IMP metabolic mechanisms and IMPDH targeting strategies in tumor metabolic reprogramming and therapy (Review)

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Abstract. Metabolic reprogramming is a hallmark feature of malignant tumors. These metabolic pathways are regulated in a cell-autonomous manner by oncogenic signaling and transcriptional networks, and tracking their metabolic reprogramming is frequently used in the diagnosis, detection and treatment of cancer. There are currently promising therapeutic prospects for a variety of types targeting fixed core metabolic pathways in tumor metabolic reprogramming. Among these, inosine monophosphate (IMP) is an essential intermediate in purine nucleotide synthesis that demonstrates significant target potential. Nevertheless, further research is needed to elucidate the regulatory networks that control IMP metabolism in tumor cells. This review combines the latest insights into IMP metabolism into an interesting conceptual framework. This includes the supply of IMP precursor substrates (reprogramming of glucose metabolism, serine/one-carbon metabolism, glutamine and mitochondrial metabolism), the dynamic regulation of important enzymes [phosphoribosyl pyrophosphate synthetase, phosphoribosyl pyrophosphate amidotransferase, IMP dehydrogenase (IMPDH)], purinosomes and signaling pathways (RAS-ERK, PI3K/AKT-mTORC1 and Hippo-YAP) that ultimately regulate IMP synthesis in tumor cells. Additionally, it focused on downstream associations between IMPDH and the immune microenvironment, offering a fresh perspective for current research on tumor therapy targeting IMP metabolism.

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Contents

1. Introduction

Inosine monophosphate (IMP), as a crucial intermediate in the metabolism of purine nucleotides, is essential for both *de novo* synthesis and salvage synthesis pathways (1). The body effectively recovers ~90% of free bases in the salvage pathway through hypoxanthine-guanine phosphoribosyltransferase, using resources to synthesize the necessary IMP and guanine monophosphate. The regular demands of the body are mainly satisfied by this mechanism (2). However, salvage synthesis is unable to keep up with the growing need for purines due to the rapid proliferation of tumor cells. The primary mechanism at this stage is *de novo* synthesis (3,4), which uses 5'-ribose-5'-phosphate as its absolute starting substrate (a common precursor for all purine nucleotide synthesis, usually not listed separately) and catalyzes reactions through trifunctional enzymes [trifunctional glycinamide nucleoside transcarboxylase (GART) protein containing glycinamide nucleoside synthase, GART and aminoimidazole nucleoside synthase domains], bifunctional enzymes [phosphoribosylaminoimidazole carboxylase and succinocarboxamide synthetase (PAICS) containing carboxyaminoimidazole ribonucleotide and succinylaminoimidazolecarboxamide ribonucleotide domains], 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC) containing 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and IMP cyclohydrolase domains] and monofunctional enzymes [phosphoribosyl pyrophosphate amidotransferase (PPAT), formylglycinamide ribonucleotide synthase (FGAMS)

and adenylosuccinate lyase (ADSL)] (5-7). This process consumes large amounts of ATP, glutamine, formate, glycine, aspartate and carbon dioxide to synthesize the necessary purine nucleotides. Among these, IMP is crucial for adenine and guanine monophosphate, which are indicators of cellular proliferation and development (5,8). Furthermore, the need for purine synthesis precursors is significantly increased because of the rapid proliferation characteristics of tumor cells. This drives the regulation of related metabolic pathways, such as reprogramming of glucose metabolism, regulation of serine and glutamine metabolism, the one-carbon cycle and mitochondrial function. Collectively, these processes constitute an extensive metabolic network that surrounds the primary axis of IMP metabolism (9-11). Major metabolic pathways are intricately linked and mutually reinforced within the dysregulated tumor cell, continuously delivering IMP to support its rampant proliferation (11). These pathways also include RAS-ERK, PI3K/AKT-mTORC1 and Hippo-Yes-associated protein (YAP), which modulate various enzymes and metabolic changes through demand-driven and feedback-regulated mechanisms, thereby maintaining the uncontrolled growth of tumor cells. Numerous enzymes, including hypoxanthine dehydrogenase, purinosomes, which are multi-enzyme complexes responsible for *de novo* purine biosynthesis, and modifications in the immune microenvironment linked to hypoxanthine metabolism, have been identified as important targets for preventing tumors or suppressing pathogens. Although it has been thoroughly examined in disciplines such as protozoology and immunology, research on its function in tumor cells has accelerated recently. The objective is to develop novel IMP inhibitors for treating tumors (12-14) (Fig. 1).

Numerous previous studies have suggested targeting IMP metabolism as a highly promising cancer therapeutic strategy, precisely because of the critical role of hypoxanthine. We have developed an integrated conceptual framework that includes precursor supply, dynamic enzyme regulation and signaling pathway modulation based on a series of metabolic reprogramming events in tumor cells. This framework has excellent potential to understand and exploit IMP metabolism in tumor cells. Additionally, targeted inhibition strategies for hypoxanthine dehydrogenase and the effects of IMP metabolism on the immune microenvironment were systematically reviewed. Certain techniques have demonstrated successful reduction of tumor cell proliferation in preclinical models. These studies shed light on the physiological significance of IMP synthesis regulation and offer more precise targets and theoretical foundations for developing IMP metabolism-targeted cancer therapies.

2. Precursor supply: The metabolic network driving de novo synthesis of IMP flux

Reprogramming of glucose metabolism. Aerobic glycolysis in tumor cells serves as the foundation for producing IMP synthesis precursors. Most cancer cells adhere to the Warburg effect, which prioritizes glycolysis to convert glucose into lactate even in the presence of abundant oxygen, whereas normal cells usually generate energy by mitochondrial oxidative phosphorylation. According to the theory by early Warburg, tumor cells prefer aerobic glycolysis, an inefficient ATP production method that yields only 2 ATP molecules, whereas oxidative phosphorylation produces 36 ATP. Warburg explained that this was a passive adaptation due to mitochondrial dysfunction caused by hypoxia, lactate accumulation and other factors, which results in irreversible respiratory impairment (15). However, subsequent studies revealed that most cancer cells have normal mitochondrial function and are still capable of oxidative phosphorylation; their metabolic activity has changed to glycolysis (16-18). It has been found that cancer cells preferentially use aerobic glycolysis to meet the biosynthetic demands of proliferation by allocating glucose-derived carbon toward biosynthesis rather than complete oxidative phosphorylation. The pentose phosphate pathway (PPP) converts ~10% of glucose into 5-phosphoribose to supply nucleotide synthesis; another portion is metabolized into acetyl-CoA for lipid synthesis; and only a small fraction is completely oxidized to carbon dioxide (CO_2) to meet basic ATP requirements. Cancer cells coordinate the PPP with glutamine metabolism in an integrated process, in addition to allocating carbon through aerobic glycolysis (19). A total of three vital enzymes are critical to the aerobic glycolysis of tumor cells: Hexokinase 2 (HK2), pyruvate kinase M2 (PKM2) and lactate dehydrogenase A (LDH-A) (20). HK2 is highly expressed in many tumors and localizes to the outer mitochondrial membrane to bind with the voltage-dependent anion channel (VDAC) along with hexokinase 1 and hexokinase domain component 1. This arrangement allows direct use of VDAC-derived ATP for glucose phosphorylation, thereby improving hexokinase activity, accelerating glucose-6-phosphate (G-6-P) synthesis, modulating glycolytic flux and inhibiting G-6-P accumulation (21). By contrast, LDH-A inhibition significantly suppresses cell proliferation. LDH-A-specific inhibitors (such as oxaloacetate) block lactate production in tumor cells, causing intracellular carbon accumulation, impaired diversion of glycolytic intermediates toward nucleotide and lipid synthesis, decreased NAD^+ regeneration, reduced glycolytic flux and diminished NADPH production, because glutamine metabolism depends on glycolysis-coupled NAD^+ regeneration, ultimately leading to growth arrest or apoptosis. Therefore, LDH-A is crucial for preserving the precursors needed for IMP synthesis (22). Furthermore, proliferative signals inhibit the activity of PKM2, a tumor-specific isoform. Glycolytic intermediates, such as 3-phosphoglycerate (3-PG) and phosphoenolpyruvate (PEP), in their low-activity dimeric forms, are inefficiently converted to pyruvate and are instead redirected into anabolic pathways. Particularly, 3-PG and fructose-6-phosphate enter the non-oxidative branch of the PPP to produce ribose-5-phosphate, whereas PEP facilitates the biosynthesis of alanine and serine (23,24).

