 expression correlated with matrisome and DNA repair gene signatures in PDAC.	[141,142]
	GBM	Upregulated	Oncogene	GMPS promoted cell invasion and metastasis	GMPS enhanced DNPB and activated RNA Pol I for the synthesis of rRNA and tRNA	[122]
	Melanoma	Upregulated	Oncogene		/	[148]
	HCC	Upregulated	Oncogene	Tumor immune evasion is driven in HCC	GMPS mediated STT3A dependent PD-L1 glycosylation modification to drive tumor immune evasion in HCC	[155]
	BC	Upregulated	Oncogene	Inhibition of GMPS reduced cell invasion	mtp53 upregulated the expression of NMG and the GTP concentration, thus activating	[151]

Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
	PCa	Upregulated	Oncogene	Inhibition of GMPS inhibited cell proliferation	GTP binding protein Knocking down GMPS led to the accumulation of purine metabolites	[147]
	Esophageal cancer	Upregulated	Oncogene	Related to poor prognosis in the early stage	The up-regulation of RFC4 and GMPS expression may be mediated by the change of DNA copy number	[146]
	NPC	Downregulated	Suppressor	The low expression of GMPS promoted radiotherapy resistance	TRIM21-SERPINB5 mediated the degradation of GMPS and promoted the inhibition of TP53, thus protecting cells from apoptosis	[152]
	Cervical cancer	Upregulated	Oncogene	Cervical cancer progression was promoted	GMPS promoted cervical cancer progression through the STAT3/P53 pathway	[153]
	NSCLC	Upregulated	Oncogene	Cell migration and other cellular functions were inhibited when GMPS was knocked down	The knockdown of GMPS regulated the SERPINB2 molecular pathway; DNMT1 and SERPINB2 inhibited cell migration and other cellular functions through uPA	[154]
GMPR	Melanoma	Downregulated	Suppressor	GMPR inhibited cell invasion	1. EPHA4 phosphorylated GMPR at Tyr 267 and increased GMPR activity, reducing the level of GTP and GTP-bound RAC1. 2. Down-regulated MITF combined with the promoter of GMPR, thus downregulating GMPR expression and increasing RAC1 activity.	[254–256]
ADSS	NSCLC	Upregulated	Oncogene	Related to prognosis	ADSS enriched nucleotide biosynthesis	[257]
HPRT(<i>HPRT1</i>)	ALL	Downregulated	Suppressor	Related to poor prognosis	Correlated with white blood cell count and tumor load	[258]
	Osteosarcoma	Downregulated	Suppressor	Related to poor prognosis	DNPB enhanced to meet the high metabolic needs	[259]
	HNSCC	Upregulated	Oncogene	HPRT promoted EMT and proliferation, and reduced sensitivity to EGFR inhibitors	1. HPRT directly bound to STAT3, and promoted the phosphorylation of STAT3. 2. The up-regulation of <i>HPRT1</i> was partially caused by the down-regulation of miR-125b-5p.	[185,190, 260]
	OSCC	Upregulated	Oncogene	HPRT promoted cell chemoresistance to cisplatin	HPRT activated MMP1/PI3K/AKT pathway	[184]
	Endometrial carcinoma	Upregulated	Oncogene	Related to tumor grade and prognosis	/	[261]
	CRC	Upregulated	/	/	Purine salvage synthesis increased	[262,263]

