

The Crucial Roles of Intermediate Metabolites in Cancer

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Abstract: Metabolic alteration, one of the hallmarks of cancer cells, is important for cancer initiation and development. To support their rapid growth, cancer cells alter their metabolism so as to obtain the necessary energy and building blocks for biosynthetic pathways, as well as to adjust their redox balance. Once thought to be merely byproducts of metabolic pathways, intermediate metabolites are now known to mediate epigenetic modifications and protein post-transcriptional modifications (PTM), as well as connect cellular metabolism with signal transduction. Consequently, they can affect a myriad of processes, including proliferation, apoptosis, and immunity. In this review, we summarize multiple representative metabolites involved in glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, lipid synthesis, ketogenesis, methionine metabolism, glutamine metabolism, and tryptophan metabolism, focusing on their roles in chromatin and protein modifications and as signal-transducing messengers.

Keywords: oncometabolites, extra-metabolic functions, epigenetic modification, signaling transduction, post-transcriptional modifications

Introduction

Cell metabolism comprises an intricate network of chemical reactions that sustain normal growth and reproduction. Metabolism comprises catabolism and anabolism, the former supplying energy and the latter producing the necessary cellular components for cell proliferation. Cancers are characterized by uncontrolled cell proliferation and heterogeneous microenvironment. On the one hand, cancer cells adjust their metabolic preference to balance their energy needs with the need to generate biosynthetic precursors for growth;¹ on the other hand, they develop nutrient-scavenging strategies to survive under nutrient-starvation and oxygen-limiting conditions.² Cancer cells undergo extensive metabolic alterations, including in glycolysis, mitochondrial biogenesis, lipid metabolism, and the pentose phosphate pathway (PPP),³ by either reprogramming the activities of existing metabolic pathways or rewiring new connections.⁴

Metabolic reprogramming in cancer cells results in the accumulation or depletion of intermediate metabolites through a variety of mechanisms.⁵ The first one is the alteration of metabolic enzyme activity. For example, during glycolysis, the preferred way for cancer cells to obtain energy and biosynthetic building blocks, the activation of glycolysis-related enzymes leads to the accumulation of a series of glycolytic intermediates.⁶ In contrast, the loss of the activities of succinate dehydrogenase (SDH) and fumarate hydratase (FH) contributes to the accumulation of

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succinate and fumarate, respectively.⁷ Secondly, mutations arising in cancer cells can result in neomorphic enzyme activity. For instance, wild-type isocitrate dehydrogenase (IDH) converts isocitrate to α -ketoglutarate (α -KG), while IDH with specific single-site mutations further catalyzes the conversion of α -KG to 2-hydroxyglutarate (2-HG).⁸ Thirdly, cancer cells generate several active by-products of metabolic pathways, such as reactive oxygen species (ROS), NAD^+/NADH , and $\text{NADP}^+/\text{NADPH}$.

Since the discovery of the oncogenic roles of some mitochondrial metabolites, such as 2-HG, succinate, and fumarate, research has increasingly focused on investigating the roles of these “oncometabolites” in cancer.^{9,10} Oncometabolites affect processes such as epigenetic modifications, post-transcriptional modifications (PTMs), and signaling transduction.¹⁰ Metabolic remodeling can promote DNA hypermethylation and histone hyperacetylation, thereby silencing tumor suppressor genes and promoting tumorigenesis.¹¹ As for PTMs, a wide spectrum of metabolites can conjugate to proteins and regulate their functions. Various types of PTMs have been reported, among which acetylation and succinylation have attracted extensive research interest.¹² To illustrate metabolite sensing and signaling, Wang and colleagues proposed a ternary model consisting of a sensor, a transducer, and an effector.¹³ In their model, metabolites were first recognized by sensors. Transducers subsequently transmitted the signal information to effectors, which finally stimulated the corresponding biological reactions.¹³ They grouped a variety of metabolite sensing events into three modes: metabolite sensor-mediated signaling (MeSr), metabolite-sensing module (MeS), and sensing by conjugating (SC).¹³ In the first category, a sensor physically interacts with the metabolite and transduces the signals to downstream. In the metabolite-sensing module, molecules like protein complexes are disrupted by the metabolites without direct binding through a structurally conserved site, causing downstream changes. The last mode is the conjugation of metabolites to proteins or nucleotides, causing functional alterations.¹³

Besides oncometabolites, numerous intermediate metabolites can directly bind to proteins or nucleotides, leading to their dysfunction. In addition, these intermediate metabolites can act as ligands for transmembrane receptors, activating downstream signaling cascades. In this review, we will introduce the roles of multiple intermediates classified by metabolic pathways in cancer. For each intermediate metabolite, we will

briefly introduce its source, and then discuss in-depth its effects on epigenetic modifications, PTM, and signaling transduction (Table 1).

Metabolites in Glycolysis

Glycolysis consists of energy-requiring and energy-releasing phases.¹⁴ In the first step of the energy-requiring phase, hexokinase catalyzes the phosphorylation of glucose, generating glucose-6-phosphate (G6P). G6P is then transformed to glyceraldehyde-3-phosphate (GA3P) through several steps. GA3P is oxidized to 1,3-bisphosphoglycerate (1,3-BPG) by glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which is the first step in the energy-releasing phase. 1,3-BPG loses a phosphate and becomes 3-phosphoglycerate (3-PG), which is further converted to 2-phosphoglycerate (2-PG) by phosphoglycerate mutase (PGAM). After losing one molecule of H_2O , 2-PG is converted to phosphoenolpyruvate (PEP). Dephosphorylation of PEP yields pyruvate. Under oxygen-rich conditions, pyruvate is transferred to the mitochondria and participates in the tricarboxylic acid (TCA) cycle; under hypoxic conditions; however, pyruvate is converted to lactate by lactate dehydrogenase (LDH)¹⁴ (Figure 1).

1,3-BPG

1,3-BPG brings about PTMs to a variety of glycolytic proteins. During the modification process, active 1,3-BPG binds to lysine residues in these proteins, generating 3-phosphoglyceric-lysine (pgK) in an enzyme-independent manner. Under high-glucose conditions, the generation of pgK inhibits glycolysis and redirects glycolytic intermediates to alternative biosynthetic pathways, which represents a crucial feedback regulatory mechanism (SC mode).¹⁵ Additionally, 1,3-BPG can activate PGAM1 by directly phosphorylating its histidine residues (Figure 1), thereby maintaining glycolytic flux and supporting cell growth in HCT116 or MDA-MB-231 cancer cells.¹⁶

3-PG and 2-PG

3-PG competitively occupies the active site of phosphoglucuronate dehydrogenase (PGD), the rate-limiting enzyme in the PPP, resulting in impaired PGD function and the suppression of the PPP flux¹⁷ (Figure 1). Increased expression of PGAM1 in tumor cells leads to enhanced 3-PG consumption, PPP activation, and increased 2-PG levels. 2-PG can further downregulate the level of 3-PG by enhancing the phosphoglycerate dehydrogenase (PHGDH)-mediated production of

Table I Roles of Metabolites in Chromatin and Protein Modifications, Signal Transduction and Their Effects on Cancer

