Abnormal metabolic networks participate in invasion and migration of tumors of the digestive system (Review)

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Abstract. Digestive system neoplasms are the most common malignant tumor worldwide. Tumor metastasis is also an important factor in tumor-related mortality. Deregulation of cellular metabolism is as a major indicator of cancer, and reprogramming of metabolism is thought to be necessary to meet the increased energy demands of tumors. Reprogramming of the metabolism is crucial for the spread of tumors. The present review summarizes the role of enzymes and molecules involved in abnormal metabolism in digestive system neoplasms and their crosstalk with oncogenic signaling pathways in tumor metastasis. Elucidation of the network regulating metabolic reprogramming of cancer may identify novel cancer therapies, which may improve the poor prognosis of patients with cancer.

Contents

1. Introduction

Digestive system neoplasms are the most common malignant tumor in China, mainly including esophageal squamous cell carcinoma (ESCC), gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC) and pancreatic cancer (PC) (1,2). Notably, CRC is the second leading cause of global cancer mortality, and GC ranks fourth. Furthermore, the incidence rates of both cancers remain persistently high. A pivotal reason for the high mortality is metastasis, which accounts for ~90% of cancer deaths. The metastatic process entails essential steps such as epithelial-mesenchymal transition (EMT), tumor invasion, intravasation, extravasation and mesenchymal-epithelial transition (MET), culminating in the establishment of distant metastases (Fig. 1). In the present review, 'invasion' specifically refers to the ability of cells to degrade and penetrate the extracellular matrix or basement membrane, emphasizing its destructive nature; 'migration' describes the motility of cells such as tumor cells; and 'metastasis' denotes the multistep process by which tumor cells disseminate from the primary site to distant organs and form secondary tumors (3,4).

Emerging evidence indicates that metabolic reprogramming of tumor cells serves as a critical driver of tumor metastasis. Malignant tumor cells alter metabolic reprogramming through the modulation of conventional activities of key enzymes, as well as the regulation of their non-canonical roles (5-7). Meanwhile, several metabolic pathways have been reported to be involved in metabolic reprogramming to meet increased bioenergetic and biosynthetic needs to support cancer cell proliferation, invasion and metastasis (8). With the growing identification of aberrantly expressed non-coding (nc)RNAs in tumors, these regulatory molecules have been reported to induce extensive metabolic crosstalk through targeting rate-limiting enzymes, ultimately forming sophisticated regulatory networks. The present review summarizes abnormal substance metabolism in digestive system tumor metastasis and the related metabolic pathway networks.

2. Glucose metabolism is involved in tumor metastasis

A hallmark of cancer is aberrant metabolism. Cells often metabolize glucose, and cancer cells preferentially use glycolysis over mitochondrial oxidative phosphorylation to create glucose-dependent ATP and glycoferment intermediates for macromolecular biosynthesis, even in conditions where oxygen supply is sufficient. This is referred to as the Warburg effect (9-11). Important players in glycolytic pathways include pyruvate kinase (PK), phosphofructokinase (PFK) and HK. Moreover, research has reported that a number of coding

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RNAs and ncRNAs are notable regulators of the metabolic enzymes and signaling pathways involved in the metabolism of glucose in cancer cells (12,13) (Table I and Fig. 2).

Key enzymes of the glycolysis-related network in cancer metastasis. HK phosphorylates glucose to G6P in an ATP-dependent manner, catalyzing the first irreversible step in the glycolytic pathway. The four primary isoenzymes, HK1, HK2, HK3 and HK4, are encoded by several genes (12). The primary isoenzyme, HK2, is engaged in the first and rate-limiting phases of glycolysis, which transforms glucose into glucose-6-phosphate. Several cancer types show elevated levels of this compound due to its ability to enhance glucose uptake in cells and the Warburg effect (13,14). Guo *et al* (15) identified a putative competing endogenous (ce)RNA regulatory network in which the lysyl oxidase like 1 (LOXL1)/microRNA (miR)-1224-5p/miR-761/HK2 axis was shown to promote cell proliferation and metastasis by regulating aerobic glucose metabolism in CRC HCT-116 and SW480 cells, wherein the long non-coding (lnc)RNA LOXL1 modulated HK2 expression through competitively binding to endogenous miR-1224-5p and miR-761. Similarly, lncRNA MIR210HG was reported to be abnormally upregulated in PC, and promote lactate accumulation through the miR-125b-5p/HK2/PKM2 axis, ultimately affecting malignant phenotypes, including proliferation, invasion and migration in PC PANC-1 and MIA PaCa-2 cells (16). Additionally, Chen *et al* (17) reported that sponging of miR-125b reduced the HK2-mediated Warburg effect in HCC Hep3B cells, and sponging of miR-125b down-regulated hsa_circ_0001806 expression, thereby suppressing the HK2-mediated Warburg effect, primarily through inhibiting lactate accumulation and ATP production. This ultimately impeded tumor proliferation and migration. Several studies have reported that circPRMT5, hsa_circ_0045932 and circRPS19 actively regulate the expression of HK2 via sponge miRNAs, thereby accelerating glycolysis and promoting tumor development (18-20). Another isoenzyme of hexokinase, HK1, is reported to be positively regulated by the lncRNA ARSR. This lncRNA binds to miR-34a-5p through a sponge adsorption mechanism, thereby promoting glucose uptake, lactate and ATP production in CRC Caco-2 cells, and ultimately enhancing the invasion and migration capabilities of tumor cells (21).