The PPP, which is an essential part of carbohydrate metabolism, is primarily responsible for producing 5'-phosphoribulose and NADPH. The former serves as a critical precursor for IMP synthesis within the body, whereas the latter is essential for maintaining redox homeostasis (25). The PPP consists of two functionally complementary branches: Oxidative and non-oxidative. The oxidative branch in tumor cells, driven mainly by glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase, produces NADPH to support antioxidant defense and lipid biosynthesis, while the non-oxidative branch is adapted to hypoxic and highly proliferative conditions. This branch circumvents the limitations of

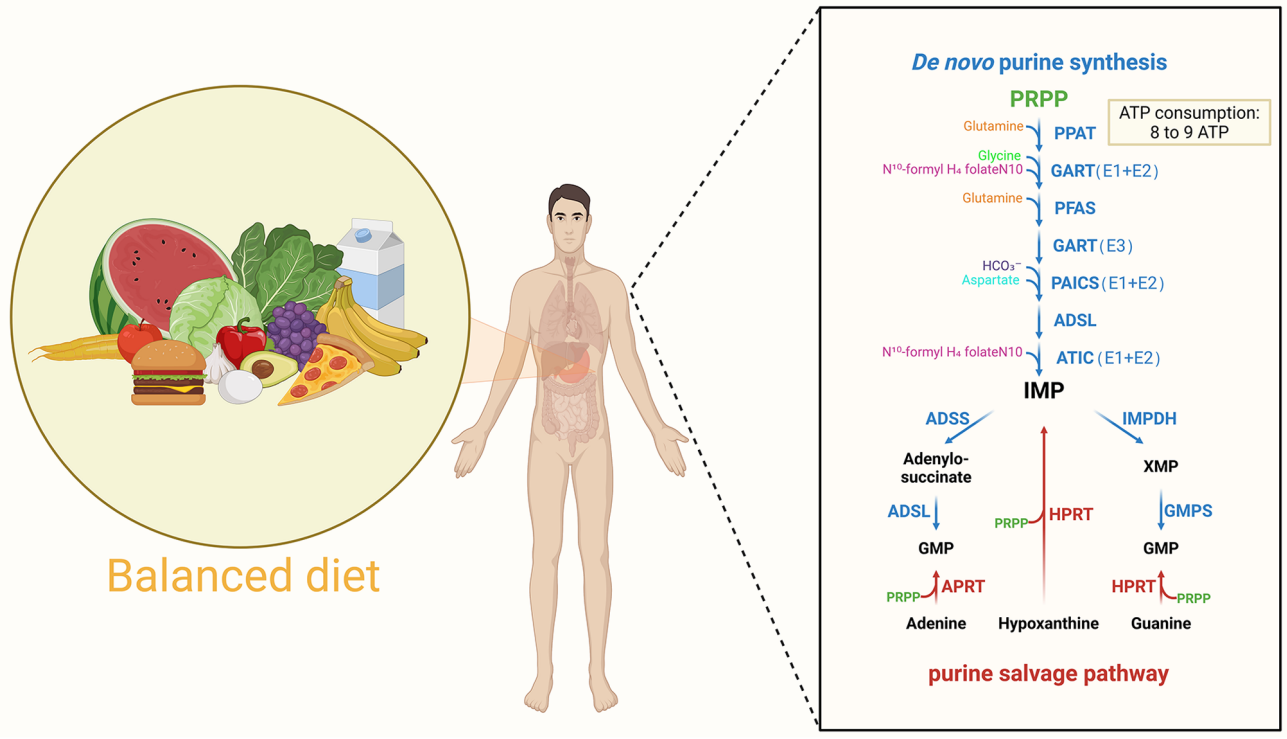

Figure 1. The synthesis process of purine nucleotides in the human body. The organism synthesizes the required purine nucleotides by taking in energy and raw materials from the external environment. PRPP, phosphoribosyl diphosphate; PPAT, phosphoribosyl pyrophosphate amidotransferase; GART, glycinamide ribonucleotide transformylase; PFAS, phosphoribosylformylglycinamidine synthase; PAICS, phosphoribosylaminoimidazole succinocarboxamide synthetase; ADSL, adenylosuccinate lyase; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; ADSS, adenylosuccinate synthetase; IMPDH, inosine monophosphate dehydrogenase; GMPS, guanosine monophosphate synthetase; APRT, adenine phosphoribosyltransferase; HPRT, hypoxanthine-guanine phosphoribosyltransferase.

oxidative phosphorylation under hypoxia by converting glycolytic intermediates into 5-phosphoribose independently of mitochondria. It is catalyzed by transketolase-like 1 (TKTL1) and transaldolase. This reversible pathway supplies >60% of the 5-phosphoribose required by tumor cells and dynamically connects glycolysis to biosynthetic pathways to distribute carbon in accordance with energetic and anabolic requirements (26,27). These two branches are interconnected rather than independent: The oxidative branch produces NADPH, which is generated by the oxidative branch, protects non-oxidative enzymes such as TKTL1 from reactive oxygen species (ROS)-mediated damage, whereas the non-oxidative branch replenishes G-6-P for the oxidative pathway by recycling intermediates into glycolysis, forming a metabolic cycle that collectively supports tumor proliferation, apoptosis resistance and metastatic potential (26). It is now recognized that tumor cells exhibit upregulation of the PPP pathway, particularly in rapidly growing tumors such as glioblastoma. Increased expression of enzymes such as G6PD indicates enhanced PPP activity, providing an abundance of ribose-5-phosphate and promoting *de novo* IMP synthesis. Elevated IMP, adenosine monophosphate (AMP) and guanosine monophosphate (GMP) levels were verified in five patient-derived glioblastoma models, maintaining cellular proliferation and stemness. Furthermore, concurrent NADPH synthesis also improves invasive phenotypes by maintaining tumor cell redox homeostasis. In conclusion, tumor cells modulate the PPP pathway to boost 5-phosphoribose needed for IMP synthesis and NADPH to maintain a stable tumor microenvironment (28). It has been demonstrated that combining therapy with G6PD and glycolysis inhibitors significantly improves radiosensitivity in human gliomas, suggesting that this combination may be a novel targeted treatment approach (29).

Co-regulation of serine metabolism and glucose metabolism in cancer cells. Glucose is taken up by cancer cells and metabolized into precursors such as serine and glycine, which are essential for one-carbon metabolism and provide the carbon units needed to synthesize IMP and glycine (30). The primary source of cytoplasmic serine is extracellular uptake through the alanine/serine/cysteine/threonine transporter 1 and the diversion of ~10% of the glycolytic intermediate 3-PG into *de novo* serine synthesis, which is catalyzed by phosphoglycerate dehydrogenase (PHGDH). Serine is subsequently produced through transamination by phosphoserine aminotransferase 1 and dephosphorylated by phosphoserine phosphatase. Cytoplasmic serine hydroxymethyltransferase 1 (SHMT1) or mitochondrial serine hydroxymethyltransferase 2 (SHMT2) then catalyze the combination with tetrahydrofolate (THF) to produce glycine and 5,10-methylenetetrahydrofolate (31-33). Most cancer cells preferentially use mitochondrial SHMT2 to boost mitochondrial folate synthesis rather than cytoplasmic SHMT1 to convert serine to glycine; SHMT2 knockout leads to increased accumulation of AICAR, an intermediate in IMP synthesis (34). It is interesting to note that SHMT2 generates S-adenosylmethionine (SAM) through one-carbon metabolism, increasing N6-methyladenosine (m^6A) modification of PPAT mRNA. This modification

enables recognition and stabilization by insulin-like growth factor (IGF) 2 mRNA-binding protein 2, which eventually increases PPAT expression to promote renal cell cancer development (35). Tumor cells synthesize required IMP through extracellular serine uptake when serine availability is limited. This finding suggests that lowering IMP synthesis may enhance the efficacy of therapies in specific tumor cells (36). The primary carbon source for purine ring formation in the cancerous tissues of non-small cell lung cancer (NSCLC) is glucose. This process involves the activation and compartmentalization of the glucose-to-serine pathway in the cytoplasm, as well as an enhanced reverse one-carbon flux that reduces the incorporation of external serine into purine synthesis (30,37). Numerous types of tumor cell have been shown to exhibit a significant increase in gene expression linked to serine metabolism. For instance, PHGDH is markedly overexpressed in melanoma, breast cancer and NSCLC, particularly in 70% of triple-negative breast cancers, which is associated with poor prognosis (37,38).

Serine metabolism and glycolysis are closely related due to complex feedback regulation. Elevated serine levels activate the low-activity M2 isoform of PKM2, which catalyzes the conversion of phosphoenolpyruvate to pyruvate in the final stage of glycolysis (39). This process maintains glycolytic flux while restricting diversion of 3-PG into *de novo* serine synthesis. Serine depletion lowers PKM2 activity, impairs the terminal glycolytic step and results in 3-PG accumulation that is redirected into the serine biosynthetic pathway. Simultaneously, elevated 2-phosphoglycerate (2-PG) activates PHGDH, a crucial enzyme in serine and glycine synthesis, thereby increasing *de novo* serine production; 2-PG is converted to 3-PG by phosphoglycerate mutase, which is immediately upstream of PHGDH. As a result, rapid tumor proliferation and high IMP consumption cause serine deficiency, inhibit PKM2 activity, increase 3-PG accumulation and promote compensatory serine synthesis. This feedback circuit partially explains the limited effectiveness of the purine synthesis inhibitor methotrexate. Furthermore, ribonucleotides-purine biosynthetic intermediates-can allosterically activate PKM2 under glucose-restricted conditions, offering an additional adaptive mechanism for cancer cell survival (40). Thus, focusing on the association between serine metabolism and glycolysis may provide a viable strategy for managing cell growth and developing cancer therapies.

Glutamine: Core mechanisms from tricarboxylic acid (TCA) cycle supplementation and nitrogen supply for the maintenance of redox homeostasis. Glutamine is necessary for cancer cell proliferation and, together with its metabolite aspartate, serves as a crucial precursor for IMP synthesis. Rapid tumor proliferation diverts vital tricarboxylic acid cycle (TCA cycle) intermediates toward biosynthesis, disrupting the balance of the TCA cycle. Glutamine is converted to glutamate through the glutaminase pathway and then metabolized by glutamate dehydrogenase 1 into α-ketoglutarate, which enters the TCA cycle to replenish carbon sources (41,42). Furthermore, α-ketoglutarate can be further oxidized to produce succinate and fumarate. These metabolites assist the TCA cycle in cancer cells by providing ATP, NADH and $FADH_2$. They also act as essential tumor metabolites that promote rapid tumor cell proliferation (41,43,44). Additionally, glutamate is converted by glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) into alanine and aspartate, which provide tumor cells with nitrogen sources. In particular, GPT catalyzes the conversion of glutamate and pyruvate into α-ketoglutarate and alanine, with α-ketoglutarate replenishing the TCA cycle and alanine supporting protein synthesis. It has been demonstrated that GPT2 has a crucial role in breast cancer, glioblastoma and KRAS-driven colorectal cancer (45-47). GOT catalyzes the transformation of glutamate and oxaloacetate into α-ketoglutarate and aspartate. Endogenous synthesis is essential since cancer cells have a limited ability to absorb exogenous aspartate. Aspartate production exerts a central oncogenic function by promoting nucleotide and protein synthesis and contributing to the malate-aspartate shuttle, which produces NADPH to maintain tumor cell redox homeostasis (43,48). Additionally, asparagine synthetase (ASNS) utilizes glutamate as a substrate to produce asparagine. This process consumes significant amounts of aspartate and stimulates its synthesis in tumor cells (49). Research has revealed the involvement of ASNS in tumor development and metastasis, in addition to its link to poor survival rates in several cancers, including NSCLC (50). Notably, glutamate catalyzed from glutamine serves as an important precursor for glutathione (GSH). It produces GSH, an essential reducing agent that scavenges ROS and protects cancer cells from apoptosis, together with cysteine and glycine (51). Furthermore, the ability of this metabolic pathway to convert glutamine into biosynthetic precursors is particularly critical in hypoxic conditions (52).