Metabolites	Roles in Modification or Signal Transduction	Effects on Cancer	References
1,3-BPG	pgK modification	Feedback regulation of glycolysis	[15]
	PGAM1 phosphorylation	Maintaining glycolytic flux and support cell growth	[16]
3-PG and 2-PG	Inhibiting PGD, activate PHGDH	Balancing the glycolysis and anabolic biosynthesis	[17]
PEP	Suppressing SERCA-Ca ²⁺ -NFAT signaling	Suppressing the antitumor function of T cells	[18,19]
Lactate	Inhibiting HDAC	Histone hyperacetylation and deregulating gene transcription	[33]
	Histone lactylation	Stimulating gene transcriptions	[34]
	PHD-mediate signaling	Angiogenic and proliferative effects	[22,24]
	Arg1/GPR81/MAVS signaling	Driving immune evasion	[25–30,32]
Ru-5-P and 6-PGL	Disrupting the LKB1-MO25-STRAD complex; Binding to Src and inhibiting PP2A activity	Regulating AMPK activity	[38,39]
2-HG Succinate Fumarate	Inhibiting TET/KDMs	DNA/histone hypermethylation	[53,54,56–60] [68–73] [68]
	Inhibiting PHD	Inhibiting HIF signaling and pseudohypoxia response	[61–63] [74,75] [73]
Succinate	Lysine succinylation	Maintaining the activity of multiple chromatin and metabolic enzymes	[76–78]
	SUCNRI-mediated signaling	Activating oncogenic signaling pathways, including ERK, STAT3, and PI3K/HIF-1 α	[80,81]
Fumarate	Succination	Activating multiple glycolytic enzymes	[83–87]
Ac-CoA Acetate	Acetylation	Acetylation of histones and proteins, promoting tumorigenesis	[95–98,100,101] [104]
Acetate	GPR signaling	Preventing cancer cells from stress-induced damage	[106]
LCFA	FABP5 mediated signaling	SLCFA and ULCFA orchestrally regulate PPAR β/δ signaling	[107,108]
AA	Binding to BRAF ^{V600E}	Activation of MEK-ERK signaling and promoting tumor growth	[111–113]
3-OHB	Inhibiting Class I HDAC	Increasing histone acetylation	[118]
	Kbhb modification	Activating multiple oncogene promoters	[119,120]
	GPR109A signaling	Enhancing colonic cancer cells apoptosis and depressing survival	[121]
SAM	Methylation	Methylating numerous nucleic acids and histones	[123–127]
	Repressing β -catenin and IL-6 signaling	Reducing inflammation	[128,129]

(Continued)

Table I (Continued).

Metabolites	Roles in Modification or Signal Transduction	Effects on Cancer	References
GSH	S-glutathionylation	S-glutathionylation of proteins, protecting cancer cells from ROS attack	[133–135]
Kyn and KA	AhR signaling	Pro-carcinogenic effects	[139–143]
KA	Glutamate receptors	Promoting glioma cell proliferation	[145]

Abbreviations: 1,3-BPG, 1,3-bisphosphoglycerate; 3-PG, 3-phosphoglycerate; 2-PG, 2-phosphoglycerate; PEP, phosphoenolpyruvate; 6-PGL, 6-phosphogluconolactone; Ru-5-P, ribulose-5-phosphate; 2-HG, 2-hydroxyglutarate; Ac-CoA, Acetyl-CoA; LCFA, long chain fatty acid; AA, acetoacetate; 3-OHB, 3-hydroxybutyrate; SAM, S-adenosyl-methionine; GSH, glutathione; Kyn, kynurenine; KA, kynurenic acid.

3-phosphohydroxypyruvate (pPYR) (Figure 1), which is the first committed step in serine synthesis. Through these mechanisms, tumor cells precisely adjust 3-PG and 2-PG levels, thereby regulating glycolysis and anabolic biosynthesis.¹⁷

PEP
In intratumoral T cells, PEP suppresses the activity of sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA), a calcium transporter that mediates Ca²⁺ uptake into the endoplasmic reticulum, resulting in Ca²⁺ accumulation in

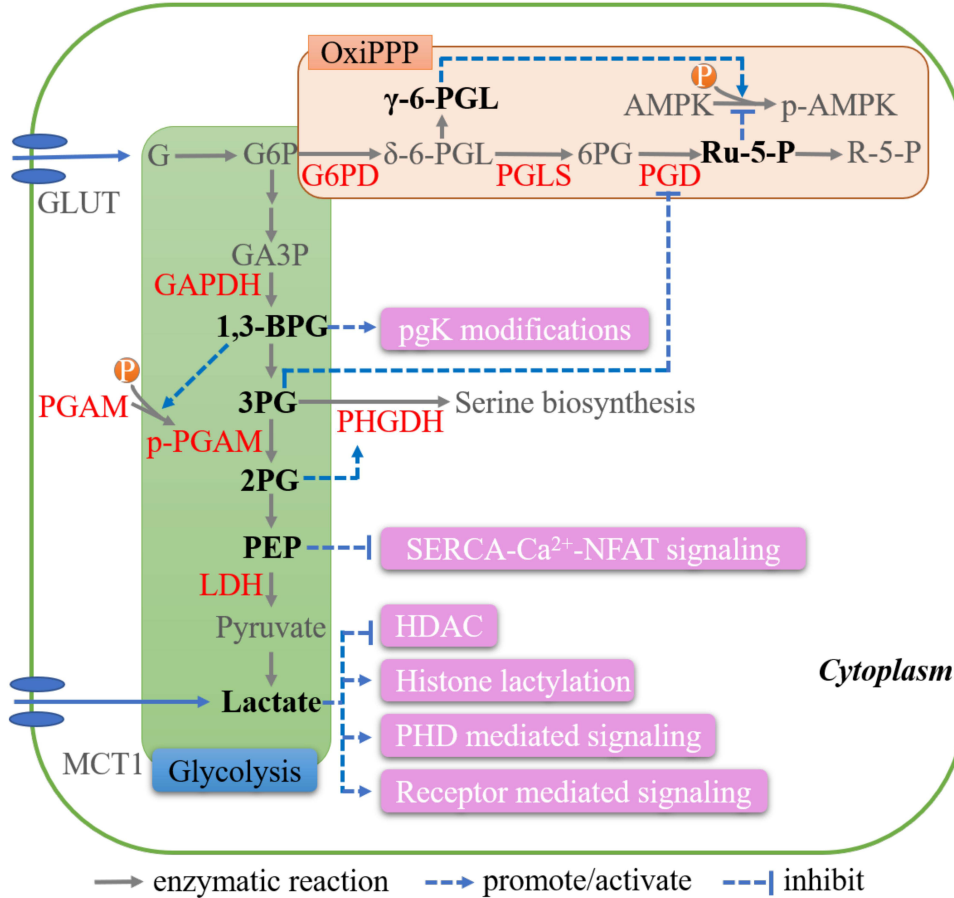


Figure 1 Key metabolites in glycolysis and oxidative PPP. Schematic representations of the biologic effects of those metabolites, including 1,3-BPG, 3PG, 2PG, PEP, lactate, γ-6-PGL and Ru-5-P, are in pink.
Abbreviations: PPP, pentose phosphate pathway; G6P, glucose 6-phosphate; GA3P, glyceraldehyde-3-phosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; 1,3-BPG, 1,3-bisphosphoglycerate; PGAM, phosphoglycerate mutase; 3-PG, 3-phosphoglycerate; 2-PG, 2-phosphoglycerate; PEP, phosphoenolpyruvate; LDH, lactate dehydrogenase; PHGDH, phosphoglycerate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; δ-6-PGL, δ-6-phosphogluconolactone; γ-6-PGL, γ-6-phosphogluconolactone; PGLS, 6-phosphogluconolactonase; 6PG, 6-phosphogluconate; PGD, phosphogluconate dehydrogenase; Ru-5-P, ribulose-5-phosphate; R-5-P, ribose-5-phosphate.

the cytosol and further nuclear factor of activated T cells (NFAT) signaling activation, which is vital for T cells to exert their antitumor effects.^{18,19} This process of metabolite sensing and signaling can be classified as the MeS mode.