The rate-limiting enzyme PK catalyzes the last stage of glycolysis, which is the conversion of phosphoenol pyruvate to pyruvate (22). There are several subtypes of mammalian PK, of which PKM2 is directly involved in cancer aerobic glycolysis. Although mitochondrial oxidative phosphorylation generates more net energy than aerobic glycolysis in tumors, cancer cells use the Warburg effect to digest glucose more quickly in response to higher energy demands. PKM2 is thought to be a crucial metabolic enzyme for the Warburg effect in cancer cells, and the overexpression of this enzyme is primarily associated with an increased use of glucose and altered redox balance in cells (23). Increasing evidence points to the possible involvement of PKM2 in tumor metastasis (24-26). PKM2 proteins are bound by the lncRNA FEZF1-antisense RNA (AS)1 (FEZF1-AS1), which enhances their stability and raises the amounts of PKM2 in the cytoplasm and nucleus. Whilst FEZF1-AS1 regulates PKM2/STAT3 signaling and glycolysis to increase the proliferation and migration of CRC LoVo and HCT116 cells, an increase in cytosolic PKM2 stimulates PK activity and lactate generation (27). Notably, under hypoxic conditions, miR-338-3p interacts with circRNA MAT2B, thereby upregulating PKM2 expression levels and enhancing glycolysis in HCC Huh7 and HepG2 cells. The ATP generated from this metabolic reprogramming directly fuels cytoskeletal remodeling and membrane fluidity, whilst lactate accumulation contributes to creating an acidic microenvironment conducive to invasion, collectively promoting tumor progression (28).

One of the major glycolytic enzymes, lactate dehydrogenase A (LDHA) is highly associated with thyroid cancer, CRC and pancreatic ductal adenocarcinoma (PDAC) malignancies due to its aberrant expression and overexpression (29-31). Regenerating islet-derived protein 1-α (REG1α), for instance, was reported to be upregulated in CRC serum and tissues. By enhancing glycolysis mediated by the β-catenin/MYC axis, REG1α promoted invasion in CRC DLD-1 and HCT-116 cells, and lung metastasis in BALB/c nude mouse models. Furthermore, the Wnt/β-catenin/MYC axis or glycolysis pathway could be silenced to successfully reverse the malignant phenotype controlled by REG1α. Furthermore, REG1α expression was moderated by methyltransferase-like 3 (METTL3). The METTL3/REG1α/β-catenin/MYC axis in CRC suggests that REG1α may serve as a novel biomarker and a possible target for treatment in patients with CRC. REG1α drives glycolysis to provide both the energy and carbon sources required for the synthesis and activation of matrix metalloproteinases, which are essential for extracellular matrix degradation during tumor cell invasion (30). Nucleolar and spindle associated protein 1 (NUSAP1) was markedly over-expressed in PDAC, and in several PDAC cell lines, NUSAP1 expression was consistent with that of LDHA. Additionally, NUSAP1 facilitated PDAC metastasis and LDHA-mediated glycolysis in BALB/c nude mouse models (31). This suggests that NUSAP1 promotes the formation of distant metastases by regulating lactate production and consequently influencing the pH of the TME. Phosphoglycerate kinase 1 (PGK1) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB), are key components of the glycolytic pathway. Furthermore, PFKFB has four isoenzymes (PFKFB1, PFKFB2, PFKFB3 and PFKFB4), and studies have reported that PFKFB3 and PFKFB4 are involved in EMT and associated with tumor metastasis (32). Moreover, linc01572 modulated HCC Huh7 and SNU-449 cells invasion and migration by increasing PFKFB4 levels by sponging miR-195-5p and subsequently enhancing glycolysis and PI3K-AKT signaling activation (33).

Glucose transporter (GLUT)-related network in the regulation of tumor metastasis. The Warburg effect begins with the transfer of glucose from the extracellular milieu. Using simple diffusion, the transport capacity of glucose is determined by its hydrophilicity. Consequently, certain membrane transporters are needed for this process. In this mechanism, the GLUT family is crucial (34). Out of the 14 GLUT family members, GLUT1 is most frequently expressed, which is also recognized as the basal switch for glycolysis in tumor cells (35). Research has revealed that low survival rates in human cancer are associated with elevated GLUT1 expression, potentially due to its association with the presence of metastases (36). The promotion