Mitochondria: Metabolic hub for tumor IMP synthesis. Mitochondria, as the primary metabolic organelles in cells, coordinate cellular energy production and provide the raw materials needed for cell proliferation, given the marked demand of tumor cells for TCA cycle precursors and the energy produced by *de novo* IMP synthesis. Their critical role in the IMP metabolic pathway is undeniable. Mitochondria replenish TCA cycle intermediate metabolites by oxidizing glutamine-derived α-ketoglutarate or acetyl-CoA and maintain TCA cycle activity (53). Furthermore, mitochondrial respiration produces aspartate, which increases IMP synthesis in low-oxygen environments, promoting tumor growth and the progression of cancer (54,55). The blocking of mitochondrial respiration reduces intracellular aspartate levels, which in turn restricts the production of asparagine, which is derived from aspartate (56). Interestingly, fibroblasts associated with cancer serve as an additional source of aspartate, which promotes the proliferation of tumor cells (54). Furthermore, SHMT2 converts serine into glycine and one-carbon units in mitochondria, whereas mitochondria produce ATP and CO_2 by oxidative phosphorylation (57). Therefore, mitochondria serve as factories for the synthesis of *de novo* IMP precursors and are crucial for IMP metabolism. Additionally, purinosomes involved in IMP synthesis are intrinsically linked to mitochondria. Targeting mitochondrial function may be a viable strategy for inhibiting purine biosynthesis due to this mitochondrial dependence (8) (Fig. 2).

3. Dynamic regulation of xanthine deoxynucleotidyl transferase in cancer

The rate-limiting enzyme is the one that catalyzes the slowest step in a metabolic pathway; its activity controls the overall

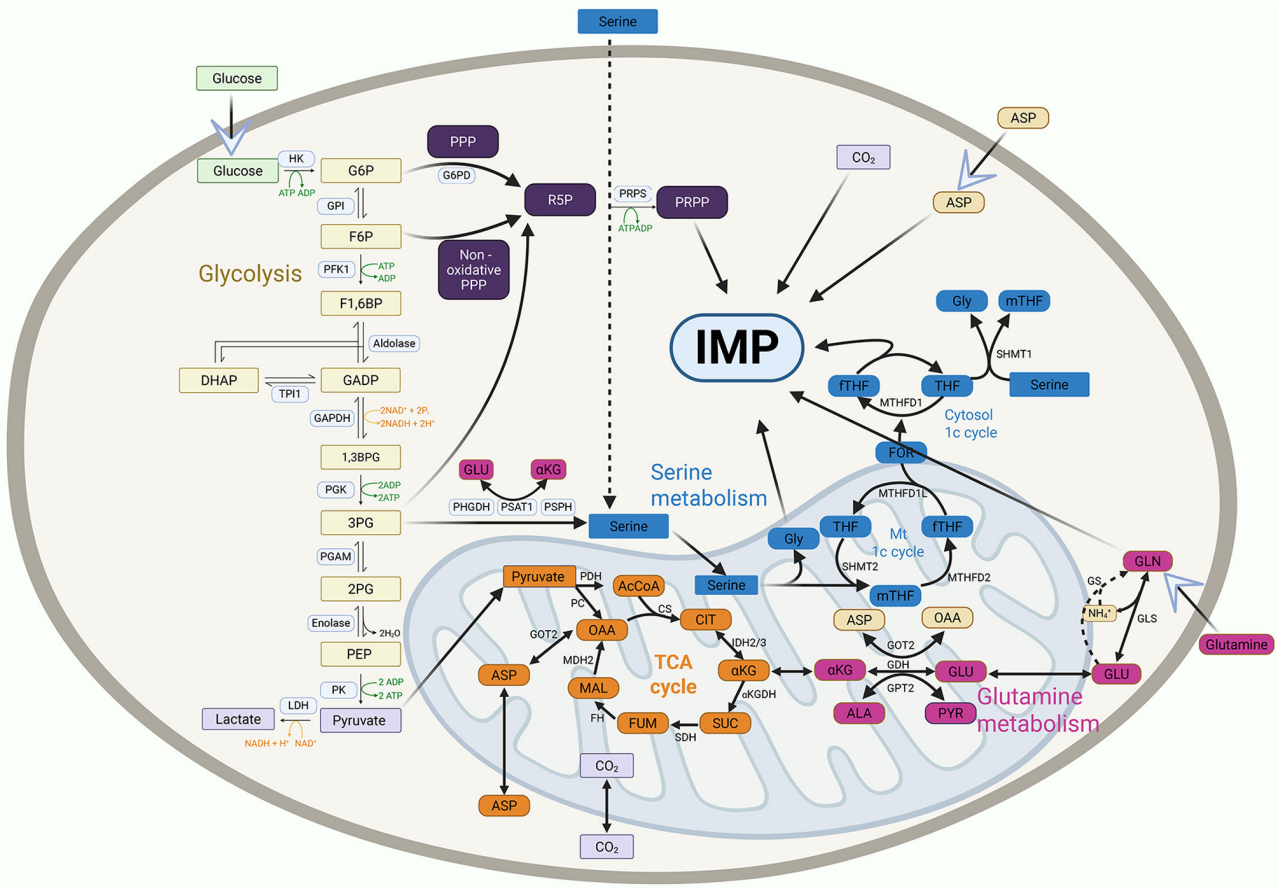

Figure 2. During *de novo* IMP synthesis, multiple metabolic pathways precisely converge to provide essential carbon skeletons and nitrogen sources. The figure illustrates key reactions in central metabolism, including how glucose, glutamine, serine/glycine, one-carbon and mitochondrial metabolism supply substrates for *de novo* IMP synthesis. IMP, inosine monophosphate; HK, hexokinase; G6P, glucose-6-phosphate; GPI, glucose-6-phosphate isomerase; F6P, fructose-6-phosphate; PFK1, phosphofructokinase 1; F1,6BP, fructose-1,6-bisphosphoglycerate; aldolase, fructose-bisphosphate aldolase; DHAP, dihydroxyacetone phosphate; TPI1, triosephosphate isomerase 1; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; 1,3BPG, 1,3-bisphosphoglycerate; PGK, phosphoglycerate kinase; 3-PG, 3-phosphoglycerate; PGAM, phosphoglycerate mutase; 2-PG, 2-phosphoglycerate; PEP, phosphoenolpyruvate; PK, pyruvate kinase; LDH, lactate dehydrogenase; PPP, pentose phosphate pathway; G6PD, glucose-6-phosphate dehydrogenase; Non-oxidative PPP, non-oxidative pentose phosphate pathway; R5P, ribose-5-phosphate; PRPS, phosphoribosyl pyrophosphate synthetase; PRPP, 5-phosphoribosyl-1-pyrophosphate; GLU, glutamate; PHGDH, phosphoglycerate dehydrogenase; PSAT1, phosphoserine aminotransferase 1; PSPH, phosphoserine phosphatase; PDH, pyruvate dehydrogenase; PC, pyruvate carboxylase; AcCoA, acetyl-CoA; TCA cycle, tricarboxylic acid cycle; CS, citrate synthase; CIT, citrate; IDH2/3, isocitrate dehydrogenase 2/3; αKGDH, α-KG dehydrogenase; SUC, succinate; SDH, succinate dehydrogenase; FUM, fumarate; FH, fumarate hydratase; MAL, malate; MDH2, malate dehydrogenase 2; OAA, oxaloacetate; GOT2, glutamate oxaloacetate transaminase 2; ASP, aspartate; Gly, glycine; mTHF, 5,10-methylenetetrahydrofolate; fTHF, 10-formyltetrahydrofolate; THF, tetrahydrofolate; SHMT1/2, serine hydroxymethyltransferase 1/2; FOR, formate; Mt 1C cycle, mitochondrial one-carbon cycle; MTHFD1L, methylenetetrahydrofolate dehydrogenase 1-like; GLN, glutamine; NH_4^+, ammonium; GLS, glutaminase; GS, glutamine synthetase; ALA, alanine; PYR, pyruvate; GDH, glutamate dehydrogenase; GPT2, alanine aminotransferase 2.

flux of the pathway and is a crucial component of metabolic regulation. Tumor cells have been demonstrated to stimulate proliferation by enzymatically modulating the metabolism of hypoxanthine nucleotides. Rate-limiting enzymes such as phosphoribosyl pyrophosphate (PRPP) synthetase (PRPS), PPAT and IMPDH are important players. Additionally, purinosomes, functional assemblies of enzymes involved in *de novo* purine synthesis, are critical for the metabolic reprogramming of nucleotides in tumors. This review systematically summarizes how these enzymes dynamically modulate IMP production to satisfy tumor proliferative demands and explores variations in IMPDH dependency among tumor cell types (58-72) (Table I).