Lactate

Due to higher glucose-to-lactate flux, lactate overproduction is commonly detected in a subset of cancer cells, especially under hypoxic conditions. In oxygenated tumor cells, monocarboxylate transporter 1 (MCT1) can also mediate lactate import from hypoxic cancer cells^{20,21} (Figure 1).

Although widely known as an energy source, lactate displays active nonmetabolic characteristics. Lactate can inhibit α -KG-dependent prolyl hydroxylase domain proteins (PHDs), which are involved in the hydroxylation of hypoxia-inducible factor 1- α (HIF-1 α) and I κ B kinase β (IKK β). Inhibition of HIF-1 α leads to its stabilization, leading to the activation of HIF-1-mediated vascular endothelial growth factor (VEGF) signaling.²² Meanwhile, the inhibition of IKK β hydroxylation results in I κ B α degradation, which activates nuclear factor kappa B (NF- κ B) signaling.²³ The effects of lactate on VEGF and NF- κ B signaling can be classified as the MeS mode. Lactate can also interrupt the association between PHDs and N-Myc downstream-regulated protein (NDRG3) by directly binding to the latter in a manner that is independent of HIFs, which is an MeSr mode. This prevents the proteasomal degradation of NDRG3 and further activates Raf/ERK signaling, contributing to angiogenic and proliferative effects in cancer cells.²⁴

In terms of driving immune evasion, the lactate-induced expression of arginase 1 (Arg1) promotes the functional polarization of tumor-associated macrophages (TAMs).^{25,26} In breast cancer, lactate was reported to induce TAM polarization through the ERK/STAT3 pathway.²⁷ There are several examples of MeSr mode about lactate driving immune evasion. G protein-coupled receptor 81 (GPR81) is a lactate receptor that is highly expressed in multiple cancer cell lines.²⁸ Lactate-GPR81 signaling stimulates the expression of programmed cell death ligand 1 (PD-L1) through the transcriptional coactivator TAZ, thereby suppressing interferon-gamma production in lung cancer.^{29,30} Lactate also suppresses innate immune responses in cancer. By binding to GPR81, lactate inactivates yes-associated protein (YAP) and further disrupts the interaction of YAP and NF- κ B in macrophages,

resulting in the reduced production of macrophage pro-inflammatory cytokine.³¹ Furthermore, Zhang et al reported that lactate prevented the aggregation of mitochondrial antiviral-signaling protein (MAVS) by directly binding to its transmembrane domain. This suppressed the production of downstream type I interferons triggered by retinoic acid-inducible gene I-like receptor (RLR)-MAVS signaling, impairing cancer immunosuppression.³²

Lactate also regulates gene expression by inhibiting histone deacetylases (HDACs),³³ and can provide the lactyl group for lysine residues in histone tails, known as histone lactylation. Histone lactylation is active in TAMs, implying that this process has a role in immune surveillance.³⁴

Metabolites in the PPP

The PPP consists of oxidative and nonoxidative phases, and leads to the production of metabolites and NADPH, which are pivotal for nucleotide biosynthesis, lipogenesis, and the maintenance of redox homeostasis. In the first step, G6P is oxidized to δ -6-phosphogluconolactone (δ -6-PGL) by glucose-6-phosphate dehydrogenase (G6PD). Then, one carbon of hydrolytically unstable δ -6-PGL is cleaved by 6-phosphogluconolactonase (PGLS), yielding 6-phosphogluconate (6-PG). 6-PG is further converted to ribulose-5-phosphate (Ru-5-P) by PGD. Ru-5-P is isomerized into ribose-5-phosphate (R-5-P), which serves as the main building block for ribonucleotide synthesis.³⁵ Notably, there is another form of 6-PGL— γ -6PGL—that is generated by the intramolecular rearrangement of δ -6PGL. It is relatively stable, represents a “dead-end” byproduct, and is not subsequently involved in the PPP (Figure 1).

Ru-5-P and 6-PGL

AMP-activated protein kinase (AMPK), a central metabolic sensor, is activated by upstream kinases and inactivated by phosphatase-mediated dephosphorylation. Liver kinase B1 homolog (LKB1) can form a complex with STE20-related adaptor protein (STRAD) and mouse protein 25 (MO25), acting as a major upstream activator of AMPK.³⁶ Protein phosphatase 2A (PP2A) is a serine/threonine protein phosphatase that dephosphorylates AMPK at Thr172, thereby inactivating it.³⁷ Ru-5-P can disrupt the LKB1-MO25-STRAD complex, resulting in the inactivation of AMPK.³⁸ In contrast, γ -6PGL binds to Src and inhibits PP2A activity by dephosphorylation, leading to AMPK activation³⁹ (Figure 1). The action of Ru-5-P and γ -6PGL belongs to

the MeS and MeSr mode, respectively. Cancer cells exhibit an active oxidative PPP, accompanied by decreased γ -6PGL and increased Ru-5-P levels. These alterations collectively inactivate AMPK, activate acetyl-CoA carboxylase 1, and, finally, enhance lipogenesis and tumor growth.^{38,39}

Metabolites in the TCA Cycle

The TCA cycle, also called the Krebs cycle or the citric acid cycle, comprises a series of enzyme-catalyzed reactions and is the major energy production pathway in cells.⁴⁰ The third step is catalyzed by IDH, in which isocitrate undergoes oxidation to form α -KG, releasing NADH. α -KG is further converted to succinate, which is enzymatically catalyzed to fumarate by SDH. Fumarate is further oxidized to malate by FH. Finally, malate is oxidized to oxaloacetate (OAA) by malate dehydrogenase (MDH). Notably, MDH catalyzes the interconversion of malate and OAA. There are two isoforms of MDH, namely MDH1 and MDH2, which are localized to the cytoplasm and mitochondria, respectively. Similarly, IDH has three isoforms—cytosolic IDH1 as well as

mitochondrial IDH2 and IDH3—with IDH3 primarily functioning in normal enzymatic processes⁴⁰ (Figure 2).

2-HG

2-HG consists of two enantiomers, namely D-2-HG (also known as R-2-HG) and L-2-HG (also known as S-2-HG) (Figure 2). 2-HG has attracted extensive research interest since the discovery of the neomorphic enzymatic activity of mutant IDH (mIDH) in 2009.^{8,10,41} Specific missense mutations in both IDH1 and IDH2 result in a neomorphic enzymatic activity that catalyzes α -KG to D-2-HG, but not L-2-HG. The most common mutations are Arg132 in IDH1 and Arg172 plus Arg140 in IDH2, occurring in ~80% of low-grade gliomas and ~20% of cases of acute myeloid leukemia (AML),^{42–44} as well as in a spectrum of other malignancies, including cartilaginous tumors, intrahepatic cholangiocarcinoma, and angioimmunoblastic T cell lymphoma.^{45,46} In addition to being produced by mIDH in the TCA cycle, 2-HG can also be generated through several promiscuous enzymatic reactions. PHGDH, which normally catalyzes the first step of serine