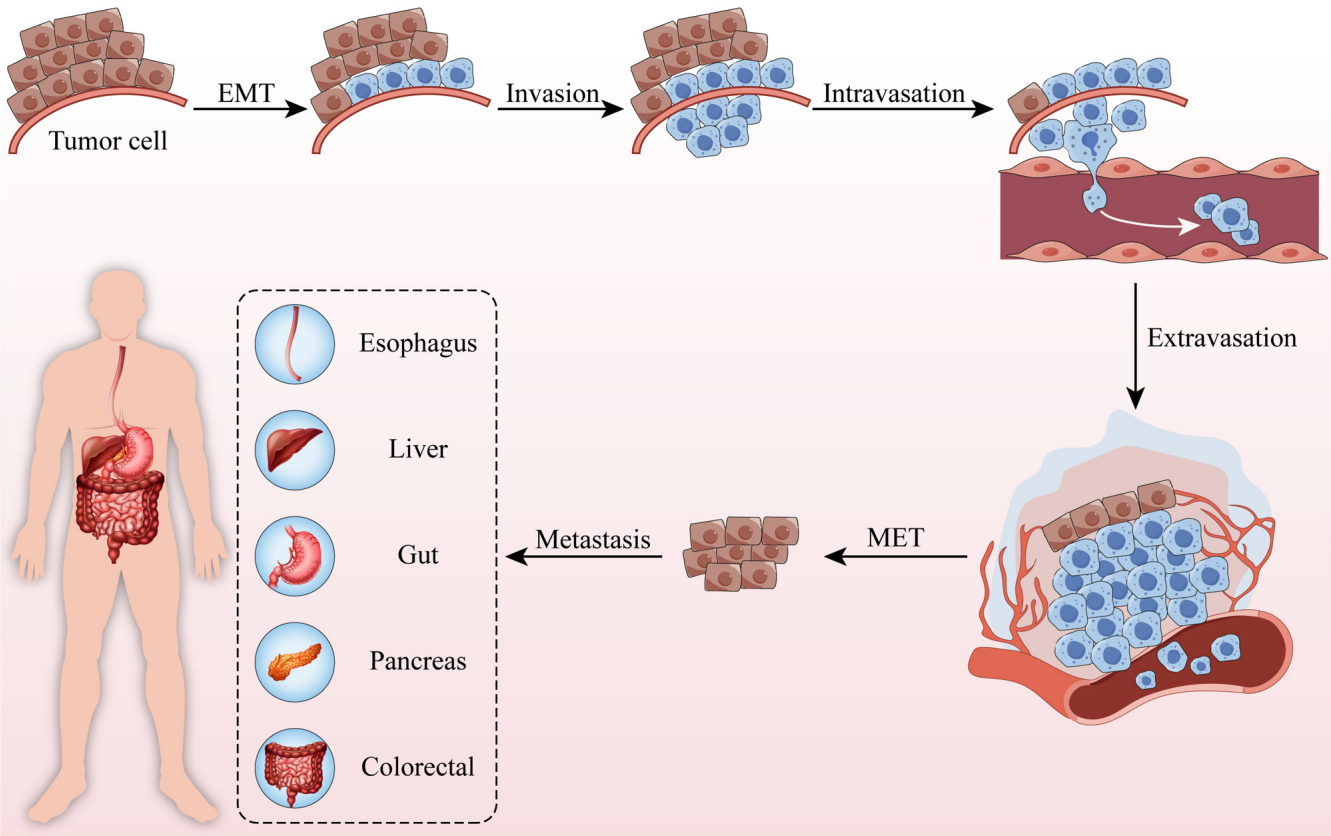

Figure 1. Process of cancer metastasis. EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition.

of cancer cell proliferation and metastatic behavior is closely associated with GLUT1 overexpression (37). Shang *et al* (38) reported that lncRNA SLC2A1-AS1 is downregulated in liver cancer tissues. This lncRNA was shown to inhibit aerobic glycofermentation and the progression of HCC MHCC97-H and Huh7 cells by inactivating GLUT1, which is encoded by the opposite-strand-encoding gene SLC2A1. Meanwhile, lncRNA SLC2A1-AS1 enhanced GLUT1 expression through sponging miR-378a-3p, thereby promoting aerobic glycolysis in ESCC EC9706, TE1 and KYSE180 cells, and ultimately facilitating tumor cell invasion and migration through the EMT pathway (39). Furthermore, FOXD1 was upregulated in PC, and it activated SLC2A1 and the lncRNA HOXA11-AS by sponging miR-148b. Reduced FOXD1 inhibited MIA PaCa-2 and PANC-1 PC cells invasion, migration and aerobic glycolysis. Furthermore, a positive correlation was observed between FOXD1 and GLUT1, suggesting their synergistic role in driving oncogenesis (40). According to recent research, GLUT3 stimulates the EMT process via the TGF-β/JNK/ATF2 signaling pathway, suggesting that this system may be a target for the treatment of metastatic CRC (41). Moreover, by controlling aerobic glycolysis to stimulate GC tumor growth and migration, the oncogenic role of GLUT12 may be targeted by the let-7a-5p/GLUT12 pathway to amplify the anticancer properties of everolimus, suggesting a promising and viable therapeutic strategy (42).

Hypoxia-inducible factor (HIF)-1α-related network in the regulation of tumor metastasis. Solid tumors are characterized by hypoxia, which is a diminished oxygen supply that promotes tumor growth. Hypoxic conditions induce molecular responses in both normal and tumor cells, driving the activation of the key transcription factor HIF (43). As a crucial regulator of oxygen balance, HIF-1 is a heterodimer transcription factor made up of stable HIF-1β subunits and unstable HIF-1α subunits (44). HIF-1α is a transcription factor that is frequently activated by the hypoxic milieu found in tumors and is intimately associated with the growth, metastasis and angiogenesis of tumors (45). It has been established that lncRNA SNHG11 stimulates HIF-1α downstream targets to enhance CRC HCT-116 and RKO cell invasion and migration (46). It has also been reported that upregulation of TMEM161B-AS1 promoted the expression of HIF1AN via absorbing miR-23a-3p, inhibiting Eca109 and KYSE30 proliferation, invasion and glycolysis, further inducing the downregulation of glycoenzyme-associated proteins, and ultimately leading to the inhibition of ESCC progression (47). Furthermore, research has reported that circRNF13 expression increased in PC and was associated with a low rate of survival. The signaling pathway activated by HIF-1α and RNF13 used the miR-654/PDK3 axis to increase PC cell invasion *in vitro* and metastasis in BALB/c nude mouse lung and liver metastasis models (48). By enhancing PDK3 activity, this axis strengthens glycolytic metabolism, thereby providing the energy required for the formation of invaders and the activation of proteases, which mediate the degradation of extracellular matrix during distant local invasion and extravasation processes. Exosome release was stimulated by hypoxia, and miR-301 expression was raised. Exosomes may carry enhanced miR-301a-3p from

Table I. Abnormal glucose metabolism in tumors of the digestive system.