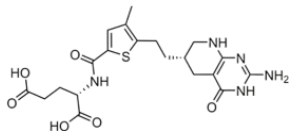
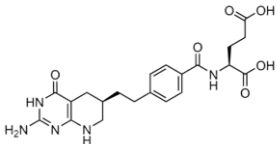
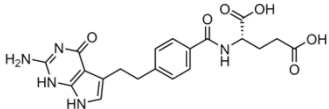
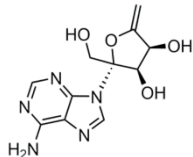
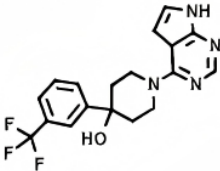
Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
PNP	BC	Upregulated	Oncogene	/	Regulated genes related to cancer pathway	[182]
	GBM	Upregulated	Oncogene	HPRT promoted DNA damage repair and increased cell chemoresistance to TMZ	HPRT/AMPK/RRM1 signal cascade increased RNR activity and dNTPs production	[193]
	Diffuse midline glioma subtype DMG-H3K27M	Upregulated	Oncogene	HPRT promoted radiotherapy resistance	HPRT promoted the increase of guanine nucleotide salvage synthesis, bypassing the inhibition of DNPB	[264]
	Hereditary leiomyomatosis and RCC	Upregulated	Oncogene	Inhibition of purine salvage synthesis led to cell cycle arrest and restricted tumor growth	FH inactivation drove ADSL activity to reverse to produce SAICAR, which limited DNPB and upregulated purine salvage synthesis pathway	[265]
	SCLC	Upregulated	Oncogene	1. Inhibition of HPRT inhibited tumor growth. 2. The activation of purine salvage synthesis pathway mediated cell resistance to PI3K pathway inhibitors.	HPRT inhibition blocked purine salvage synthesis pathway and increased the dependence on DNPB in DMS273 and H1048 cell lines	[188,266,267]
	NSCLC	Upregulated	Oncogene	1. Inhibition of HPRT made cells sensitive to ETC defect. 2. Oleic acid downregulated HPRT and purine salvage synthesis, inhibiting cell proliferation.	1. ETC defect inhibited DNPB, activated PPP and provided PRPP to enhance purine salvage synthesis in H460 cells. 2. Oleic acid activated AMPK/mTORC1/macrophagy/lysosome pathway in A549 cells.	[268,269]
	PCa	Upregulated	Oncogene	Related to tumor malignant degree	HPRT, localized on the cell membrane of DU145 cells, can be used as a target antigen for immune cells to specifically attack cancer cells	[192]
	CLL	Downregulated	/	/	/	[270]
	PCa	Upregulated	Oncogene	Knocking down PNP inhibited cell proliferation, migration and invasion	miR-1 and miR-133a bound to the 3' UTR of PNP mRNA to negatively regulate PNP expression in PC-3 and DU145 cells	[271]
	PCa	Downregulated	Suppressor	1. Alternol treatment enhanced XOR activity and induced cell apoptosis. 2. XOR inhibitor induced apoptosis.	1. Alternol enhanced XOR activity and increased superoxide production in PC-3 and C4-2 cells. 2. XOR inhibitor increased the expression of CHOP, thus activating DR5 and TRAIL-induced apoptosis in PC-3 and DU145 cells.	[272,273]
XOR	BLCA	Downregulated	/	/	/	[274]

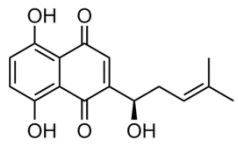
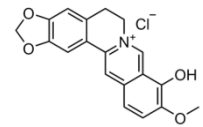
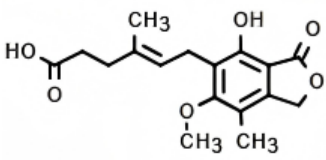
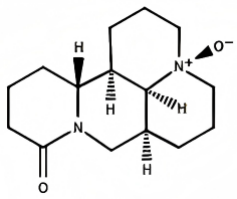
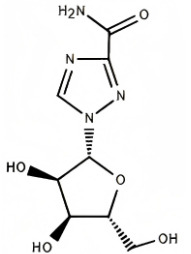
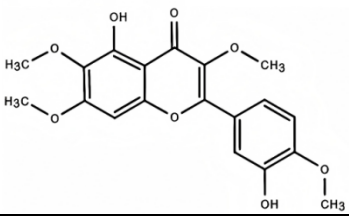
Enzymes	Cancer type	Expression status	Identified gene function	Phenotype	Mechanism	Reference
	RCC	Downregulated	Suppressor	XOR promoted apoptosis	C1QBP promoted XOR transcription, thus promoting hypoxanthine degradation and mediating ROS production in 786-O and ACHN cells	[227,275]
	HCC	Downregulated	Suppressor	Loss of XOR expression promoted EMT and migration	Loss of XOR expression activated TGF- β -Smad2/3 signal transduction	[276–278]
	BC	Downregulated	Suppressor	XOR overexpression inhibited cell migration	XOR probably derived ROS and reduced COX-2 and MMP levels in MDA-MB-231 cells	[279,280]
	CRC	Downregulated	Suppressor	1. The low expression of XOR was related to poor prognosis. 2. XOR expression increased with Caco-2 cell differentiation.	Excessive ROS production induced by XOR caused cell damage.	[262,281]
	GC	/	/	The prognosis with high XOR expression of Chinese was lower than that with low XOR expression	Single nucleotide polymorphism of rs207454 affected XOR expression levels	[282]