Function and regulation of purinosomes in tumor cells. Purinosomes, initially identified in 2008, are dynamic intracellular structures made up of six enzymes involved in *de novo* purine synthesis. The core scaffold comprises PPAT, GART and FGAMS, while PAICS, ADSL and ATIC are associated with peripheral structures. This spatial organization facilitates metabolic channeling in order to produce IMP and downstream purines to meet cellular demands effectively. Notably, purinosomes are functionally coupled to mitochondria, suggesting a link between *de novo* purine synthesis and cellular energy metabolism. The primary function of purinosomes in growth-related pathways makes them attractive therapeutic targets, despite the fact that their significance in cancer is still unclear (8,73-75). Its formation is driven by reduced cellular purine levels and increased metabolic demand. Enzymes of the *de novo* synthesis pathway assemble into purinosomes when cells require high purine levels, such as during G_1/S-phase proliferation or when salvage pathways are compromised. This organization improves metabolic efficiency by channeling substrates, limiting diffusion or

Table I. A summary of enzymes playing key roles in the *de novo* synthesis pathway of nucleotides in cancer.

Gene	Protein	Cancer	(Refs.)
PRPS	Phosphoribosyl pyrophosphate synthetase	Burkitt's lymphoma	(58,59)
		Liver tumour	(60)
		Relapsed acute lymphoblastic leukemia cancer	(61)
		Breast cancer	(62)
PPAT	Phosphoribosyl pyrophosphate amidotransferase	Lung cancer	(63)
		Thyroid cancer	(64)
		Nasopharyngeal carcinoma	(65)
		Hepatoblastoma	(66)
IMPDH	Inosine-5'-monophosphate dehydrogenase	Lung cancer	(67,68)
		Hepatocellular carcinoma	(69)
		Glioblastoma	(70,71)
		Mixed linage leukemia-fusion leukemia	(72)

degradation of intermediates, and increasing *de novo* synthesis flux by ~50%, thereby increasing IMP production threefold as compared to normal growth conditions. Pyrimidine body production rises by 25% in cells with impaired salvage pathways, such as HGPRT knockout cells, thereby compensating to maintain purine supply. Pathway flux may be markedly more noticeable during the G_1 phase of cell proliferation because these investigations are asynchronous (8,76,77). Functional loss of any purinosomes component disrupts its stability and structure (78,79), and purine supplementation causes complete or significant depletion of purinosomes (8). According to time-lapse fluorescence microscopy analysis, the proportion of purinosome-positive cells peaked during the G_1 phase, providing essential purine nucleotides for cell growth, and progressively decreases throughout the course of the remaining cell cycle. Interestingly, expression levels of *de novo* purine synthesis enzymes did not change across the cell cycle, suggesting that mechanisms other than purinosome assembly and disassembly may also regulate this process (77). Available evidence suggests that a significant portion of purinosomes in purinosome-positive cells localize to mitochondria rather than being randomly distributed throughout the cytoplasm, indicating a close mitochondrial association due to the high energetic needs of purine synthesis. Microtubules provide a structural foundation for purinosome function, as evidenced by the spatial regulation of purinosome assembly being dependent on microtubules. Purinosomes travel along the microtubule network, and microtubule depolymerization disrupts their mitochondrial colocalization, leading to a roughly 50% reduction in the flux of *de novo* purine synthesis. Super-resolution fluorescence microscopy further revealed colocalization of purinosomes with mitochondria, with at least nine purinosome components located at the microtubule-mitochondria interface. This organization allows purinosomes to directly access ATP, one-carbon units (formate), aspartate and glutamine, thereby maximizing the efficiency of purine synthesis. Notably, purinosome formation is increased by defects in mitochondrial functions, including electron transport or oxidative phosphorylation, whereas excessive purinosome accumulation can impair mitochondrial function (5,80,81). Although the role of purine synthase in cancer has not been extensively studied, it is a promising target for possible treatments due to its crucial involvement in notable cellular growth pathways. Furthermore, its dependence on mitochondria suggests that targeting mitochondria can be a strategy to inhibit purine biosynthesis (8). Additionally, molecular chaperones heat shock protein (HSP70)/HSP90 actively contribute to purinosomes assembly, stability maintenance and functional execution by direct binding, folding assistance and degradation regulation. They serve as essential regulators of the biophysical properties and structural integrity of purinosomes, and they also provide a potential therapeutic strategy targeting purinosomes by interfering with chaperone function (82-84). Tumor cells use mechanisms to regulate the assembly and disassembly of purinosomes or their interactions with other organelles to meet their high IMP demand. Tumor cells use microtubules to assemble purinosomes when IMP is deficient, a crucial adaptive mechanism that enables cancer cells to respond to purine scarcity. The process can be inhibited by docetaxel, a microtubule-stabilizing chemotherapeutic agent (85) (Fig. 3).

Unresolved questions and emerging hypotheses regarding purinosomes in cancer. Numerous vital concerns about the structure and function of purinosomes remain unresolved despite initial observations. The present review summarized the main knowledge gaps and emerging hypotheses in purine vesicle biology to highlight their potential for cancer research.

Purinosomes play a central role in cellular metabolism, but little is known about their regulatory mechanisms and functional properties in the tumor context. First, whether various tumor types exhibit distinct patterns of purinosome assembly remains unknown. For instance, although myelocytomatosis oncogene (MYC)-driven tumors frequently exhibit increased *de novo* purine synthesis flux (86), systematic studies of assembly principles unique to tumor subtypes are limited. Second, purinosomes are markedly enriched in the vicinity of mitochondria; nevertheless, the functional mechanism

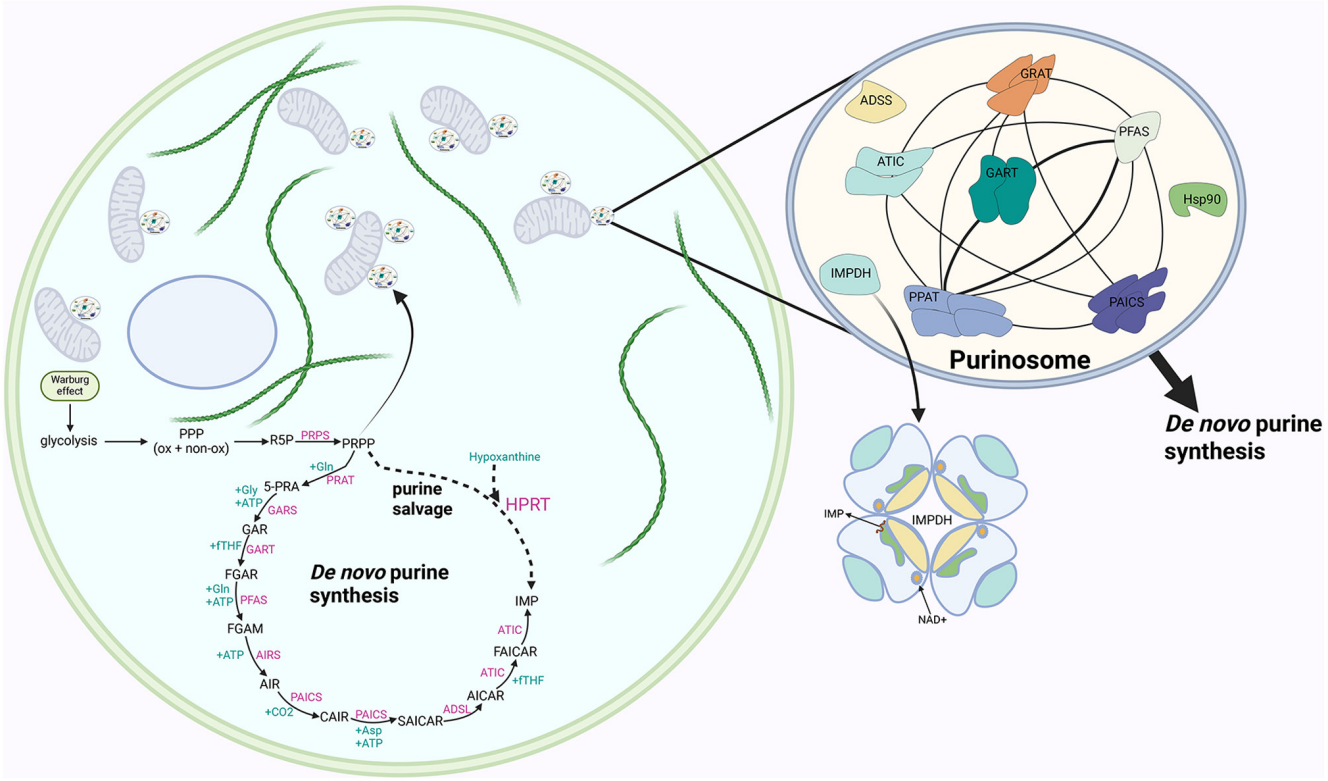

Figure 3. The *de novo* synthesis and salvage pathways for IMP starting from R5P. In cancer cells, the Warburg effect enhances glycolytic flux, which in turn fuels the PPP through both oxidative and non-oxidative branches, thereby increasing the availability of R5P for purine biosynthesis. Under conditions of elevated metabolic demand, purine biosynthetic enzymes assemble into dynamic purinosomes to promote efficient metabolic flux toward IMP production. The purinosome core components (PPAT, GART and PFAS) interact with PAICS, ADSL and ATIC, which also dynamically associate with each other. PPP, pentose phosphate pathway; ox, oxidative; non-ox, non-oxidative; R5P, ribose-5-phosphate; PRPS, phosphoribosyl pyrophosphate synthetase; PRPP, 5-phosphoribosyl-1-pyrophosphate; Gln, glutamine; Gly, glycine; PRAT, phosphoribosyl pyrophosphate amidotransferase; 5-PRA, 5-phosphoribosylamine; GARS, glycinamide ribonucleotide synthetase; GAR, glycinamide ribonucleotide; GART, glycinamide ribonucleotide transformylase; fTHF, 10-formyltetrahydrofolate; FGAR, formylglycinamide ribonucleotide; PFAS, phosphoribosylformylglycinamidine synthase; FGAM, formylglycinamidine ribonucleotide; AIRS, aminoimidazole ribonucleotide synthetase; AIR, aminoimidazole ribonucleotide; PAICS, phosphoribosylaminoimidazole succinocarboxamide synthetase; CAIR, carboxyaminoimidazole ribonucleotide; Asp, aspartate; SAICAR, succinylaminoimidazolecarboxamide ribonucleotide; ADSL, adenylosuccinate lyase; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; FAICAR, 5-formamidoimidazole-4-carboxamide ribonucleotide; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate; Hsp90, heat shock protein 90.

responsible for this spatial coupling remains undefined. Additionally, purinosomes may receive essential substrates from mitochondria, such as ATP, formate and aspartate (8). Can purinosomes specifically inhibit tumor cells by disrupting mitochondrial colocalization, potentially developing a new therapeutic avenue?