Target	Gene	Mechanism	Metabolic process	Function	Cancer type	(Refs.)
HK2	lncRNA LOXL1	miR-1224-5p/miR-761/ HK2 axis	Enhance glycolysis	Promote cell invasion and migration	Colorectal cancer	(15)
	lncRNA MIR210HG	miR-125b-5p/HK2/ PKM2 axis	Enhance glycolysis	Promote cell invasion and migration	Pancreatic cancer	(16)
	hsa_circ_0001806	Sponge of miR-125b	Enhance glycolysis	Promote cell migration	Hepatocellular carcinoma	(17)
	circ_PRMT5	Sponge of miR-188-5p	Enhance glycolysis	Promote cell migration	Hepatocellular carcinoma	(18)
	hsa_circ_0045932	Sponge of miR-873-5p	Enhance glycolysis	Promote cell invasion and migration	Colorectal cancer	(19)
	circ_RPS19	Sponge of miR-125a-5p	Enhance glycolysis	Promote cell proliferation	Gastric cancer	(20)
HK1	lncRNA ARSR	Sponge of miR-34a-5p	Enhance glycolysis	Promote cell invasion and migration	Colorectal cancer	(21)
PKM2	lncRNA SOX2OT	Sponge of miR-122-5p	Enhance glycolysis	Promote cell invasion and lung metastasis	Hepatocellular carcinoma	(25)
	miR-142-3p	Target PKM2	Inhibit glycolysis	Inhibit cell invasion and migration	Colorectal cancer	(26)
	lncRNA FEZF1-AS1	Activate PKM2/STAT3 signaling	Enhance glycolysis	Promote cell proliferation and migration	Colorectal cancer	(27)
	circ_MAT2B	Sponge of miR-338-3p	Enhance glycolysis	Promote cell invasion and lung metastasis	Hepatocellular carcinoma	(28)
LDHA	REG1α	Activate β-catenin/MYC/ LDHA axis	Enhance glycolysis	Promote cell invasion, migration and lung metastasis	Colorectal cancer	(30)
	NUSAP1	Bind to c-Myc and HIF-1α	Enhance glycolysis	Promote cell invasion, migration and lung metastasis	Pancreatic cancer	(31)
PFKFB4	linc01572	Sponge miR-195-5p and activates PI3K-AKT signaling	Enhance glycolysis	Promote cell invasion and migration	Hepatocellular carcinoma	(33)
GLUT1	lncRNA SLC2A1-AS1	Sponge of miR-378a-3p	Enhance glycolysis	Promote cell invasion and migration	Esophageal squamous cell carcinoma	(39)
	lncRNA HOXA11-AS	Sponges of miR-148b	Enhance glycolysis	Promote cell invasion and migration	Pancreatic cancer	(40)
GLUT3	TGF-β	Activate JNK/ATF2 signaling	Enhance glycolysis	Promote cell invasion	Colorectal cancer	(41)
GLUT12	-	AR/GLUT12	Enhance glycolysis	Promote cell invasion and migration	Gastric cancer	(42)
HIF-1α	lncRNA SNHG11	Binds with HIF-1α	Repress HIF-1α degradation	Promote cell invasion and migration	Colorectal cancer	(46)
HIF1AN	lncRNA TMEM161B-AS	Sponge of miR-23a-3p	Induce glycose down-regulation	Inhibit cell invasion	Esophageal squamous cell carcinoma	(47)
PDK1	circRNF13	HIF-1α-induced circRNF13 via miR-654/PDK1	Enhance glycolysis	Promote cell invasion and lung metastasis	Pancreatic cancer	(48)
PHD3	miR-301a-3p	HIF-1α/miR-301a-3p positive feedback loop	Enhance glycolysis	Promote cell invasion and migration	Gastric cancer	(49)
G6PD	-	Activates STAT3 signaling	Enhance PPP	Promote cell invasion and migration	Hepatocellular carcinoma	(52)
	circ_0003215	Sponge of miR-663b	Inhibit PPP	Inhibit cell invasion, migration and lung metastasis	Colorectal cancer	(54)

Table I. Continued.

Target	Gene	Mechanism	Metabolic process	Function	Cancer type	(Refs.)
	circNOLC1	Interacting with AZGP1circNOLC1/ miR-212-5p/c-Met axis	Enhance PPP	Promote migration and liver metastasis	Colorectal cancer	(55)
	NeuroD1	Positively regulated G6PD	Enhance PPP	Promote cell proliferation	Colorectal cancer	(56)
TKT	lncRNA TSLNC8	Activate IL6/STA T3 signaling	Inhibit PPP	Inhibit cell migration	Hepatocellular carcinoma	(60)
	S100A11	Interacting with SMYD3	Enhance PPP	Inhibit cell migration	Pancreatic ductal adenocarcinoma	(61)
PDK1	circ_0000284	Sponge of miR-152-3p	Transition from OXPHOS to glycolysis	Promote cell migration	Intrahepatic cholangiocarcinoma	(65)
	lncRNA PTPRG-AS1	Sponge of miR-599	Transition from OXPHOS to glycolysis	Promote cell migration	Esophageal squamous cell carcinoma	(66)
PDK2	miR-422a	miR-422a/PDK2	miR-422a/PDK2 axis may convert additional pyruvate to acetyl-CoA, thus fueling the TCA cycle	Inhibit cell migration and peritoneal metastasis	Gastric cancer	(67)

lncRNA, long non-coding RNA; miR, microRNA; HK1, hexokinase 1; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; GLUT1, glucose transporter 1; HIF-1α, hypoxia-inducible factor 1α; HIF1AN, HIF-1α subunit inhibitor; PDK1, pyruvate dehydrogenase kinase 1; PHD3, prolyl hydroxylase domain-containing protein 3; G6PD, glucose-6-phosphate dehydrogenase; TKT, transketolase; PRMT5, protein arginine methyltransferase 5; RPS19, ribosomal protein S19; MAT2B, methionine adenosyltransferase 2B; RNF13, ring finger protein 13; NOLC1, nucleolar and coiled-body phosphoprotein 1; REG1α, regenerating family member 1α; NUSAP1, nucleolar and spindle associated protein 1; TGF-β, transforming growth factor β; NeuroD1, neuronal differentiation 1; S100A11, S100 calcium binding protein A11; STAT3, signal transducer and activator of transcription 3; MYC, myelocytomatosis oncogene; c-Myc, cellular myelocytomatosis; JNK, c-JUN N-terminal kinase; ATF2, activating transcription factor 2; AR, androgen receptor; AZGP1, α-2-glycoprotein 1, zinc-binding; SMYD3, SET and MYND domain containing 3.