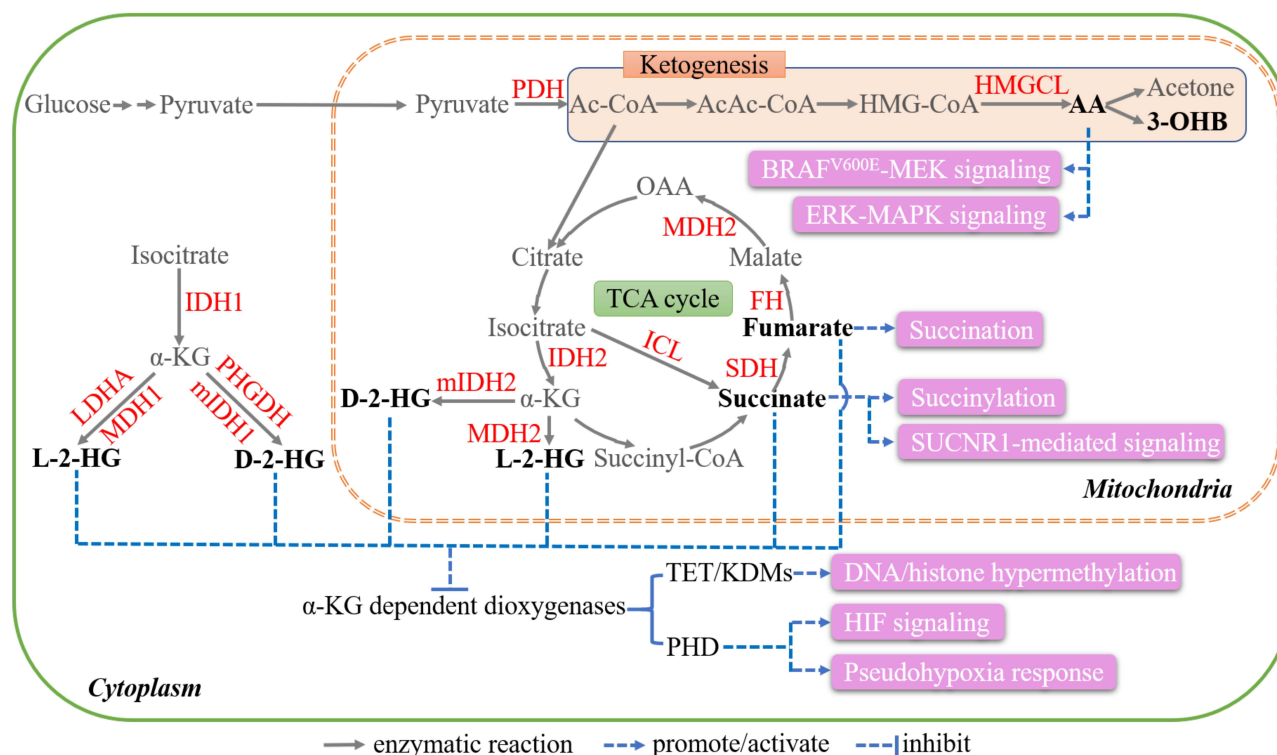


Figure 2 Key metabolites in TCA cycle and ketogenesis. The blue arrows and pink boxes highlight the extrametabolic functions of 2-HG, succinate, fumarate, AA, and 3-OHB.

Abbreviations: TCA cycle, tricarboxylic acid cycle; PDH, pyruvate dehydrogenase; IDH, isocitrate dehydrogenase; SDH, succinate dehydrogenase; FH, fumarate hydratase; α -KG, alpha-ketoglutarate; 2-HG, 2-hydroxyglutarate; MDH, malate dehydrogenase; OAA, oxaloacetate; PHGDH, phosphoglycerate dehydrogenase; LDH, lactate dehydrogenase; ICL, isocitrate lyase; Ac-CoA, acetyl-CoA; AcAc-CoA, acetoacetyl-CoA; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCL, 3-hydroxy-3-methylglutaryl-CoA lyase; 3-OHB, 3-hydroxybutyrate.

biosynthesis, has been reported to be a source of D-2-HG in human breast cancer cell lines at quite low efficiency.⁴⁷ In contrast, and surprisingly, L-2-HG is produced through the activities of MDH and lactate dehydrogenase A (LDHA). MDH catalyzes the production of L-2-HG in mammals, although this reaction is 10^{7,8} times less efficient when compared with OAA production.⁴⁸ LDHA has been identified as the major L-2-HG-producing enzyme under hypoxic conditions⁴⁹ (Figure 2). D-2-hydroxyglutarate dehydrogenase (D2HGDH)^{50,51} and L-2-hydroxyglutarate dehydrogenase (L2HGDH)⁵² catalyze the conversion of D-2-HG and L-2-HG to α -KG, respectively. Mutations in these two enzymes result in 2-HG accumulation and lead to 2-hydroxyglutaric acidurias (2HGAs).^{50,52}

2-HG functions as an antagonist of α -KG as they have highly similar structures.⁴⁵ Crystallographic structural studies revealed that 2-HG competitively occupies the active binding sites of multiple α -KG-dependent enzymes, including the JmjC domain-containing histone demethylases (KDMs) and the ten-eleven translocation (TET) family of 5-methylcytosine (5mC) hydroxylases, and hence inhibits their activities.^{53–55} These enzymes remove methyl moieties through sequential reactions, the inhibition of which by 2-HG increases global DNA methylation and epigenetically silences multiple proteins with known and postulated roles in tumor suppression⁵³ (Figure 2).

Histone demethylases are classified into two subfamilies, ie, the lysine demethylase 1 (KDM1) subfamily and the JmjC domain-containing KDMs (consisting of over 30 enzymes in humans, including KDM2, KDM3, KDM4, KDM5, KDM6, and others).⁵⁶ Enzymes in the latter group are the major targets of D-2-HG. The related inhibition potencies vary, with KDM4A/JMJD2A being the most sensitive to D-2-HG, followed by KDM4C/JMJD2C, KDM2A/FBXL11, AlkB homolog 2 (ALKBH2), factor inhibiting HIF (FIH), PHD, and BBOX-1.⁵⁴ Studies showed that the addition of D-2-HG or the stable overexpression of mIDH1 augments histone demethylation in glioma, including H3K4, H3K9, H3K27, and H3K79, an effect that can be counteracted by α -KG treatment.^{53,57} D-2-HG activates the mechanistic (previously mammalian) target of rapamycin (mTOR) signaling pathway in brain cancer by inhibiting KDM4A,⁵⁸ which is an MeSr mode.

TET sequentially converts 5mC first to 5-hydroxymethylcytosine (5hmC), then to 5-formylcytosine, and finally to 5-carboxylcytosine.⁵⁹ Biochemical assays

showed that D-2-HG exerts a direct inhibitory effect on recombinant TET2 (Figure 2), which can be rescued by α -KG. mIDH expression leads to the consistent reduction of TET2-dependent 5hmC levels.⁵³ Moreover, both mIDH expression and TET2 silencing impair hematopoietic differentiation, implying that they have similar proleukemogenic effects.⁶⁰

2-HG can also modulate the activity of several α -KG-dependent dioxygenases independently of epigenetic alterations. PHD, which is involved in the hydroxylation of HIF1 α , was the first dioxygenase reported to be inhibited by 2-HG (MeSr mode).^{61,62} The inhibition of hydroxylation leads to HIF-1 α stabilization and the subsequent activation of genes containing HIF response elements (HREs), such as glycolytic enzymes, further contributing to tumor development.⁶³ Additionally, D-2-HG has been reported to directly inhibit ALKBH2,⁵⁴ a protein that repairs DNA damage caused by alkylating agents. Cells with mIDH accumulate double-strand breaks (DSBs) in their DNA, leading to genetic instability.⁶⁴

Succinate

Succinate accumulation results primarily from loss-of-function mutations in SDH, which are found in a variety of cancer types, such as paraganglioma/pheochromocytoma (PGL/PCC), renal carcinoma, ovarian cancer, neuroblastoma, and gastrointestinal stromal tumor.^{65,66} Impairment of SDH activity can also lead to succinate accumulation. For example, tumor necrosis factor receptor-associated protein 1 (TRAP1) downregulates SDH activity by inhibiting respiratory complex II.⁶⁷ Tumor-associated inflammatory responses can also suppress SDH activity, while isocitrate lyase (ICL) also likely contributes, as it directly converts isocitrate to succinate⁶⁶ (Figure 2).