Furthermore, the assembly of purinosomes depends on molecular chaperones such as HSP90/HSP70, indicating that they constitute functional targets for chaperone inhibitors (83). However, the extent of their dependence on the chaperone system and their specificity in tumor cells remains to be confirmed. Finally, the morphological, dynamic and functional traits of the purinosome closely resemble those of liquid-liquid phase separation (LLPS)-formed aggregates (82,87,88). Although LLPS is the most favored proposed mechanism to explain its development and characteristics, there is still limited evidence. There are likely other/further mechanisms.

Overall, these unresolved issues constitute important areas of research in purine metabolism. An in-depth investigation of their mechanisms may help clarify patterns of nucleotide metabolism in tumors and provide crucial information for developing novel metabolic-targeted treatment approaches.

Multifunctional regulation of PRPS. PRPS is an important enzyme involved in the early phases of the *de novo* purine synthesis pathway. PRPS1 is an essential isoform in normal cells, whereas PRPS2 is a crucial dependence subtype in tumor cells (particularly those that overexpress MYC) (89). It catalyzes the synthesis of PRPP, an essential precursor of IMP that provides the phosphoribose backbone for IMP. The reaction proceeds as follows: 5'-ribose-5'-phosphate + ATP → PRPP + AMP. Mutations that cause hyperactivation or overexpression of this enzyme have been identified in several cancers. PRPS2-dependent nucleotide synthesis is a crucial factor in determining cancer cell survival in hepatocellular carcinoma, diffuse large B-cell lymphoma, lung squamous cell carcinoma, lung adenocarcinoma and colorectal adenocarcinoma. Consequently, increased PRPS activity results in elevated PRPP production, thereby accelerating nucleotide synthesis to meet the high nucleic acid demands of proliferating tumor cells (60,90,91). Additionally, PRPS2 evades classical ADP/GDP-mediated allosteric feedback inhibition by using four non-conservative key residues, which leads to sustained ATP production that promotes tumor cell proliferation and survival. Studies

further demonstrated that PRPS2 has unique carcinogenic roles in regulating RNA methylation in tumor cells. PRPS2, by sustaining ATP production, promotes SAM synthesis and improves methionine adenosyltransferase 2A stability through direct interaction, thereby increasing ATP use and SAM availability. This subsequently promotes RNA m^6A methylation through the methyltransferase-like 3 (METTL3)-METTL14-Wilms tumor 1-associated protein complex, thereby aiding the growth and metastasis of lung tumors. These results highlight that PRPS2 is an important regulator of tumor progression and a potential therapeutic target (92). Notably, increased glycolysis, PPP and PRPS activities were observed in tumor cells overexpressing cellular myelocytomatosis oncogene protein (c-MYC) (86). Additional research has documented a feedback loop involving phosphoribosyl PRPS1 and its substrate 5-phosphoribose (R-5P) in regulating the PPP. These results indicate that elevated PRPS activity in tumor cells consumes significant amounts of R-5P from the PPP, increasing PPP flux and supplying biosynthetic substrates to promote tumor proliferation (93). Simultaneously, PRPS2 facilitates the synergistic regulation of 'protein synthesis-nucleotide metabolism' by MYC, which maintains tumor metabolic homeostasis (89). From a metabolic perspective, improving the PPP and coordinating protein synthesis probably extends beyond PRPS; these two traits may be shared by enzymes regulating *de novo* IMP synthesis pathways. Beyond this, several aspects of PRPS mechanisms within tumor cells require further investigation, including their coordinated interactions with other enzymes. Comprehensive studies may offer a scientific basis for targeted combination treatments.

PPAT-mediated metabolic regulation. PPAT is the first key/rate-limiting enzyme involved in the *de novo* synthesis of purine nucleotides, which catalyzes the following initial step of this process: PRPP + Gln → 5-phosphoribosylamine + Glu + PPi. This reaction provides a critical precursor for the subsequent synthesis of IMP, AMP and GMP, directly determining the overall flux of purine nucleotide synthesis (94,95). It has been demonstrated that PPAT has a high expression level in several tumors, including nasopharyngeal carcinoma, renal cell carcinoma, small cell lung cancer, thyroid cancer, gastric cancer and colorectal cancer. Its elevated expression promotes *de novo* synthesis of purine nucleotides, which supports tumor cell growth and invasion. Silencing PPAT significantly reduces cell proliferation and clonogenic potential, arresting the cell cycle in the G0/G1 phase and reducing migration and invasion. This further underscores the crucial role of PPAT in maintaining the proliferation and malignant behavior of tumor cells (65). Furthermore, PPAT connects glutamine metabolism and purine synthesis pathways. Elevated PPAT expression in tumor cells diverts glutamine from the TCA cycle to purine synthesis, thereby reducing its contribution to the TCA cycle. This metabolic shift meets the high nucleotide requirements of tumor cells and also affects cellular energy metabolism and other biosynthetic processes, thereby supporting the growth and survival of tumor cells (96). Other studies demonstrated that various factors in the tumor microenvironment, such as hypoxia and fluctuations in nutrient concentrations, may also impact the activity and expression of PPAT. Tumor cells may regulate PPAT under hypoxic conditions through specific signaling pathways and may synergize with other metabolic regulators to increase its activity. This regulation maintains purine synthesis, which provides vital nucleotides and energy to support tumor cell survival and progression in harsh conditions (97-99).

Rate-limiting role of IMPDH. The human genome encodes two isoforms of IMPDH: IMPDH1, located on chromosome 7, and IMPDH2, located on chromosome 3. These isoforms are essential enzymes that catalyze the conversion of IMP to xanthosine monophosphate, regulating the influx of guanine nucleotides. Interestingly, they are found in nearly all organisms (100). The assembly of intracellular IMPDH filaments forms rod-like and ring-like structures. This process enables proliferating cells to maintain high levels of guanine nucleotides, which are necessary for rapid cell division. Furthermore, IMPDH is frequently overexpressed in numerous types of tumor cells (101).

According to available data, IMPDH is highly expressed in a variety of tumor types, with IMPDH2 expression being particularly high. Increased IMPDH activity enhances the GMP biosynthetic pathway, leading to markedly elevated GMP and GTP production. This elevated nucleotide output meets tumor cell demands for purines, energy and signaling necessary for DNA and RNA synthesis, thereby promoting proliferation (102). For instance, increased expression of IMPDH in colorectal cancer encourages cell proliferation, invasion and migration. Similar results were observed in acute myeloid leukemia, glioblastoma and small-cell lung cancer (67,70,103,104). There is evidence that the conversion of IMP to GMP consumes NAD^+ and produces NADH. This process is accelerated by high IMPDH expression in tumor cells, which increases NADH synthesis and significantly lowers the cytoplasmic NAD^+/NADH ratio. This change impairs GAPDH activity and disrupts glycolytic flux because the glycolytic enzyme GAPDH needs NAD^+ as a cofactor. As a result, glucose-derived intermediates are redirected toward the PPP, thereby increasing 5-phosphoribose synthesis and accelerating *de novo* nucleotide synthesis in tumor cells (105,106). Furthermore, IMPDH is essential in the tumor microenvironment. *De novo* purine synthesis is inhibited when important substrates such as 5'-ribose-5-phosphate and glucose are limited; under these conditions, increased IMPDH expression compensates by using salvage pathway-derived IMP to maintain GMP and GTP production (1). According to recent research, cellular hypoxia also increases IMPDH expression, which encourages GMP production to sustain basal proliferation in hypoxic conditions (107). However, further research on this mechanism is still needed.

Differences in IMPDH dependency among tumor types. The dependence of different tumor types on *de novo* IMP synthesis varies significantly; this heterogeneity is controlled by factors such as tissue origin, driver mutations, metabolic status and the tumor microenvironment (108). Cellular dependency is mainly determined by the differential expression and functional divergence of the IMPDH1 and IMPDH2 isoforms. This section summarizes IMPDH reliance in various tumor types and its potential treatment implications.

Malignant tumors of the hematopoietic system exhibit a high degree of dependence on IMPDH2. This dependency arises from their high rates of proliferation, reduced ability to recycle purines and a MYC-driven increase in purine synthesis metabolism. For instance, acute myeloid leukemia (AML) with mixed lineage leukemia (MLL) rearrangements exhibits high sensitivity to IMPDH inhibition, highlighting the crucial role of IMPDH2 in the initiation and maintenance of leukemia (72). Multiple myeloma and certain acute lymphoblastic leukemia subtypes also depend on IMPDH2 to maintain GTP supply, thereby sustaining their proliferative capacity (109,110). These tumors frequently struggle to maintain nucleotide homeostasis through metabolic compensation pathways when IMPDH is inhibited, making IMPDH inhibition a unique metabolic vulnerability in such tumors.

By contrast, solid tumors exhibit subtype-specific dependence on IMPDH. IMPDH2 is consistently increased in glioblastoma and is involved in ribosome biosynthesis and DNA damage repair. Inhibiting IMPDH2 improves the effectiveness of radiotherapy and Temozolomide chemotherapy, indicating a distinct metabolic therapeutic window (70). IMPDH2 is also markedly elevated in highly proliferative solid tumors such as ovarian cancer, and is associated with disease progression and poor prognosis. Its suppression influences purine synthesis and may also regulate microenvironmental processes, including inflammation and angiogenesis (111,112). Despite having higher IMPDH2 levels, colorectal cancer is more sensitive to local pharmacokinetic features (104). Meanwhile, IMPDH1 expression can be increased in certain solid tumors under conditions such as hypoxia or nutritional deprivation to maintain oxidative metabolism and NADPH homeostasis, thereby reducing sensitivity to pure D-type IMPDH inhibitors. This implies that combination strategies must be considered (70).