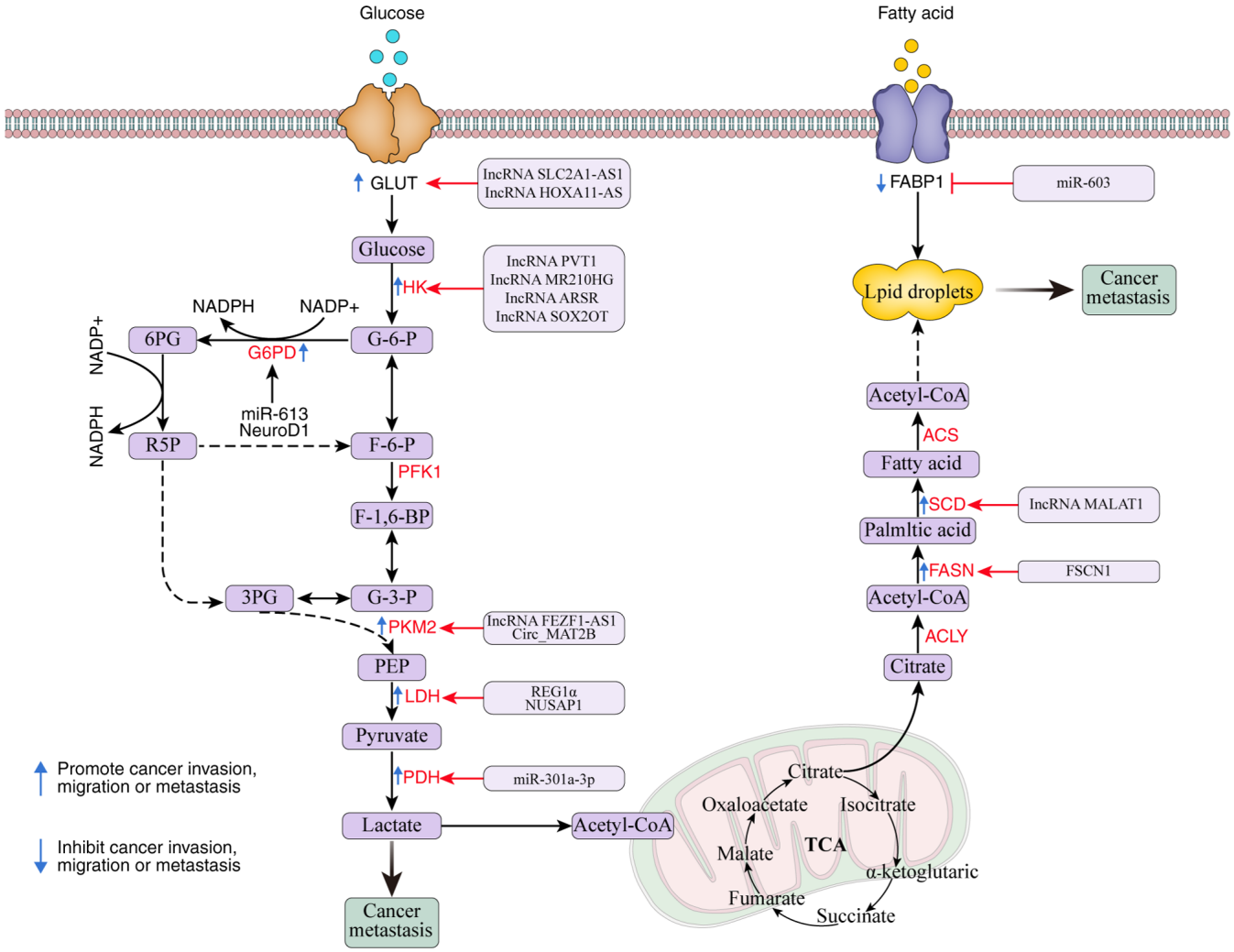

Figure 2. Key regulatory roles of ncRNAs in energy metabolism of tumor cells. Several ncRNAs, such as lncRNA PVT1, lncRNA FEZF1-AS1 and lncRNA SLC2A1-AS1, enhance glycolytic activity by regulating key proteins involved in glycolysis. miR-613 and NeuroD1 upregulate G6PD to promote the PPP. miR-603 inhibits fatty acid transport through downregulation of FABP1. lncRNA MALAT1 enhances lipogenesis by regulating SCD. Additionally, FSCN1 facilitates lipid synthesis by promoting the expression of fatty acid synthase FASN. ncRNA, non-coding RNA; lncRNA, long ncRNA; miR, microRNA; PPP, pentose phosphate pathway; FEZF1-AS1, FEZF1 antisense RNA 1; SLC2A1-AS1, solute carrier family 2 member 1 antisense RNA 1; NeuroD1, neuronal differentiation 1; G6PD, glucose-6-phosphate dehydrogenase; FABP1, fatty acid binding protein 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; SCD, stearoyl-CoA desaturase; FSCN1, fascin actin-bundling protein 1; FASN, fatty acid synthase; G6P, glucose-6-phosphate; 6PG, 6-phosphogluconate; R5P, ribose-5-phosphate; F-6-P, fructose-6-phosphate; F-1, 6-BP, fructose-1,6-bisphosphate; G-3-P, glyceraldehyde-3-phosphate; 3-PG, 3-phosphoglycerate; PEP, phosphoenolpyruvate.

one GC cell to another. The transferred miR-301a-3p subsequently helped to block HIF-1α degradation by focusing on prolyl hydroxylase domain-containing protein 3, which could hydroxylate HIF-1α subunits and ubiquitinate their destruction. HIF-1α and miR-301a-3p created a positive feedback loop that promoted GC invasion, migration, proliferation and EMT in BALB/c nude mouse models of lung metastasis (49).

Pentose phosphate pathway (PPP) and tumor metastasis. An important glucose catabolic route is the PPP. The PPP involves numerous enzymes and is essential in controlling the proliferation of cancer cells (50).