Like 2-HG, succinate can competitively inhibit α -KG-dependent KDMs and TETs,⁶⁸ resulting in epigenetic alterations. Succinate promotes proliferation, epithelial-to-mesenchymal transition (EMT), migration, and invasion by regulating the activities of a plethora of downstream genes.^{69–72} For example, increased succinate levels due to SDH mutations lead to DNA and histone hypermethylation in PGL/PCC, thereby suppressing EMT and neuroendocrine differentiation.^{69,73} Succinate also inhibits PHD and impairs HIF-1 α signaling (MeSr mode)^{74,75} (Figure 2).

Besides, succinate provides a succinyl moiety for lysine succinylation, a PTM that occurs in both chromatin and metabolic enzymes such as GLUT1, LDHA, and GAPDH,⁷⁶ regulating their activities in cancer (SC

mode)^{10,77,78} (Figure 2). For example, Li et al proved that succinylation of LDHA decreased its lysosomal degradation, promoting cell proliferation, invasion, and migration in gastric cancer.⁷⁹

In addition, succinate can activate signaling pathway by the MeSr mode. Succinate binds to GPR91 (also known as succinate receptor 1 [SUCNR1]), which leads to increased VEGF expression and further triggers downstream signaling cascades, including those associated with extracellular regulated kinase (ERK) 1/2 and signal transducer and activator of transcription 3 (STAT3).⁸⁰ Succinate secreted by cancer cells binds to GPR91, further activating PI3K/HIF-1 α signaling and triggering TAM polarization (Figure 2). This promotes cancer cell migration, invasion, and metastasis.⁸¹

Fumarate

Abnormal fumarate accumulation is attributed to inactivating mutations in FH, which have been reported in skin leiomyomata, uterine fibroids, and papillary renal cell cancer.⁸² Fumarate appears to be multifaceted.¹⁰ Like 2-HG and succinate, fumarate can allosterically inhibit α -KG-dependent enzymes, including KDMs, TETs, and PHDs (MeSr mode),^{68,73} regulating the epigenetic landscape and producing pseudohypoxia. A distinct PTM related to fumarate is succination, during which the thiol group of a cysteine residue is converted to S-(2-succino)-cysteine (2SC)⁸³ (Figure 2). Fumarate accumulation affects the normal succination of glycolytic enzymes, adiponectin, cytoskeletal proteins, and endoplasmic reticulum chaperones, impairing their functions.^{84,85} For instance, when succinated, Kelch-like ECH-associated protein-1 (KEAP1) is dissociated from nuclear factor erythroid 2-related factor 2 (NRF2). The latter is then stabilized, translocated to the nucleus, and modulated the transcription of several genes involved in antioxidant signaling and cytoprotection.^{86,87} In addition, the direct binding of fumarate to glutathione⁸⁸ or glutathione succination⁸⁹ leads to persistent oxidative stress and cellular senescence.

Metabolites in Lipid Synthesis

Acetyl-CoA

Acetyl-CoA (Ac-CoA) is the main intermediate for lipid synthesis and is located in several cellular compartments, including the cytosol, mitochondria, and the nucleus. Generally, pyruvate is transferred to the mitochondria and decarboxylated to Ac-CoA by pyruvate dehydrogenase (PDH).⁹⁰ Interestingly, Ac-CoA synthetase (ACSS) is another

major enzyme that catalyzes the ATP-dependent incorporation of acetate into Ac-CoA. In mammalian cells, there are two ACSSs, namely, mitochondrial ACSS1 and cytosolic ACSS2. The expression of ACSS1 is markedly upregulated in multiple tumors.⁹¹ Under hypoxia, mitochondrial citrate is preferentially shuttled to the cytoplasm and converted to Ac-CoA and OAA by ATP citrate lyase (ACL).⁹² Acetate uptake, which is catalyzed by ACSS2, is also responsible for increased Ac-CoA levels.⁹³ Reductive glutamine metabolism by IDH1 is another source of Ac-CoA under hypoxic conditions⁹⁴ (Figure 3).

Ac-CoA is the starting material for fatty acid synthesis, while also being indispensable for the acetylation of histones and proteins (SC mode). There is a strong correlation between Ac-CoA levels and global histone acetylation.^{95,96} By modulating epigenetic alterations, Ac-CoA regulates the expression of numerous genes and ultimately promotes tumorigenesis.⁹⁷ For example, in pancreatic ductal adenocarcinoma harboring KRAS mutations, ACL-mediated H3K27 acetylation (H3K27ac) is increased, thereby promoting tumor development.⁹⁸ H3K27ac due to upregulated Ac-CoA level also promotes the progression and chemoresistance of nasopharyngeal carcinoma.⁹⁹ In human hepatocellular carcinoma, hypoxic cells show increased histone H3 acetylation due to an increase in Ac-CoA levels catalyzed by ACSS, which promotes lipid synthesis and tumor growth.¹⁰⁰ Numerous proteins are also modulated through post-translational acetylation. For example, when acetylated at K540, 546, and 554, ACL tends to be stabilized, leading to increased Ac-CoA production through a feedforward mechanism¹⁰¹ (Figure 3). After K413 acetylation, mutant IDH2 (mIDH2) R140Q presents higher enzyme activity, producing sufficient 2-HG for the transformation in AML.¹⁰²

Acetate

Exogenous acetate is mainly derived from saccharolytic fermentation in the colon, but can also be obtained from other sources, such as ethanol oxidation. Endogenously, acetate is generated via deacetylation and hydrolysis reactions that release acetyl groups. Recent studies have shown that acetate is produced *de novo* from pyruvate, via either ROS-dependent oxidative decarboxylation or incomplete oxidation by ketoacid dehydrogenases (KDHs) in a thiamine- and glutathione-dependent manner¹⁰³ (Figure 3).