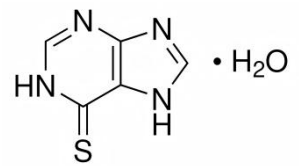
20. Targeting purine metabolism as cancer therapeutics strategies

Maintenance of purine nucleotide pool homeostasis has emerged as an effective strategy to limit cellular proliferation and tumor progression, and the development of pharmacological inhibitors targeting purine metabolism represents a promising therapeutic approach [283]. In this section, we highlight inhibitors against key enzymes that have garnered consistent research interest in recent years, and summarize current progress in understanding their mechanisms of action and therapeutic potential (summarized in Table 2).

Table 2. Inhibitors against enzymes involved in purine metabolism.

Name	Structural formula	Target	Status and limitations	Cancer (cell) types tested	Reference
Pelitrexol (AG2037)		GARFT	Phase II clinical development terminated due to lack of single-agent efficacy; used as preclinical chemical probe to study purine metabolism and mTORC1 inhibition	NSCLC (NCI-H460, A549, A427)	[284]
Lometrexol (LMX)		GART	Preclinical tool compound with Phase I/II clinical evaluation	Breast cancer (MBC, LumA), AML, Neuroblastoma (MYCN-amplified)	[285,286]
Pemetrexed (PEM)		GART、DHFR、TS	FDA-approved multitargeted antifolate for nonsquamous NSCLC and MPM	NSCLC, MPM	[287,288]
MRT 252040	/	PAICS	Preclinical PAICS inhibitor with <i>in vitro</i> and <i>in vivo</i> activity	MYC-positive (DLBCL)	[289]
Angustmycin A		GMPS	Preclinical/tool compound employed for the inhibition of metabolic enzymes	Melanoma (SK-Mel-28, SK-Mel-103)	[148]
G180439		GMPS	Preclinical lead identified by virtual screening, requires further validation	HeLa	[290]

Name	Structural formula	Target	Status and limitations	Cancer (cell) types tested	Reference
Shikonin		IMPDH2	Preclinical; potential therapeutic candidate for TNBC	TNBC (MDA-MB-231、4T1)	[291]
Berberubine (BRB)		IMPDH2	Preclinical/tool compound employed for the inhibition of metabolic enzymes	CRC(SW620、LS174T)	[292]
Mycophenolic Acid		IMPDH2	Preclinical IMPDH inhibitor; synergizes with chemotherapeutic agents in GBM cells	GBM (U87, U251)	[293]
Oxymatrine		IMPDH2	Preclinical/tool compound employed for the inhibition of metabolic enzymes	Cervical cancer (HeLa/DDP cisplatin-resistant cell line)	[251]
Ribavirin		IMPDH	Preclinical/tool compound employed for the inhibition of metabolic enzymes	Glioma (U251, C6)	[250]
Vitexicarpin		IMPDH2	Preclinical/tool compound employed for the inhibition of metabolic enzymes	CRC (HCT116, LOVO, Colo205, HT29)	[294]