Furthermore, IMPDH2 upregulation and elevated nucleolar activity are observed in certain virus-associated or immune-coupled tumors (such as Epstein-Barr virus-associated lymphoproliferative disorders), a dependency resulting from GTP metabolic requirements and aberrant immune regulation (108,113). IMPDH inhibition may have both antiproliferative and immunomodulatory effects in these diseases, providing unique therapeutic potential.

Overall, the dependencies of various tumors on IMPDH vary widely, ranging from high-proliferation-dependent types centered on IMPDH2 to adaptive dependency types regulated by the microenvironment and pharmacokinetics, and finally to metabolism-immune coupling types. These differences imply that IMPDH-targeted therapies should be customized through specialized investigation of tumor type, subtype characteristics, IMPDH1/2 expression patterns and metabolic compensatory capacity to improve treatment selectivity and clinical translation potential.

4. Cellular signaling pathways regulate the production of *de novo* IMP

Significant progress is being made in studying the regulation of purine synthesis through multiple signaling pathways. Currently, the most commonly acknowledged signaling pathways implicated in IMP synthesis are RAS-ERK, PI3K/AKT-mTORC1 and Hippo-YAP.

Additionally, mTORC1 serves as a major hub for signaling and metabolism and regulates the balance between anabolic and catabolic processes in cells (114). Growth factors enhance mTORC1 signaling by activating the PI3K/Akt pathway, and establishing the PI3K/AKT-mTORC1 signaling axis (Fig. 4A) (115). Furthermore, mTORC1 signaling triggers the synthesis of *de novo* IMP through its regulatory mechanisms by activating the transcription factors activating transcription factor 4 (ATF4) and MYC (116,117). ATF4, a metabolic effector of mTORC1, increases the synthesis of enzymes in the serine/glycine synthesis pathway and the mitochondrial THF cycle upon induction. These pathways respectively generate glycine and one-carbon acyl units for *de novo* IMP synthesis (116). The production of activated ribose needed for nucleotide synthesis is also increased by the regulation of the mTORC1's oxidative branch of the PPP through the transcription factor sterol regulatory element-binding protein 1 (118). Growth signals activate TKT through Akt signaling, which in turn activates the non-oxidative PPP pathway to promote PRPP production (119). Notably, ATF4 increases the expression of the cystine transporter solute carrier family 7 member 11 in its mTORC1 function, which improves cellular cystine uptake. After being converted to cysteine, cystine acts as a direct precursor for the synthesis of GSH, which reduces oxidative stress in tumor cells driven by rapid nucleotide and protein synthesis (120).

Furthermore, mTORC1 activation stimulates MYC-driven purine biosynthesis by upregulating *de novo* purine synthase. MYC plays a crucial function in regulating genes involved in nucleotide synthesis by directly binding to the promoters of most nucleotide metabolism genes and increasing their expression. For instance, MYC upregulates the expression of genes such as PPAT, carbamoyl-phosphate synthetase 2/aspartate transcarbamylase/dihydroorotase and IMPDH by directly binding to the promoters (121). MYC increases the expression levels of IMPDH1 and IMPDH2 in both an *in vitro* human B-lymphocyte model and an *in vivo* mouse inducible MYC transgenic hepatocarcinoma model. MYC directly binds to the promoter regions of these two genes, recruiting histone acetyltransferases and chromatin remodeling complexes, such as transketolase, to induce histone acetylation, alter chromatin structure and initiate transcription (122,123). Furthermore, MYC regulates the expression of GPN-loop GTPase 1 and 3, leveraging their connections with GTP and RNA polymerase I (Pol I), while improving Pol II assembly efficiency to fulfill global transcription demands, thereby modulating related enzymes and ribosomal biogenesis pathways (124). Furthermore, growth factors (such as insulin, IGF1 and EGF) activate mTORC1 and selectively promote mRNA translation of the bicarbonate cotransporter solute carrier family 4 member 7 (SLC4A7) via S6K-dependent eukaryotic translation initiation factor 4B phosphorylation, thereby increasing intracellular HCO_3^- levels. Additionally, SLC4A7 deficiency reduces HCO_3^- uptake and *de novo* IMP synthesis in tumor cells without affecting intracellular pH. Simultaneously, SLC4A7 deficiency increases tumor sensitivity to the mTORC1 inhibitor rapamycin, demonstrating that mTORC1 regulates HCO_3^- metabolism through SLC4A7 to promote IMP synthesis and cellular growth (125).

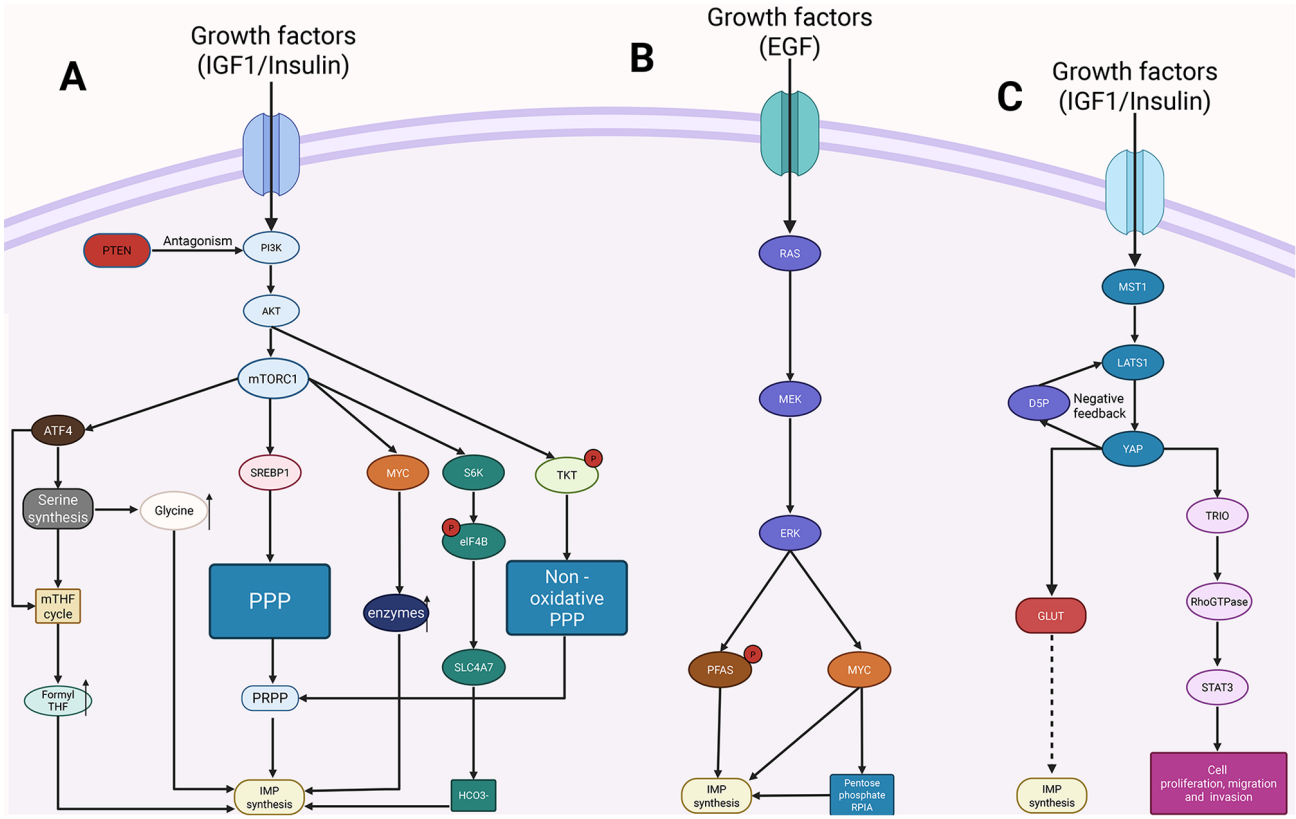

Figure 4. Regulation of *de novo* IMP synthesis by cellular signaling networks. (A) Under growth factor stimulation, mTORC1 is activated downstream of the PI3K/Akt pathway, stimulating SLC4A7 mRNA translation via s6k-dependent eIF4B phosphorylation. This increases cellular bicarbonate abundance, thereby promoting IMP resynthesis. Downstream of mTORC1, transcription factor SREBP1 stimulates the oxidative PPP, enhancing *de novo* IMP synthesis by increasing PRPP availability; Akt activates the non-oxidative PPP via TKT phosphorylation, promoting PRPP-dependent IMP synthesis. Furthermore, mTORC1 activates MYC, which upregulates *de novo* purine synthase expression, thereby promoting *de novo* IMP synthesis. Furthermore, mTORC1 activation enhances ATF4 expression, promoting serine/glycine synthesis and fTHF production to increase IMP *de novo* synthesis. Crucially, PTEN antagonizes PI3K/AKT activation, acting as a counterbalance. (B) Under growth factor influence, ERK phosphorylates PFAS, promoting IMP *de novo* synthesis. Concurrently, MYC, a downstream transcription factor of RAS-ERK, regulates gene expression involved in *de novo* IMP synthesis. (C) Under growth factor stimulation, MST1/LAST1 activates YAP, upregulating glutamine synthase GLUL expression to enhance glutamine synthesis and thereby promote *de novo* IMP synthesis. YAP directly activates TRIO to regulate the Rac1/RhoA switch and STAT3, forming the YAP-TRIO-RhoGTPase-STAT3 signaling network that governs cell migration and invasion. PPP, pentose phosphate pathway; IMP, inosine monophosphate; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTORC1, mechanistic target of rapamycin complex 1; ATF4, activating transcription factor 4; SREBP1, sterol regulatory element-binding protein 1; PRPP, 5-phosphoribosyl-1-pyrophosphate; IMP, inosine monophosphate; MYC, MYC proto-oncogene, bHLH transcription factor; S6K, ribosomal protein S6 kinase; eIF4B, eukaryotic translation initiation factor 4B; TKT, transketolase; SLC4A7, solute carrier family 4 member 7; HCO3-, bicarbonate; mTHF, 5,10-methylenetetrahydrofolate; THF, tetrahydrofolate; RAS, rat sarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; PFAS, phosphoribosylformylglycinamidine synthase; RP1A, ribose phosphate isomerase A; D5P, D-ribose-5-phosphate; LATS1, large tumor suppressor kinase 1; YAP, yes-associated protein; GLUT, glucose transporter; TRIO, triple functional domain protein; RhoGTPase, Rho family GTPase; STAT3, signal transducer and activator of transcription 3.