As previously mentioned, acetate maintains the Ac-CoA pool in cancer cells, thereby influencing multiple Ac-CoA-associated biological processes.¹⁰⁴ Acetate is also an

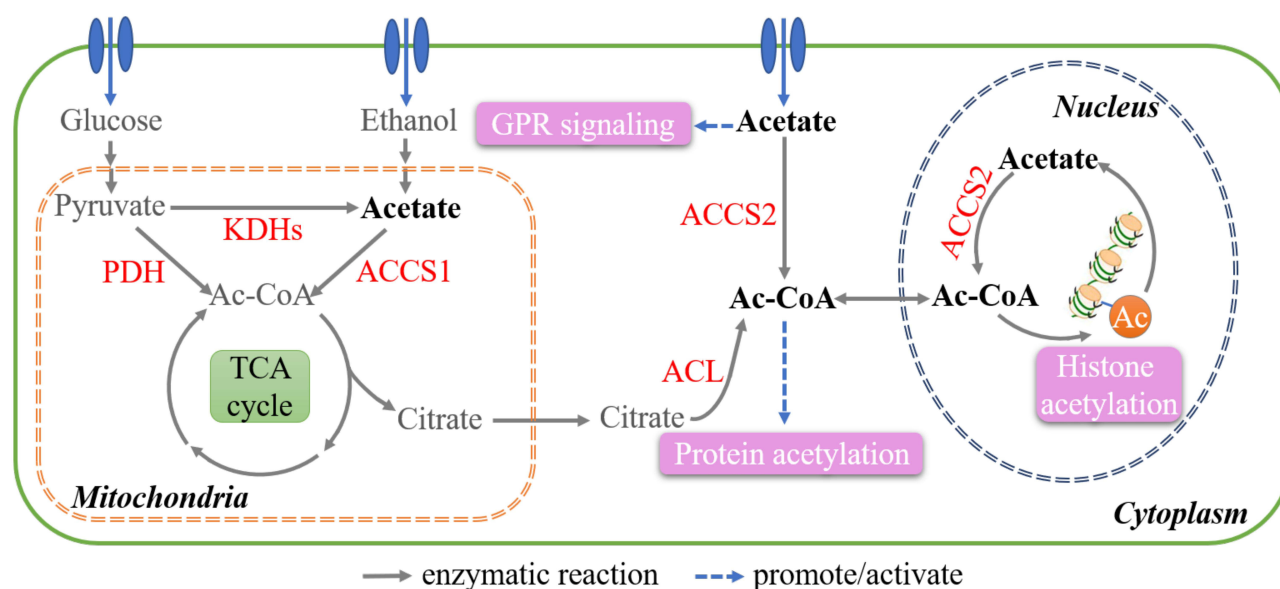


Figure 3 Key metabolites in lipid synthesis. Schematic diagram shows the Ac-CoA pool in different cell compartments. The functions of Ac-CoA and acetate outside metabolism are marked in pink.

Abbreviations: Ac-CoA, acetyl-CoA; PDH, pyruvate dehydrogenase; ACSS, Ac-CoA synthetase; ACL, ATP citrate lyase; KDHs, ketoacid dehydrogenases.

agonist of free fatty acid receptors (FFARs), which belong to the GPR family. Acetate activates FFAR2 in 3T3 fibroblasts, potentiating their malignant transformation.¹⁰⁵ In breast cancer, acetate-GPR signaling, which belongs to the MeSr mode, activates p38 mitogen-activated protein kinase (MAPK) and, subsequently, heat shock protein 27 (HSP27), thereby preventing stress-induced damage¹⁰⁶ (Figure 3).

Long Chain Fatty Acids (LCFA)

Besides the role of energy source, LCFA also functions as signaling molecules. By displacing retinoic acid, saturated LCFA (SLCFA) binds to and inhibits fatty acid-binding protein 5 (FABP5) (MeSr mode). This suppresses the nuclear localization of peroxisome proliferator-activated receptor β/δ (PPAR β/δ), inhibiting the growth of carcinoma cells in vitro and in vivo.^{107,108} Interestingly, unsaturated LCFA (ULCFA) displays opposing effects.¹⁰⁷

Metabolites in the Ketogenesis Pathway

In a fasted state, the body switches to breaking down fatty acids to ketone bodies (ketogenesis) to satisfy the energy requirements of key organs, including the brain, muscles, and other tissues. Ketogenesis occurs primarily in the mitochondria and begins with the condensation of Ac-CoA to acetoacetyl-CoA (AcAc-CoA). Subsequently,

3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS) catalyzes the condensation of Ac-CoA and AcAc-CoA to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which is further cleaved to acetoacetate (AA) by 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL). AA is then either dehydrogenized to 3-hydroxybutyrate (3-OHB) or decarboxylated to acetone. Finally, AA, 3-OHB, and AcAc-CoA acetone are transferred to the circulation and taken up by cells as alternative energy sources¹⁰⁹ (Figure 2).

AA and 3-OHB

AA has been reported to activate ERK1/2 and p38 MAPK signaling in primary cultured rat hepatocytes in a ROS- and oxidative stress-dependent manner¹¹⁰ (Figure 2). Kang et al conducted a systematic screen for metabolic synthetic lethal partners of BRAF^{V600E} and found that HMGCL and HMGCS1 could specifically promote the growth of BRAF^{V600E}-positive melanoma.¹¹¹ The authors further demonstrated that AA bound to BRAF^{V600E}, which enhanced the binding of BRAF^{V600E} and MEK1, thereby promoting the activation of MEK-ERK signaling (MeSr mode).^{111,112} Meanwhile, a different study reported that a high-fat ketogenic diet could increase serum AA concentrations, resulting in the enhanced growth of tumors derived from BRAF^{V600E}-positive melanoma cells in xenografted mice.¹¹³ Conversely, both reducing circulating AA levels with hypolipidemic agents and treating with an inhibitory

AA homolog could effectively attenuate the growth of BRAF^{V600E}-positive tumors.¹¹³ Collectively, these findings suggest that AA mediates the crosstalk between the ketogenesis metabolic pathway and the MAPK signaling pathway (Figure 2).

Of note, 3-OHB is known to have functions beyond metabolism, including inhibiting HDACs and transducing signals through GPRs, effects that are closely correlated with diabetes and lifespan.^{114–117} Similarly, 3-OHB could inhibit Class I HDACs in cancer cells, which increases histone acetylation.¹¹⁸ Moreover, the generation of lysine β -hydroxybutyrylation (Kbhb), a novel type of histone posttranslational modification, is specifically attributed to 3-OHB. This new epigenetic regulatory is enriched in active gene promoters and closely linked with gene expression.¹¹⁹ For example, p53 is a well-known tumor suppressor gene. Its activity was significantly attenuated after Kbhb modification, leading to reduced cell growth arrest and apoptosis in cancer cells.¹²⁰

As an intracellular signal mediator, 3-OHB also works as the only endogenous ligand of G-protein coupled receptors 109A (GPR109A), which is a potent tumor suppressor. In colonic epithelial cells, 3-OHB activates GPR109A, enhancing colonic cancer cells apoptosis and depressing survival (MeSr mode).¹²¹

Metabolites in Methionine Metabolism

S-Adenosyl-Methionine

S-adenosyl-methionine (SAM) is produced from methionine through the activity of methionine adenosyltransferase 2A (MAT2A), which represents the first step in the methionine cycle. In the following step, which is catalyzed by methyltransferases (MTs), SAM donates the methyl group and is converted to S-adenosyl-homocysteine (SAH)¹²² (Figure 4).

As a universal methyl donor, SAM can greatly influence the methylation status of nucleic acids¹²³ and histones,¹²⁴ thereby modulating diverse and critical cellular processes in cancer (SC mode). For example, SAM inhibits the expression of urokinase-type plasminogen activator (uPA) and matrix metalloproteinase-2 (MMP-2) through the hypermethylation of their promoters, which suppresses invasiveness and tumorigenesis in prostate¹²⁵ and breast cancer.¹²⁶ Moreover, SAM can reverse the hypomethylation of the promoters of the oncogenes c-Myc and H-Ras, resulting in the inhibition of cell growth in gastric and colon cancer.¹²⁷

SAM is also reported to reduce inflammation by repressing β -catenin and interleukin-6 (IL-6) signaling in liver and colon cancer,^{128,129} and also exerts proapoptotic effects through the ERK1/2 and STAT3 pathways in osteosarcoma cells¹³⁰ (Figure 4). However, further studies are needed to elucidate the mechanism underlying its role in signaling transduction.