Name	Structural formula	Target	Status and limitations	Cancer (cell) types tested	Reference
6-mercaptopurine(6-MP)		HPRT	FDA-approved antimetabolite for ALL maintenance therapy; preclinical evidence supports HPRT-mediated inhibition of purine salvage in SCLC, particularly in combination with methotrexate and methionine sulfoximine .	ALL, SCLC	[188,295]

21. GART inhibitor

GART inhibitors have shown antitumor activity in multiple malignancies by suppressing *de novo* purine synthesis. Pelitrexol (AG2037), a specific inhibitor of GART, has been shown to have therapeutic effect in the treatment of metastatic colorectal cancer [296]. Mechanistically, AG2037 reduces intracellular guanine levels, decreases GTP-bound RHEB, and inhibits mTORC1 activity, thereby arresting cell-cycle progression in NCI-H460 NSCLC cells [284]. In xenograft models, intraperitoneal administration of AG2037 (10 or 20 mg/kg) also suppresses mTORC1 signaling and retards tumor growth and dissemination [284]. These data suggest a clue that inhibition of mTORC1 enhances the therapeutic effects of purine biosynthesis inhibitors. Lometrexol, an antifolate inhibitor of GART activity, also blocks DNPB and exerts antitumor effects in several tumor models. In breast cancer cells, lometrexol inhibits proliferation and induces apoptosis and cell-cycle arrest [285]. In MYCN-amplified neuroblastoma, it promotes neuronal differentiation while inhibiting proliferation, migration, and clonogenicity [286]. Pemetrexed, another inhibitor of the GARFT activity of GART, likewise exhibits antitumor activity in multiple myeloma by suppressing DNPB and attenuating stemness and malignant phenotypes. And its antitumor activity is closely linked to the inactivation of the HSP90 α /CDK6/ β -catenin signaling axis [50].

Combination strategies further improve the efficacy of purine biosynthesis inhibition. In AML, lometrexol enhances the antileukemic activity of venetoclax and synergistically suppresses cell growth [297]. Lometrexol also acts synergistically with ME-344, an oxidative phosphorylation (OXPHOS) inhibitor, leading to greater depletion of purine biosynthetic metabolites and prolonged survival in AML-bearing mice [297]. However, although numerous GART inhibitors have been experimentally validated for their antitumor effects, to date only pemetrexed has been approved by the FDA for clinical treatment of non-squamous NSCLC and MPM [287,288]. Future advancement of clinical trials for these inhibitors may provide additional targeted therapeutic options for cancer treatment.

22. PAICS inhibitor

MRT252040, a newly developed inhibitor of PAICS, has been shown to be a potential therapeutic strategy for MYC-positive DLBCL. It suppresses MYC-driven DLBCL cell proliferation by inducing cell-cycle arrest and apoptosis *in vitro* and also shows efficacy in patient-derived xenograft models [289]. These findings support PAICS as a promising therapeutic target in MYC-positive diffuse large B-cell lymphoma (DLBCL), particularly in cases with poor response to conventional treatment. In addition, virtual screening has identified six candidate PAICS inhibitors, although their antitumor activity remains to be validated [298]. Overall, with increasing understanding of the role of PAICS in tumor metabolism, PAICS inhibitors may emerge as promising therapeutic agents, either alone or in combination with other treatments such as immunotherapy.

23. IMPDH inhibitor

Inosine monophosphate dehydrogenase (IMPDH) is a key rate-limiting enzyme in guanine nucleotide biosynthesis and represents an attractive therapeutic target in cancer [291,292,299]. Its inhibition disrupts guanine nucleotide homeostasis, leading to replication stress, DNA damage, and apoptosis.