Glucose-6-phosphate dehydrogenase (G6PD)-related networks in the PPP. One of the essential enzymes in the PPP oxidation branch, 6PGD is involved in redox and nucleotide biosynthesis (51). In several studies, elevated G6PD levels have been reported to enhance the cancer progression in several tumor types (52-54). Through the modulation of important enzymes, ncRNAs perform their roles in PPP regulation. In HCC MHCC97H and HCCLM3 cells, G6PD promotes migration and invasion by activating the STAT3 pathways, which in turn causes EMT (52). circ_0003215 inhibits invasion and migration in CRC SW480 and HT29 cells by suppressing the PPP through DLG4-mediated, K48-linked ubiquitination and degradation of G6PD (54). Additionally, circNOLC1 interacts with AZGP1 to activate the mTOR/SREBP1 signaling pathway, or functions as a sponge for miR-212-5p to upregulate c-Met expression. Collectively, these mechanisms induce G6PD to enhance the PPP in CRC HCT116 and LoVo cells, promoting liver metastasis in CRC (55). Furthermore, it has been reported that NeuroD1 positively regulates G6PD in CRC and alters tumor cell metabolism by stimulating the PPP, therapy enhancing CRC tumorigenesis (56).

Transketoenzyme (TKT)-related networks in the PPP. In the non-oxidized phase of PPP, TKT is an essential enzyme that helps to maintain the levels of ribose 5-phosphate. The transketase family includes three human genes, TKT and TKT-like genes 1 and 2 (57). TKT has been reported to be upregulated in HCC and CRC (58,59), and it has been demonstrated to have a positive association with HCC metastasis and proliferation. Previous research reported that TKT controlled metastasis in CRC via attaching to GRP78, which changed AKT phosphorylation to influence cell glycolysis (59). In the meantime, ncRNAs took part in networks connected to TKT. Through its interactions with TKT and STAT3, the lncRNA TSLNC8 inactivated the IL6/STAT3 signaling pathway, suppressing STAT3 phosphorylation and transcriptional activity in HCC Huh-7 cells. This in turn prevented the growth of tumors (60). Zeng *et al* (61) reported that downregulation of S100A11 suppressed the malignant progression of PDAC and inhibited the PPP via TKT expression.

Tricarboxylic acid (TCA) cycle and tumor metastasis. The TCA cycle satisfies the needs of cells for bioenergetics, biosynthesis and redox equilibrium, and is a key route for oxidative phosphorylation. Research indicates that certain cancer cells, particularly those with dysregulated oncogene and tumor suppressor gene expression, may heavily depend on the TCA cycle to produce energy and synthesize macromolecules, despite the earlier hypothesis that cancer cells primarily used aerobic glycolysis and avoided the TCA cycle (62).

There are four isoenzymes that make up pyruvate dehydrogenase kinases (PDKs). The pyruvate dehydrogenase complex is phosphorylated and rendered inactive by PDKs, preventing mitochondria from oxidatively metabolizing pyruvate. This procedure may stimulate anabolic pathways, which in turn may stimulate the growth of cancer cells. By raising pyruvate dehydrogenase (PDH) activity and thus increasing ROS generation, inhibition of PDK causes cell death (63).

A gatekeeper enzyme called PDK1 is involved in the growth, survival and angiogenesis of tumors in cancer. PDK1 is a regulator of PDH, a key rate-limiting enzyme of cellular glycolysis, and has been widely confirmed to be involved in the regulation of cancer progression (64). Research has reported that circ_0000284 serves an oncogene role in intrahepatic cholangiocarcinoma (ICC), which facilitates ICC HCCC-9810 and HUCCT1 cell growth and metastasis through sponging miR-152-3p to increase PDK1 expression (65). According to another study, by sponging miR-599, lncRNA PTPRG-AS1 upregulated PDK1 expression, thereby promoting migration and proliferation in ESCC TE-8 and KYSE-150 cells (66). In GC SGC7901 and MGC803 cells, to restore the activity of PDH, the gatekeeping enzyme that catalyzes the decarboxylation of pyruvate to create acetyl-CoA, miR-422a was reported to suppress PDK2. This process reduced NADPH generation, thereby compromising the ability of the cell to counteract oxidative damage incurred during migration (67).

3. Lipid metabolism participates in cancer metastasis

Lipids are taken in by mammalian cells by two different mechanisms: Uptake and *de novo* synthesis. Furthermore, fat accumulation in cells may encourage the growth, colonization and ability of tumor cells to metastasize. Tumor cells go through several stages of metastasis, requiring modifications to their metabolism and structure related to lipids (68). Moreover, there is growing evidence that lipid metabolism is essentially reprogrammed in cancer (69,70) (Table II and Fig. 2).

Fatty acid-binding protein (FABP)-related networks in lipid metabolism. A class of intracellular lipid chaperones known as FABPs binds to long-chain fatty acids and related lipids to help move them into different parts of the cell, including the nucleus (71). Humans have been found to exhibit 10 distinct FABP subtypes. FABP5, a diminutive constituent of the cytoplasmic FABP family, exhibits a strong propensity for binding to long-chain FAs. Research suggests that FABP5, through triggering EMT and controlling angiogenic responses, serves a critical role in the invasion, metastasis and development of cancer (72,73). In addition, FABP1 is overexpressed in the cytoplasm of HCC cells (74). However, IL-6 has been reported to increase the expression of miR-603 and then suppresses the production of FABP1, which promotes lipid metabolism and the manufacture of related proteins, ultimately raising the levels of cellular oxidative stress and causing HCC Huh-7 cells migration and invasion (75).