Glutamine Metabolism

Glutathione

Glutamine is another substrate that is vital for energy production and macromolecule biosynthesis in cancer cells. Glutamine is transported into cells and converted to glutamate by mitochondrial glutaminases (GLSs). Glutamate has two major metabolic fates. It can either be converted to α -KG by glutamate dehydrogenase (GLUD) or aminotransferases and used for energy production in the TCA cycle or is first converted to γ -glutamylcysteine by glutamate-cysteine ligase (GCL) and then to glutathione (GSH) by GSH synthetase (GSS).¹³¹ GSH exists in both thiol-reduced and disulfide-oxidized forms, namely, GSH and GSSG, respectively. GSH can be oxidized to GSSG by GSH peroxidase, while GSSG can be reverse-catalyzed to GSH by GSH reductase¹³² (Figure 4).

GSH is a well-known antioxidant. Abundant GSH in tumor cells protects themselves through the detoxification of carcinogens and the scavenging of free radicals. In terms of PTM, GSH binds to the cysteine residues of proteins, a process called S-glutathionylation, thereby protecting them from ROS attack. A growing number of GSH protein targets have been identified, including P53, HSP27, thioredoxin, caspase-3, and NF- κ B, involving a vast number of cellular processes (SC mode).^{133–135} The S-glutathionylation of histone H3, a GSH target, can lead to altered chromatin structure and nucleosome instability.¹³⁶

Tryptophan Metabolism

Tryptophan (Trp) is an essential amino acid. A small fraction of Trp enter either serotonin or indole pathway, which are mainly occurred in nervous or innate immune system, respectively. Over 95% of free Trp is degraded by the kynurenine (Kyn) pathway (KP), which is closely related to cancer progression. In the KP, Trp is firstly converted to N-formylkynurenine by indoleamine-2,3-dioxygenase 1 (IDO1), IDO2, and tryptophan-2,3-dioxygenase (TDO), which is the rate-limiting step. N-formylkynurenine is then catalyzed by kynurenine formamidase (AFMID) to produce Kyn. Kyn is further converted to 3-hydroxykynurenine

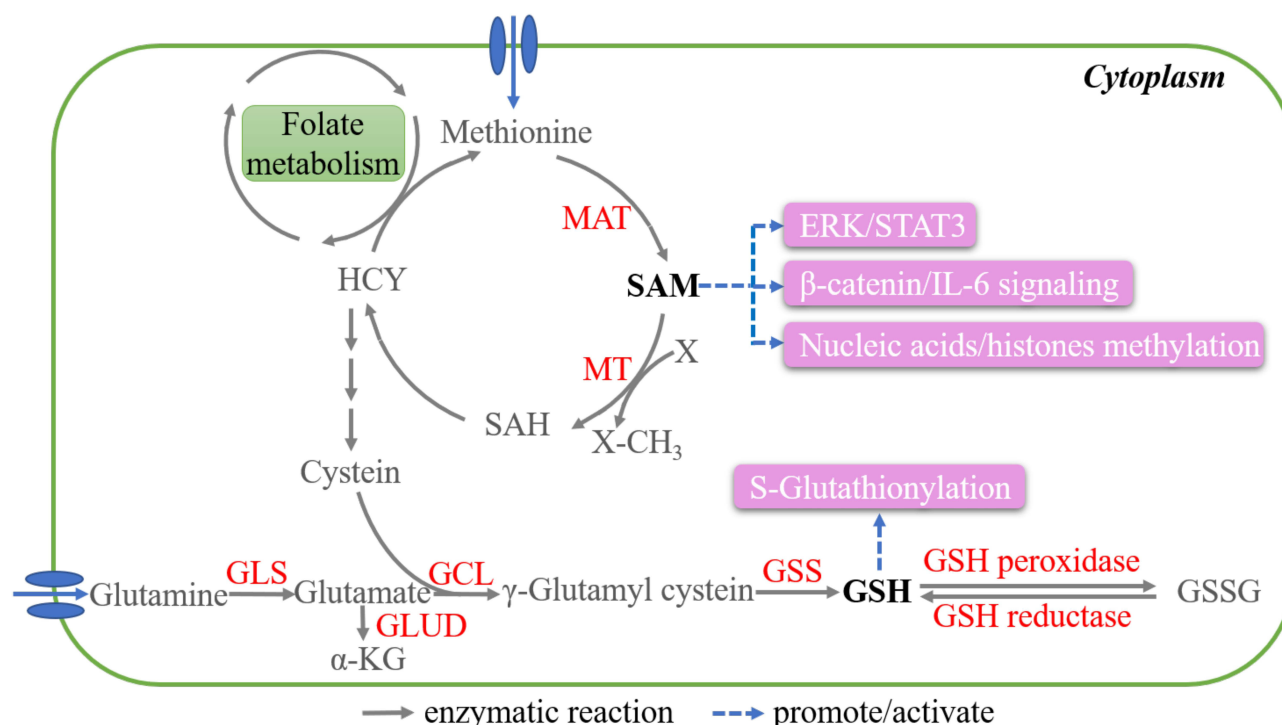


Figure 4 Key metabolites in methionine and glutamine metabolism. The metabolic reactions closely related to SAM and GSH production are shown. SAM is a universal methyl donor and primarily regulates methylation. GSH mainly modify glutathionylation through binding to the cysteine residues of proteins.

Abbreviations: GSH, glutathione; MAT, adenosyltransferase; MT, methyltransferases; SAM, s-adenosyl-methionine; SAH, s-adenosyl-homocysteine; HCY, homocysteine; GLS, glutaminases; GCL, glutamate cysteine ligase; GSS, GSH synthetase.

(3-HK) by kynurenine 3-monooxygenase (KMO), to anthranilic acid (AA) by kynureninase (KYNU), and to kynurenic acid (KA) by kynurenine aminotransferases (KATI–KATIII). After further series of enzymic reactions, multiple biologically active acids are produced, such as 3-hydroxyanthranilic acid (3-HAA), quinolinic acid (QA), picolinic acid (PA), etc. In the end of the KP, NAD^+ is generated, which is an important redox cofactor^{137,138} (Figure 5).

Kyn and KA

Both Kyn and KA are potent agonists for the human aryl hydrocarbon receptor (AhR),¹³⁹ which has extensive roles in carcinogenesis.¹⁴⁰ Thus, Kyn and KA have potential pro-carcinogenic effects in cancer. Kyn is significantly elevated in colon cancer cells and promotes the proliferation through activating the AhR.¹⁴¹ AhR blockade induces by Kyn could also interrupt the interplay between Tregs and tumor-associated macrophages, which is associated with the resistance to immune checkpoint inhibitors.¹⁴² DiNatale et al reported that KA activated AhR and subsequently induced IL-6 production in primary human hepatocytes¹⁴³ (Figure 5).

KA also works as the ligand of other receptors, including glutamate receptors, α -7 nicotinic acetylcholine

receptor (α -7 nAChR), and G-protein coupled receptor 35 (GPR35).¹⁴⁴ As antagonist for endogenous glutamate receptors, KA reverses the promotion effect of glutamate on glioma T98G cell proliferation, and enhances the anti-proliferative effect of glutamate receptor antagonists MK801 and GYKI 52466¹⁴⁵ (Figure 5). However, the anti-cancer potential of KA through binding to α -7 nAChR and GPR35 warrants further study.