Mechanistically, GTP depletion suppresses oncogenic signaling, including reduced STAT3 phosphorylation and Bcl-xL expression with concomitant Bax upregulation, thereby inducing mitochondrial dysfunction [300]. In addition, IMPDH inhibition elevates intracellular AICAR levels and activates mTORC1, further promoting replication stress in TSC2-deficient tumors [252]. It can also enhance chemosensitivity; for example, IMPDH2 silencing potentiates methotrexate efficacy via strengthened dihydrofolate reductase (DHFR) inhibition [247,253], while GTP depletion relieves allosteric inhibition of SAM and HD domain-containing deoxynucleoside triphosphate triphosphohydrolase 1 (SAMHD1) to enhance the activity of nucleoside analogues such as ara-CTP [301].

Several classes of IMPDH inhibitors have been investigated. Mycophenolic acid (MPA), a classical inhibitor, induces cell cycle arrest and apoptosis by disrupting purine metabolism [123]. It exerts antitumor effects through p53/p21-mediated G0/G1 arrest, inhibition of DNA repair [249], and downregulation of oncogenic factors such as telomerase reverse transcriptase (TERT) and O6-methylguanine-DNA methyltransferase (MGMT) [293]. Its prodrug, mycophenolate mofetil (MMF), has also been explored for anticancer applications [302]. Ribavirin similarly inhibits tumor growth, although it may induce protective autophagy, which can be therapeutically targeted to enhance its efficacy [250]. In addition to conventional agents, a range of natural compounds have been identified as IMPDH2 inhibitors. These include Shikonin [291], berberrubine [292], oxymatrine [251] and vitexicarpin [294], which suppress tumor growth by inhibiting purine synthesis, inducing apoptosis, and increasing oxidative stress. Their effects are often reversible by guanosine supplementation, indicating a purine-dependent mechanism.

Recent efforts have focused on developing novel synthetic inhibitors with improved specificity. Comp-10, an allosteric inhibitor, reduces IMPDH protein levels and overcomes drug resistance in lymphoma [303]. Other small-molecule agents, including indole acrylamide derivatives, BMS-566419, VX-497, and VX-148, have shown promising antitumor efficacy *in vitro* and *in vivo* [304]. Collectively, IMPDH inhibitors exert anticancer effects primarily through guanine nucleotide depletion and subsequent metabolic and signaling disruption. The expanding repertoire of classical, natural, and synthetic agents further supports IMPDH as a potentially actionable therapeutic target, although additional clinical validation is needed.

24. GMPS inhibitor

GMPS inhibitors have shown therapeutic potential in several cancer types, although this field remains at an early stage and requires further clinical validation. Angustmycin A (decoyinine), a well-characterized GMPS inhibitor, suppresses melanoma cell invasion and tumor growth *in vitro* and *in vivo*, supporting the therapeutic relevance of GMPS inhibition [148]. More recently, the small-molecule inhibitor G180439(G18) was identified through structure-based virtual screening and experimental validation. G18 targets the ATPase domain of GMPS and shows enzymatic inhibitory and antiproliferative activity in HeLa cells, with greater cellular efficacy than decoyinine [290]. Together, these studies support GMPS as a viable metabolic target in cancer and highlight the need for further development of more potent and selective GMPS inhibitors.

25. HPRT inhibitor

HPRT plays a central role in the purine salvage metabolism pathway. 6-mercaptopurine (6-MP), as an antimetabolic chemotherapeutic agent, competitively inhibits the activity of HPRT [305]. Its efficacy in maintenance therapy for acute lymphoblastic leukemia has been extensively validated in clinical practice [295]. Recent studies have demonstrated that beyond leukemia treatment, 6-MP can block purine salvage synthesis by inhibiting HPRT activity, thereby suppressing the growth of small cell lung cancer (SCLC). Moreover, when combined with glutamine synthetase inhibitors such as methionyl sulfoxide and methotrexate, it further inhibits SCLC progression and prolongs host survival [188]. These findings hold significant implications for expanding the clinical applications of 6-MP. Additionally, research teams have conducted screening for natural plant-derived anticancer inhibitors targeting HPRT and identified two plant-derived compounds—gibberellin A34 and chasmanthin—as potent inhibitors of the HPRT active site. However, these effects were only confirmed through target enzyme inhibition assays and computational pharmacological predictions, requiring further validation via cellular and animal studies [306]. In conclusion, pharmacological inhibition of HPRT is expected to provide a research direction with clinical translation potential for metabolic targeted therapy of small cell lung cancer and other HPRT-dependent tumors.