Purinosomes assembly in tumor cells has been linked to mTORC1, which has been demonstrated to be essential for its localization to mitochondria. Nevertheless, the precise mechanism by which mTORC1 regulates this process remains unclear. It will be fascinating to investigate the possible mechanisms behind mTOR-mediated purinosomes-mitochondrial localization and purinosomes assembly in cancer. Additionally, the increase in lysosomes within tumor cells is a particular response to purine imbalance, with mTORC1 functioning as a crucial kinase that connects purinosomes and lysosomal activity (126). Furthermore, the tumor suppressor phosphatase and tensin homolog (PTEN) inhibits the activation of PI3K/AKT, and the PI3K/AKT pathway is activated in the absence of PTEN. This then improves purine and pyrimidine *de novo* synthesis pathways through mTORC1, including upregulating IMPDH translation (127,128). It remains elusive how mTORC1 activation integrates diverse metabolic pathways to consistently stimulate metabolic output and maintain cell proliferation during tumor metabolic reprogramming. Furthermore, translational opportunities for cancer treatment are provided by the collaborative mechanisms between mTORC1 and signaling pathways such as RAS/ERK.

The ERK pathway regulates the extended expression of genes involved in purine and pyrimidine synthesis by activating the MYC transcription factor. This acts as an important mechanism for the continuous increase in nucleotide production in cancer cells, a process that is now commonly recognized (Fig. 4B) (129). The RAF-MEK-ERK pathway phosphorylates downstream 90 kDa ribosomal S6 kinase on RAS activation, which further stimulates the transcriptional activity of MYC (130). MYC, the primary regulator of nucleotide synthesis, directly binds to the promoters of essential purine synthesis enzymes such as PPAT, PAICS and ATIC, upregulating their expression to activate the

nucleotide synthesis pathway fully (28,131,132). Additionally, phosphofructokinase-platelet has been demonstrated to enhance ERK-mediated c-Myc stability (133). Furthermore, mutant K-RAS activates MYC through ERK, which upregulates ribose-5-phosphate isomerase-A, a crucial enzyme in the non-oxidative PPP. This reroutes glucose intermediates into the PPP and increases PRPP synthesis (134-137), while concurrently regulating glutamine metabolism to supply nitrogen sources for nucleotide synthesis, maintaining elevated intracellular nucleotide levels (138,139). MYC contributes to tumor growth in two ways: Promoting nucleotide synthesis and introducing a distinct oncogenic stress through activation of RNA degradation and nucleotide catabolism. Novel therapeutic approaches for MYC-driven cancers can be achieved by targeting the compensatory mechanisms of this process (140). The acute regulation of IMP synthesis by the ERK pathway is still being investigated. It is hypothesized that RAS-ERK may directly modulate the activity of purine synthase enzymes such as PPAT and PAICS because IMP synthesis is significantly higher in ERK-hyperactivated cancers than in normal cells. This mechanism guides the development of direct ERK-targeting drugs that support purine synthesis, even though the specific phosphorylation sites remain unknown. It has been revealed that ERK2 increases purine synthesis rates by directly adding a phosphate group to threonine T619 at position 619 of phosphoribosylformylglycinamidine synthase (PFAS), an important enzyme in the purine synthesis pathway (141). This implies that the ERK2-PFAS axis may be a metabolic vulnerability in RAS pathway-driven cancer cells. Concurrently targeting the purine synthesis pathway and ERK signaling may emerge as a novel treatment strategy for RAS/RAF-mutated cancers.

YAP acts as a key effector in the Hippo pathway, playing an essential role in organ size regulation and tumorigenesis (Fig. 4C). YAP improves glutamate ammonia ligase (GLUL) by directly binding and transcriptionally upregulating GLUL, thereby promoting *de novo* nucleotide synthesis. This provides the raw materials for rapid cell proliferation, which promotes liver growth and tumorigenesis (142). Yap1 stimulates *de novo* nucleotide synthesis by inducing glucose transporter glucose transporter 1, thereby boosting glucose uptake and anabolic utilization (143,144). Furthermore, YAP regulates deoxyribonucleoside triphosphate synthesis by upregulating key enzymes required for their production, such as ribonucleotide reductase regulatory subunit M2 and deoxythymidine kinase (145). YAP regulates the Ras-related C3 botulinum toxin substrate 1/Ras homolog family member A switch and STAT3 by directly activating triple functional domain protein (TRIO), forming the YAP-TRIO-RhoGTPase-STAT3 signaling network that controls cell migration and invasion (146). Additionally, it has been demonstrated that YAP is regulated by cell-cell interactions and mechanical signals in addition to serving as a crucial sensor of the cellular metabolic state, being directly controlled by the metabolite D-ribose-5-phosphate (D5P). Myosin heavy chain 9-large tumor suppressor kinase 1 (LATS1) complex assembly is induced by a decrease in intracellular D5P, which results in LATS1 degradation and subsequent YAP activation. As a result, purine nucleoside phosphorylase levels rise, causing purine nucleoside degradation and establishing a negative feedback loop that elevates the D5P concentration. This research places D5P at the center stage, establishing it as a key metabolic node that connects glucose and nucleotide metabolism with the Hippo-YAP signaling pathway (147). D5P or its precursors may serve as novel anticancer metabolites or, in conjunction with current metabolic treatments, such as GLUT inhibitors, offer new therapeutic approaches for cancers with high YAP activity.

In conclusion, while originating from distinct oncogene activations, the mTORC1, ERK and YAP pathways exhibit notable functional convergence in *de novo* IMP synthesis. First, all three pathways improve the supply of carbon, nitrogen and one-carbon units required for IMP synthesis by regulating glucose metabolism, serine/one-carbon metabolism and glutamine use. Second, the ERK-MYC axis and mTORC1 upregulate the expression or activity of necessary rate-limiting enzymes (PPAT, PFAS and IMPDH), increasing the flux of purine *de novo* synthesis. Third, mTORC1 and YAP work together to increase purinosomes assembly and mitochondrial localization, achieving spatial coupling of nucleotide synthesis with energy/substrate supply at the subcellular level. Additionally, the D5P-YAP feedback signal establishes a dynamic equilibrium between purine degradation and resynthesis, providing an adaptive mechanism for cancer cells to maintain nucleotide homeostasis under nutritional changes. Therefore, these three mechanisms ultimately promote rapid proliferation, maintain RNA/DNA synthesis and guarantee GTP-driven signaling by enhancing IMP synthesis while having differing drivers. Accordingly, IMP/GTP metabolism appears to be a downstream metabolic vulnerability shared by several signaling pathways.

Immunological significance of metabolic imbalance in IMP/GMP/GTP. IMP metabolism is a critical node in purine metabolism. The downstream conversion of its metabolites, GMP/GTP, directly or indirectly impacts T-cell activation, myeloid cell polarization and the transmission of adenosine signaling pathways, thereby exerting significant effects on the human immune system.

First, T cells exhibit a marked rise in GTP demand during activation and proliferation. GTP possesses dual roles as both an essential metabolic substrate and signaling molecule. It serves as a crucial substrate for RNA synthesis, supporting T-cell clonal expansion, while also functioning as a key molecule in receptor signaling mediated by small GTPases. GTP is involved in vital activities, including immunological synapse formation, T-cell receptor signal amplification, cytoskeletal remodeling and integrin activation (148-151). Furthermore, it is the only precursor needed to synthesize tetrahydrobiopterin (BH4). BH4 is essential for T-cell mitochondrial electron transport, ATP supply maintenance and cell cycle progression. It affects nucleotide synthesis, ultimately resulting in decreased T-cell proliferation (152). Thus, a substantial GTP pool is a metabolic requirement for T cells to progress from initial activation to effector differentiation. T cells demonstrate functional suppression when IMPDH is inhibited because intracellular GTP levels significantly decrease, and T cells are unable to maintain normal clonal expansion and effector differentiation. These mechanisms explain why IMPDH inhibitors cause immunosuppression in clinical settings (138) and suggest that the metabolic imbalance of IMPs in the tumor microenvironment may weaken antitumor immunity by

limiting GTP availability, providing an important theoretical foundation for targeting IMP metabolism to boost immune responses (153).

Second, IMP metabolism is closely associated with macrophage polarization. An adequate supply of purine nucleotides significantly increases the pro-inflammatory gene expression, migration, phagocytosis and anti-pathogen capabilities of classically activated macrophages under inflammatory conditions, suggesting that IMP/GMP/GTP levels are essential for M1 macrophage function (154). Increased purine degradation and uric acid production in the tumor microenvironment cause macrophages to adopt an immunosuppressive tumor-associated macrophage phenotype with high programmed cell death ligand 1 (PD-L1) expression, which can be re-polarized by inhibiting IMP metabolism (155). Furthermore, impaired purine degradation in monocyte-derived macrophages raises isocitrate dehydrogenase 3 activity and causes increased production of α33sdz5 d-ketoglutarate, which promotes M2-like polarization (156).