Sterol regulatory element binding protein (SREBP)-related networks in lipid metabolism. SREBPs are the most important transcription factors for regulating lipid homeostasis. Previous studies have reported that SREBP is highly upregulated and promotes tumor growth in several cancers (70). The lncRNA ZFAS1 has been reported to rewire fat metabolism to accelerate the invasion of CRC SW480 and RKO cells by binding to PABP2 and promoting the interaction between PABP2 and SREBP1 (76). Moreover, the lncRNA SNHG16 was reported to promote invasion and migration by directly controlling the miR-195/SREBP2 axis, which in turn sped up the development of PC PANC-1 and AsPC-1 cells. By increasing cholesterol synthesis, SREBP2 enhances plasma membrane fluidity, which promotes deformability and motility for cell migration. Concurrently, it supplies the essential lipid components required by metastatic cells to preserve membrane integrity (77). Furthermore, through mRNA splicing and transcription, lncRNA MALAT1 stimulates the expression of several genes in AMPK signaling and unsaturated fatty acid metabolism pathways, leading to the upregulation of glucose uptake and adipogenesis, which indicates the function of MALAT1 in tumor cell invasion and migration (78).

Stearoyl-CoA desaturase (SCD)1-related networks in lipid metabolism. Increased expression of the SCD1 enzyme has been reported to accelerate the development of several malignancies. SCD1 is involved in the synthesis of monounsaturated fatty acids, including oleic acid (79). The orthotopic CRC model demonstrated that SULT2B1 promotes metastatic progression of colorectal cancer. Furthermore, experiments in HCT116 and SW480 cells revealed that SULT2B1 directly interacts with SCD to enhance lipid metabolism, thereby facilitating the metastasis of CRC (80). In addition, low expression of miR-4310 is associated with a poor prognosis. By inhibiting SCD1 and FASN-mediated lipid synthesis, miR-4310 has been reported to inhibit HCC cell migration

Table II. Abnormal lipid metabolism in tumors of the digestive system.

Target	Gene	Mechanism	Metabolic process	Function	Cancer type	(Refs.)
FABP1	miR-603	IL-6 induced miR-603 inhibit FABP1	Suppress fatty acid transport	Promote cell invasion and migration	Hepatocellular carcinoma	(75)
FABP2/ SREBP1	lncRNA ZFAS1	Bind with FABP2 to facilitate the interaction between FABP2 and SREBP1	Promote lipid metabolism	Promote cell invasion	Colorectal cancer	(76)
SREBP2	lncRNA SNHG16	Regulate miR-195/SREBP2 axis	Promote fat production	Promote cell invasion and migration	Pancreatic cancer	(77)
SREBP1/SCD	lncRNA MALAT1	Activate AMPK signaling	Promote fat production	Promote cell invasion and migration	Hepatocellular carcinoma	(78)
SCD	SULT2B1	SULT2B1 interacted with SCD	Inhibit lipid synthesis	Promote cell invasion, migration and lung metastasis	Colon cancer	(80)
FASN/SCD	miR-4310	miR-4310 regulate FASN/SCD	Inhibit lipid synthesis	Inhibit cell invasion and migration	Hepatocellular carcinoma	(81)
FASN/SCD	FSCN1	LYAR/FSCN1 regulate FASN/SCD	Promote lipid synthesis	Promote cell invasion and migration	Colorectal cancer	(82)
CPT1A	SDPR	Activate PPARα signaling	Promoting FAO	Promote cell invasion and migration	Gastric cancer	(83)
PRKDC	HKDC1	Interact with G3BP1	Reprogramming lipid metabolism	Promote cell invasion and migration	Gastric cancer	(84)

miR, microRNA; lncRNA, long non-coding RNA; FABP1, fatty acid binding protein 1; SREBP1, sterol regulatory element-binding transcription factor 1; SCD, stearoyl-CoA desaturase; FASN, fatty acid synthase; CPT1A, carnitine palmitoyltransferase 1A; PRKDC, protein kinase, DNA-activated, catalytic subunit; SULT2B1, sulfotransferase family 2B member 1; FSCN1, fascin actin-bundling protein 1; SDPR, serum deprivation response; HKDC1, hexokinase domain containing 1; AMPK, AMP-activated protein kinase; PPARα, peroxisome proliferator-activated receptor alpha; G3BP1, ras GTPase-activating protein SH3 domain-binding protein 1.

and invasion *in vitro* and HCC tumor growth and metastasis *in vivo* (81). Furthermore, Ly1 antibody reactive (LYAR) and fascin actin-bundling protein 1 (FSCN1) has been reported to participate in CRC progression and promote cell metastasis, and LYAR partly regulates FSCN1 expression in CRC. Additionally, FSCN1 is associated with lipid metabolism, and FSCN1 silencing reduces the expression levels of FASN and SCD1 in CRC progression (82).

Networks associated with other genes in lipid metabolism. Serum deprivation-response protein (SDPR) has been reported to participate in TGF-β-induced GC metastasis. It has been shown that overexpression of SDPR inhibits TGF-β-induced GC MKN45 and MGC803 cells invasion and migration by suppressing ERK and enhancing the expression of peroxisome proliferator-activated receptor α, thereby upregulating the expression of carnitine palmitoyltransferase 1A (CPT1A), promoting fatty acid oxidation (FAO) and inducing GC metastasis. By driving FAO, CPT1A supports the TCA cycle function through acetyl-CoA production, which in turn furnishes the persistent energy required for cell migration (83). Zhao *et al* (84) reported that hexokinase domain containing 1 (HKDC1) expression was upregulated in GC. Additionally, lipid metabolism serves a critical role in the role of PRKDC as a downstream effector of HKDC1-mediated GC carcinogenesis. HKDC1 can mechanically regulate the well-known oncoprotein G3BP stress granule assembly factor 1 (G3BP1), and HKDC1 and G3BP1 collaborate to support PRKDC stability. The HKDC1/G3BP1-PRKDC axis reprograms lipid metabolism to promote GC metastasis and chemoresistance (84).