26. Concluding remarks

Current research on purine metabolism and cancer has primarily focused on the *de novo* biosynthesis pathway, with most *de novo* biosynthetic enzymes exhibiting enhanced activity or upregulated expression in tumor cells, but purine metabolic reprogramming is not confined to *de novo* synthesis. The salvage pathway maintains nucleotide pool homeostasis by recycling purine bases such as adenine, hypoxanthine, and guanine, and can compensate for *de novo* biosynthesis under conditions of metabolic stress or drug inhibition. Meanwhile, the purine catabolic pathway is not merely a terminal clearance process; key enzymes including ADA, PNP and XOR may also influence tumor biological behaviors by regulating the fate distribution of nucleosides and bases, uric acid production, and oxidative stress status. Mounting evidence suggests these enzymes act not only as central metabolic nodes regulating cancer cell metabolism, but also as modulators of multiple signaling pathways. Targeting key enzymes in the purine metabolism pathway thus represents a promising therapeutic strategy.

Importantly, *de novo* purine biosynthesis, the salvage pathway, and purine catabolism do not operate independently but are closely interconnected. Together, they help maintain the nucleotide supply required for cancer cell growth and survival. Under metabolic stress or therapeutic pressure, tumor cells can adapt by shifting their reliance among these pathways to preserve purine homeostasis. Such metabolic flexibility not only supports tumor progression but may also reduce the effectiveness of therapies targeting a single metabolic route. Therefore, understanding the interactions among these pathways may provide a basis for developing more effective combination treatment strategies.

The tumor immune microenvironment is characterized by elevated levels of ATP and its catabolite adenosine (ADO) [307]. Building on this biological basis, a variety of immunotherapeutic strategies have been developed. A recent review has summarized multiple combination therapeutic approaches currently pursued to overcome ADO metabolism-mediated immunosuppression [308]. Among these, the membrane-bound ADO-generating enzymes CD39 and CD73 have emerged as promising targets for

novel checkpoint inhibitors, demonstrating encouraging clinical translational potential [309]. In contrast, clinical intervention strategies targeting ADA, the key enzyme in the purine metabolic catabolic pathway, remain relatively limited. Nevertheless, existing studies have shown that polyethylene glycol (PEG)-modified ADA2 can efficiently degrade adenosine in the tumor microenvironment, thereby suppressing tumor growth and lung metastasis [310]. This suggests that other immunotherapy strategies aimed at reducing ADO levels by targeting ADA-mediated degradation have significant development potential. Currently, the rationale for targeting cancer metabolism is conceptually straightforward. Purine antimetabolites inhibit purine metabolism primarily through two mechanisms. First, they mimic endogenous substrates to competitively bind the same enzyme active sites, interfering with enzymatic reaction rates and reducing the production of normal metabolites [311]. Second, their binding to enzyme active sites generates inactive or toxic metabolites, leading to DNA damage and subsequent apoptosis [312]. Despite these advances, progress in developing metabolism-targeted cancer therapies has remained relatively limited over the past decade, with only a handful of agents gaining clinical approval. Importantly, metabolic targeting strategies must be evaluated within the context of an intact immune microenvironment. Suppressing metabolic pathways in antitumor immune cells could counteract the therapeutic benefits achieved by inhibiting tumor cell survival [313]. Additionally, careful consideration of specificity, binding affinity, and intracellular enzyme abundance is essential to ensure effective drug delivery and activity [314].