Furthermore, the body maintains equilibrium by an intriguing cross-regulation mechanism in which high levels of AMP and GMP block their own synthesis, while GTP stimulates AMP synthesis. By contrast, ATP promotes the synthesis of GMP. Accordingly, increased IMP/GMP/GTP metabolism in tumor cells leads to enhanced IMP/AMP/ATP metabolism. Subsequently, AMP/ATP can catalyze the production of additional adenosine using ectonucleoside triphosphate diphosphohydrolase 1/ecto-5'-nucleotidase (157,158). The role of adenosine in immunology is unmatched. It is an essential class of immunosuppressive signaling molecules in immune regulation that maintains immune homeostasis, limits inflammatory responses and modulates the tumor immune microenvironment (156,159,160). Consequently, the balance of IMP/GMP/GTP metabolism affects the operation of the adenosine signaling pathway, eventually affecting the immune microenvironment, including tumor cells.

In conclusion, immune system function depends on the equilibrium of IMP/GMP/GTP metabolism. It exhibits significant associations with T cells, macrophages, adenosine and other components and exerts an unparalleled impact on the immune microenvironment. Scientific investigation into the immunological implications of this extraordinarily complex process has never stopped.

5. IMPDH targeting strategy

Current IMPDH-targeting strategies in tumors primarily take advantage of the metabolic dependence of cancer cells on the synthesis of guanine nucleotides from scratch. These methods disrupt DNA/RNA or GTP synthesis, causing apoptosis, by inhibiting the rate-limiting enzyme IMPDH to prevent GMP production.

Targeted therapies developed specifically against IMPDH can cause the production of highly potent IMPDH inhibitors. First, it is possible to exploit tumor cell heterogeneity, which reflects the unique specificity of IMPDH across various tumor cell types. For instance, IMPDH2 is markedly expressed in cells in breast cancer and melanoma. BMS-566419 and AVN944 were designed to target this characteristic, significantly inhibiting the growth of tumors with high IMPDH2 expression. Recent studies have also revealed that berberine, a natural product, inhibits the progression of colorectal cancer by targeting IMPDH2. However, the structural basis for IMPDH2 selective inhibition remains unclear, necessitating further structural optimization to improve activity (161). By contrast, IMPDH1 is significantly elevated in high-risk groups of tumors like head and neck squamous cell carcinoma (HNSCC), with the purine biosynthesis pathway being the most notably increased metabolic pathway. MPA/MMF markedly reduced the viability of HNSCC cells, inhibited proliferation, increased apoptosis rates, and suppressed migration and invasion (162). Additionally, targeted drugs that only inhibit IMPDH activity in urothelial carcinoma associated 1 (UCA1)-overexpressing cells can be developed to reduce toxicity to normal cells by leveraging the IMPDH1/2-dependent regulation specificity of UCA1/twist family bHLH transcription factor 1 in bladder cancer (163). Furthermore, a thorough examination of the structural characteristics of IMPDH can completely clarify its distinct role in purine synthesis, which will help develop more specific inhibitors (100,164,165). For instance, highly specific inhibitors targeting the cystathionine β-synthase (CBS) domain could be developed due to the substantial homology between IMPDH1 and IMPDH2, their tetrameric structure and the presence of CBS domains capable of binding GTP/GDP for negative feedback regulation (166). Furthermore, investigating associations between IMP synthesis precursors and other metabolic pathways can lead to the identification of dual- or multi-target inhibitors. For instance, the dual-covalent inhibitor HA344 blocks both metabolic pathways to target and eradicate tumor cells by covalently binding to both PKM2, the essential enzyme in glycolysis, and IMPDH, the crucial enzyme in *de novo* purine production (167). When used in combination with immune checkpoint inhibitors (ICIs), it increases immune activation because the antitumor effect of IMPDH inhibitors balances the immunosuppressive effect of PD-L1 upregulation. Co-administration with ICIs does not affect their antitumor effectiveness (68).

Importantly, IMPDH inhibitors can reduce tumor cell progression when combined with other targeted therapies. Studies have revealed that toll-like receptor 1/2 agonists induce differentiation in MLL-fusion AML cells, complementing the mechanism of IMPDH inhibitors with significant synergistic effects (72). *In vitro* experiments verified synergistic inhibition of AML cell growth when coupled with the B-cell lymphoma 2 inhibitor venetoclax (168). When co-administered with Ataxia telangiectasia and Rad3-related protein inhibitors, they cause p53-independent replication catastrophe, significantly raising *in vitro* replication stress levels and markedly inhibiting tumor growth in MKL-1 xenograft models, suggesting a potential treatment approach for Merkel cell carcinoma (169). Even though the Food and Drug Administration has not yet approved IMPDH inhibitors for oncology indications, ongoing preclinical studies and exploratory clinical trials are still being conducted to improve their therapeutic potential (109,110,170-195) (Table II).

6. Conclusion and outlook

IMP metabolism is an essential part of tumor cell metabolic reprogramming that plays an important role in cell proliferation, energy balance and nucleotide supply. The metabolic

Table II. Clinical and preclinical development status of inosine monophosphate dehydrogenase inhibitors in cancer therapy.

Drug name	Trial phase	Targeted cancer types	Key trial progress/latest status
Mycophenolic acid/MMF	Phase I/II	Hematologic malignancies (CML-BC, AML, etc.), osteosarcoma, glioblastoma, pancreatic cancer	Preclinical studies show inhibitory effects on various tumor cells (170-173); multiple Phase II trials report acceptable tolerance, but no clear clinical benefits observed (174,175); a Phase II trial combining MMF with allopurinol for osteosarcoma is ongoing, but results have not been published (176).
MZR	Preclinical	Leukemia, lymphoma	In preclinical studies, MZR demonstrated significant anti-leukemic effects and increased survival in NT5C2+/R367Q mutation acute lymphoblastic leukemia mice (110,177).
Tiazofurin	Phase I/II	Hematologic malignancies (CML-BC, AML, etc.); various late-stage solid tumors	In multiple Phase I/II studies, tiazofurin showed anti-tumor activity in myeloid malignancies, with the highest response rate observed in CML-BC; short-lived responses were seen in AML and other diseases; overall efficacy was limited by short duration of response, resistance andNAD-related toxicity (178-180). Very low clinical benefit was observed in solid tumors, leading to termination of further development (181-183).
BR	Preclinical	Leukemia, lung cancer, colon cancer, melanoma, renal cell carcinoma, etc.	Preclinical studies show that BR exhibits stronger cytotoxicity compared to tiazofurin in various tumor cells; however, clinical application of BR is limited by its toxicity profile (184-186).
VX-944/AVN-944	Phase I/II	AML, multiple myeloma, etc.	VX-944 inhibits proliferation of multiple myeloma cell lines (109); it demonstrates 3-40 times stronger anti-tumor activity compared to mycophenolic acid in AML cell lines and FLT3 mutation cells (187). Phase I clinical trials showgood tolerance (188). A Phase II clinical trial combining VX-944 with gemcitabine for pancreatic cancer was terminated in 2009 due to lack of efficacy.
FF-10501	Phase I	Leukemia, AML, myelodysplastic syndrome	FF-10501 shows anti-leukemic effects in AML cell lines; Phase I trials evaluated its safety and efficacy, but Phase II trials were not initiated (189-191).
Ribavirin	Phase I/II (ongoing)	AML, head and neck cancer, lymphoma, etc.	Phase I/II clinical trials are ongoing to evaluate ribavirin's use in various cancers, including AML, head and neck cancer, mantle cell lymphoma and follicular lymphoma (192-195).

MMF, mycophenolate mofetil; BR, benzamide riboside; MZR, mizoribine; AML, acute myeloid leukemia; CML-BC, chronic myeloid leukemia in blast crisis.

network that supplies precursors for IMP synthesis provides a continuous material basis for tumor cell proliferation within the framework presented in this study. Dynamic regulation of crucial enzymes, such as PRPS, PPAT, IMPDH and purinosomes, ensures effective *de novo* IMP synthesis across a variety of tumor types. Simultaneously, signaling pathways such as RAS-ERK, PI3K/AKT-mTORC1 and Hippo-YAP improve the adaptability of IMP metabolism, allowing sustained tumor cell proliferation in complex microenvironments. IMPDH inhibition reveals notable differences in dependence across hematologic malignancies and some solid tumors, offering potential for precision therapies. Additionally, the interplay between IMP metabolism and the immune microenvironment provides a theoretical framework for combined metabolic-immune therapies.

IMP metabolism in tumor cells remains under investigation. According to previous studies, targeting this pathway for cancer treatment holds great potential: i) Integrating metabolic

networks based on precursor supply, such as combining IMP metabolism with aerobic glycolysis to uncover deeper mechanisms; ii) developing combined intervention strategies by focusing on intersection points between IMP metabolism and signaling pathways; iii) current IMPDH inhibitors face challenges in cancer treatment because of high therapeutic doses, notable interindividual differences and limited effectiveness against certain cancers. New, highly effective IMPDH inhibitors can be developed based on structural specificity, such as targeting the CBS domain. Furthermore, exploring combination therapies with other drugs or optimizing IMPDH inhibitor delivery routes is warranted; iv) identifying IMPDH-dependent tumors using multi-omics and metabolic imaging technologies to enable personalized treatment; v) examining synergistic effects between IMPDH inhibition and immune modulation to advance metabolic-immune combination treatment strategies. Future comprehensive investigation of IMP metabolism in tumor cellular metabolic reprogramming will contribute to building fundamental knowledge of tumor metabolism, thereby advancing the field of tumor treatment engineering.

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HZ, HW and XL wrote the original draft. XL was involved in the conceptualization of the study. YW, DY, WZ and QT contributed to manuscript editing. ZS and JS provided supervision and reviewed and edited the manuscript. All authors reviewed the manuscript and have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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