Conclusions and Future Perspectives

Metabolites are multifaceted in cancer cells, exerting metabolic as well as extra-metabolic functions. The comprehensive deciphering of these functions holds immense potential for developing new classes of therapeutics. Multiple intermediates exert extra-metabolic effects on processes such as epigenetic modifications, PTMs, and signaling transduction.

As they are highly heterogeneous, tumors have distinct metabolic signatures, and identifying tumor-specific biomarkers has the potential to improve precise cancer diagnosis. Additionally, there is ample evidence to support the anti-tumor efficacy of targeting this

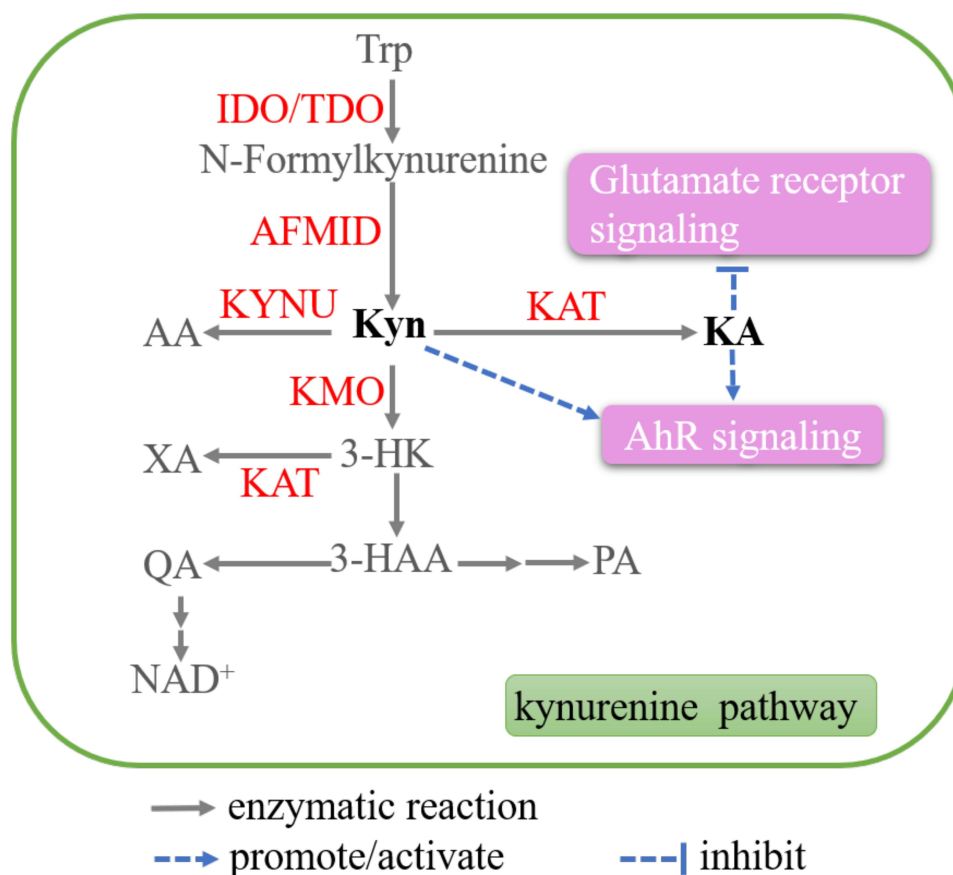


Figure 5 Key metabolites in the tryptophan (Trp) metabolism. The enzymatic reactions in kynurenine (Kyn) pathway (KP) are shown. Kyn and KA work as signal messengers, which are highlighted.

Abbreviations: Trp, tryptophan; Kyn, kynurenine; KP, Kyn pathway; IDO1, indoleamine-2,3-dioxygenase 1 (IDO1); TDO, tryptophan-2,3-dioxygenase; AFMID, kynurenine formamidase; 3-HK, 3-hydroxykynurenine (3-HK); KMO, kynurenine 3-monooxygenase; AA, anthranilic acid; KYNU, kynureninase (KYNU); KA, kynurenic acid; KAT, kynurenine aminotransferases; 3-HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; PA, picolinic acid.

metabolic vulnerability alone or in combination. Notably, metabolic pathways are intertwined and largely overlap. A complete blockade may cause active compensatory supply, impairing the inhibitory effects, highlighting the importance of monitoring metabolite dynamics and moderate intervention.

What we have described here is merely the tip of the iceberg, providing the impetus for further investigation. Studies are needed to uncover how metabolites affect the expression of specific genes and signaling pathways in more detail. Furthermore, metabolites exist both outside and inside different cellular compartments, and it would be of interest to explore how metabolite transportation and localization are regulated. It is likely that additional extra-metabolic functions of metabolites will be identified in the near future, which will have far-reaching implications for the understanding of tumor biology and improving translational clinical approaches.

Abbreviations

1,3-BPG, 1,3-bisphosphoglycerate; 2-HG, 2-hydroxyglutamate; 2-PG, 2-phosphoglycerate; 3-OHB, 3-hydroxybutyrate; 3-PG, 3-phosphoglycerate; 6-PG, 6-phosphogluconate; AcAc-CoA, acetoacetyl-CoA; Ac-CoA, acetyl-CoA; ACL, ATP citrate lyase; ACSS, ac-CoA synthetase; AhR, aryl hydrocarbon receptor; D2HGDH, D-2-hydroxyglutarate dehydrogenase; EMT, epithelial-to-mesenchymal transition; FABP5, fatty acid-binding protein 5; FH, fumarate hydratase; G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; GA3P, glyceraldehyde-3-phosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GCL, glutamate cysteine ligase; GLS, glutaminases; GLUD, glutamate dehydrogenase; GPR, G-protein coupled receptors; GSH, glutathione; GSS, GSH synthetase; HIF1 α , hypoxia-inducible factor 1-alpha; HMGCL, 3-hydroxy-3-methylglutaryl-CoA lyase; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCS, 3-hydroxy-3-methylglutaryl-CoA synthase; ICL, isocitrate lyase; IDH,

isocitrate dehydrogenase; Kbh, lysine β -hydroxybutyrylation; KDHS, ketoacid dehydrogenases; L2HGDH, L-2-hydroxyglutarate dehydrogenase; KP, kynurenine (Kyn) pathway; KYNU, kynureninase; LCFA, long chain fatty acids; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A; MAT2A, methionine adenosyltransferase 2A; MCT1, monocarboxylate transporters; MDH, malate dehydrogenase; MeS, metabolite-sensing module; MeSr, metabolite sensor-mediated signaling; MTs, methyltransferases; NF- κ B, nuclear factor κ B; PDH, pyruvate dehydrogenase; PEP, phosphoenolpyruvate; PGAM, phosphoglycerate mutase; PGD, phosphogluconate dehydrogenase; PGLS, 6-phosphogluconolactonase; PHD, prolyl hydroxylase domain; PHGDH, phosphoglycerate dehydrogenase; PPAR β/δ , peroxisome proliferator-activated receptor β/δ ; PPP, pentose phosphate pathway; PTM, post-transcriptional modifications; R-5-P, ribose-5-phosphate; Ru-5-P, ribulose-5-phosphate; SAH, S-adenosylhomocysteine; SAM, S-adenosyl-methionine; SC, sensing by conjugating; SDH, succinate dehydrogenase; TCA cycle, tricarboxylic acid cycle; δ -6-PGL, δ -6-phosphogluconolactone.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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