Purine metabolism-targeted therapies still face significant challenges, including adverse effects, tumor-microenvironment interactions, metabolic heterogeneity, and adaptive metabolic reprogramming. Future research should aim to comprehensively identify critical metabolic targets, more precisely characterize tumor metabolic reprogramming, and develop personalized metabolic and combination therapies. Integrating multi-omics approaches, single-cell sequencing, and spatial genomics will facilitate the identification of metabolic vulnerabilities within the tumor microenvironment and enable dynamic monitoring of metabolic changes.

In summary, elucidating dysregulated purine biosynthesis and metabolic pathways in cancer will provide new insights into tumor biology and therapeutic development. Targeting these pathways may provide new opportunities for anticancer drug discovery; however, further investigation is needed to optimize therapeutic efficacy and minimize off-target effects. Continued exploration and modulation of key enzymes in purine metabolism are expected to deepen our understanding of cancer biology and support the development of more effective therapeutic strategies.

Declaration of generative AI and AI-assisted technologies

The authors did not use generative AI or AI-assisted technologies in the writing of this manuscript.

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Authors' contribution

Conceptualization, M.S.; writing—original draft preparation, R.T. and M.Z.; writing—review and

editing, M.S., R.T. and M.Z.; visualization, Y.W. and S.W.; supervision, M.S.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Abbreviations

6-MP, 6-mercaptopurine; 6-TIMP, 6-thioinosine monophosphate; ADA, adenosine deaminase; ADO, adenosine; ADSL, adenylosuccinate lyase; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; AFP, alpha-fetoprotein; AIRS, aminoimidazole ribonucleotide synthetase; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AMP, adenosine 5'-monophosphate; AMPK, AMP-activated protein kinase; APRT, adenine phosphoribosyltransferase; ASB11, ankyrin repeat and SOCS box-containing 11; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; ATP, adenosine triphosphate; AZA, azathioprine; B-ALL, B-cell acute lymphoblastic leukemia; Bax, BCL2-associated X protein; Bcl-xL, B-cell lymphoma-extra-large; BC, breast cancer; BL, Burkitt lymphoma; BLCA, bladder cancer; cAMP, cyclic adenosine monophosphate; CCA, cholangiocarcinoma; CCL2, C-C motif chemokine ligand 2; CDK1, cyclin-dependent kinase 1; CDK6, cyclin-dependent kinase 6; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; CREB1, cAMP response element-binding protein 1; CRPC, castration-resistant prostate cancer; c-MYC, MYC proto-oncogene, bHLH transcription factor; DHFR, dihydrofolate reductase; DLBCL, diffuse large B-cell lymphoma; DLEU1, deleted in lymphocytic leukemia 1; DNPB, *de novo* purine biosynthesis; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; EglN2, egl-9 family hypoxia-inducible factor 2; eIF2 α , eukaryotic translation initiation factor 2 α ; eIF4E, eukaryotic translation initiation factor 4E; EMT, epithelial–mesenchymal transition; ER α , estrogen receptor α ; ERK, extracellular signal-regulated kinase; ESCC, esophageal squamous cell carcinoma; FGAMS, phosphoribosylformylglycinamide synthase; FGAR, N-formylglycinamide ribonucleotide; FGFR, fibroblast growth factor receptor; FOXK2, forkhead box K2; FOXO3, forkhead box O3; GARFT, glycinamide ribonucleotide formyltransferase; GARS, glycinamide ribonucleotide synthetase; GART, phosphoribosylglycinamide formyltransferase; GBM, glioblastoma; GC, gastric cancer; GMP, guanosine 5'-monophosphate; GMPS, guanosine monophosphate synthetase; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HIF-1, hypoxia-inducible factor 1; HIF-1 α , hypoxia-inducible factor 1- α ; HNSCC, head and neck squamous cell carcinoma; HPRT/HGPRT, hypoxanthine-guanine phosphoribosyltransferase; HPRT1, hypoxanthine phosphoribosyltransferase 1; ICB, immune checkpoint blockade; IDH3 α , isocitrate dehydrogenase 3 α ; IKK β , inhibitor of nuclear factor kappa-B kinase subunit β ; IMP, inosine 5'-monophosphate; IMPDH, inosine monophosphate dehydrogenase; IMPDH2, inosine monophosphate dehydrogenase 2; KAT2B, lysine acetyltransferase 2B; KEAP1, Kelch-like ECH-associated protein 1; KHK-A, ketohexokinase-A; KSHV, Kaposi's sarcoma-associated herpesvirus; LUAD, lung adenocarcinoma; MAT2A, methionine adenosyltransferase 2A; MBC, metastatic breast cancer; METTL3, methyltransferase-like 3; MGMT, O6-methylguanine-DNA methyltransferase; METTL14,

methyltransferase-like 14; MICA/B, MHC class I chain-related proteins A/B; MLL, mixed-lineage leukemia; MM, multiple myeloma; MMF, mycophenolate mofetil; MOCOS, molybdenum cofactor sulfurase; MPA, mycophenolic acid; MPM, malignant pleural mesothelioma; MSI-H, microsatellite instability-high; MSU, monosodium urate; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; MUC1, mucin 1; NHL, non-Hodgkin lymphoma; NLRP3, NLR family pyrin domain containing 3; NPC, nasopharyngeal carcinoma; NRF2, nuclear factor erythroid 2-related factor 2; NSCLC, non-small cell lung cancer; NSUN2, NOP2/Sun RNA methyltransferase 2; NUDT5, nudix hydrolase 5; OSCC, oral squamous cell carcinoma; TKI, tyrosine kinase inhibitor; RCC, renal cell carcinoma; PAICS, phosphoribosylaminoimidazole carboxylase/phosphoribosylaminoimidazole succinocarboxamide synthetase; PARP1, poly(ADP-ribose) polymerase 1; PCa, prostate cancer; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PDK1, 3-phosphoinositide-dependent protein kinase 1; PD-L1, programmed death-ligand 1; PEM, pemetrexed; PERK, protein kinase R-like endoplasmic reticulum kinase; PFAS, phosphoribosylformylglycinamide synthase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKM2, pyruvate kinase M2; PNP, purine nucleoside phosphorylase; PP2A, protein phosphatase 2A; PPAT, phosphoribosyl pyrophosphate amidotransferase; PRPP, phosphoribosyl pyrophosphate; PRPS1, phosphoribosyl pyrophosphate synthetase 1; PRPS2, phosphoribosyl pyrophosphate synthetase 2; PSMD14, proteasome 26S subunit, non-ATPase 14; RAC1, Rac family small GTPase 1; RHEB, Ras homolog enriched in brain; RIG-I, retinoic acid-inducible gene I; RLR, RIG-I-like receptor; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAICAR, succinylaminoimidazolecarboxamide ribonucleotide; SAMHD1, SAM and HD domain-containing deoxynucleoside triphosphate triphosphohydrolase 1; SCLC, small cell lung cancer; SERPINB2, serpin family B member 2; SERPINB5, serpin family B member 5; SHMT2, serine hydroxymethyltransferase 2; SIRT5, sirtuin 5; STING, stimulator of interferon genes; T-ALL, T-cell acute lymphoblastic leukemia; TAK1, transforming growth factor- β -activated kinase 1; TCA, tricarboxylic acid; TERT, telomerase reverse transcriptase; TNBC, triple-negative breast cancer; TRIM21, tripartite motif-containing 21; TSC, tuberous sclerosis complex; TSC2, tuberous sclerosis complex 2; UBAP2, ubiquitin-associated protein 2; UBR7, ubiquitin protein ligase E3 component n-recognin 7; UCK2, uridine-cytidine kinase 2; USP5, ubiquitin-specific peptidase 5; VGLL3, vestigial-like family member 3; WTAP, WT1-associated protein; XDH, xanthine dehydrogenase; XMP, xanthosine monophosphate; XO, xanthine oxidase; XOR, xanthine oxidoreductase; YAP, yes-associated protein; ZMP, 5-aminoimidazole-4-carboxamide ribonucleotide.

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