4. Amino acid metabolism associated with cancer metastasis

Glutamine is mostly utilized for the synthesis of energy and is regarded as a non-essential amino acid. However, when certain cancer cells proliferate quickly, when there is stress, or when proliferating cells grow quickly, glutamine becomes a conditional necessary amino acid (85,86). SLC1A5 is a sodium-coupled transporter of alanine, serine, cysteine and glutamine. It is often referred to as alanine-serine-cysteine transporter 2. The expression of circ_0001273 is upregulated in esophageal cancer (EC) tissues and cell lines. As circ_0001273 regulates miR-622 and downstream SLC1A5, it partially explains why silencing EC TE1 and ECA109 cells was reported to reduce their survival, proliferation, migration and rate of glutamine metabolism (87). Moreover, circ_0001093 has been reported to function as ceRNA by sponging miR-579-3p, raising the expression of glutaminase, enhancing glutamine metabolism and advancing malignancy in ESCC (88). Building on the established role of glutamic-oxaloacetic transaminase 1 (GOT1) in glutamate metabolism (89), further research demonstrates that silencing circ_MBOAT2 inhibits glutamine catabolism and progression in PC PANC-1 and SW1990 cells via the circ_MBOAT2/miR-433-3p/GOT1 axis (90). Furthermore, HIF-2α is markedly upregulated in PDAC Panc-1 and Capan-2 cells and promotes glutamine metabolism by targeting GOT1 via activation of the PI3K/mTOR complex 2 pathways (91). Low GOT2 expression is also associated with glutamine metabolic reprogramming to glutathione synthesis, and promotes HCC progression by activating the PI3K/AKT/mTOR pathway (92) (Table III).

5. Mitochondrial metabolism

Mitochondria influence tumorigenesis, and as the primary source of ATP, mitochondria provide building blocks for anabolism through cellular repair mechanisms, with their pivotal role in regulated cell death signaling crucial for tumor dissemination (93). For instance, transmembrane guanylate cyclase natriuretic peptide receptor 1 facilitates GC lymph node metastasis by activating lipid droplet lipolysis and enhancing mitochondrial oxidative phosphorylation (OXPHOS) (94). Moreover, organic cation transporter novel type 2 augments cancer stem-like traits in HCC through increased fatty acid β-oxidation and OXPHOS activation (95) (Fig. 3).

Mitochondrial OXPHOS. The OXPHOS metabolic pathway fulfills two critical functions in driving tumor cell metastasis: i) Providing bioenergetic demands in the form of ATP; and ii) Extracting carbon from glucose for macromolecule synthesis, serving as a central hub integrating catabolic and anabolic processes. Enzymes of the TCA cycle in the mitochondrial matrix and transmembrane protein complexes of the electron transport chain (ETC) constitute the core machinery for this process. Within the mitochondrial electron transport system, ETC complexes I-IV accept electrons from TCA cycle-derived NADH and $FADH_2$. Subsequent proton reflux through Complex V (ATP synthase) into the mitochondrial matrix generates ATP (96). Certain tumors exhibit high dependency on OXPHOS-derived ATP, which can be identified through specific genetic alterations (97). Metastasis-associated antigen 1 has been identified as a novel regulator of ATP synthase via its interaction with the ATP synthase F1 subunit α, promoting colon cancer liver metastasis through mitochondrial bioenergetic reprogramming and enhanced OXPHOS (98). Sorting nexin 17 facilitates HCC proliferation and metastasis by interacting with STAT3, thereby activating the STAT3/c-Myc signaling pathway to augment OXPHOS (99).

Mitochondrial fatty acid β-oxidation. CPT1A is a rate-limiting enzyme localized on the mitochondrial outer membrane, and catalyzes the rate-limiting step of FAO to generate ATP essential for tumor cell proliferation and metastasis. CPT1A-dependent FAO represents a vital metabolic pathway in malignancies. Elevated CPT1A expression in CRC (100) and PDAC (101) activates FAO and enhances metastatic potential. Furthermore, ALKBH5 promotes CRC progression by mediating CPT1A upregulation through m^6A demethylation, consequently facilitating M2 macrophage polarization (102).

Mitochondrial (mt)ROS metabolism. ROS exhibit a dual role in oncogenesis: At low-to-moderate levels, mtROS function as crucial signaling molecules that activate several protumor signaling pathways through oxidative modification (103). For instance, low-level mtROS stabilizes HIF-1α to enhance glycolysis and facilitate metastasis (104), whereas high-level mtROS conversely activates the SIRT3/PGC-1α axis to promote OXPHOS (105). Furthermore, fatty acid β-oxidation

Table III. Amino acid metabolism in tumors of the digestive system.

Target	Gene	Mechanism	Metabolic process	Function	Cancer type	(Refs.)
SLC1A5	Circ_0001273	Sponges of miR-622	Promote glutamine metabolism	Promote cell migration	Esophageal squamous cell carcinoma	(87)
GLS	Circ_0001093	Sponges of miR-579-3p	Promote glutamine metabolism	Promote cell invasion and migration	Esophageal squamous cell carcinoma	(88)
GOT1	Circ_MBOAT2	Sponges of miR-433-3p	Inhibit glutamine metabolism	Inhibit cell invasion and migration	Pancreatic cancer	(90)
GOT1	HIF-2α	Targeting GOT1 via activation of PI3K/mTORC2 pathway	Promote glutamine metabolism	Promote cell invasion and migration	Pancreatic ductal adenocarcinoma	(91)
GOT2	-	Activate PI3K/AKT/mTOR pathway	involved in glutamine metabolic reprogramming to GSH synthesis	Inhibit cell invasion and migration and liver metastasis	Hepatocellular carcinoma	(92)

circ, circular; miR, microRNA; SLC1A5, solute carrier family 1 member 5; GLS, glutaminase; GOT1, glutamic-oxaloacetic transaminase 1; GOT2, MBOAT2, membrane bound O-acyltransferase domain containing 2; HIF-2α, hypoxia-inducible factor 2α; mTORC2, mechanistic target of rapamycin complex 2; mTOR, mechanistic target of rapamycin.

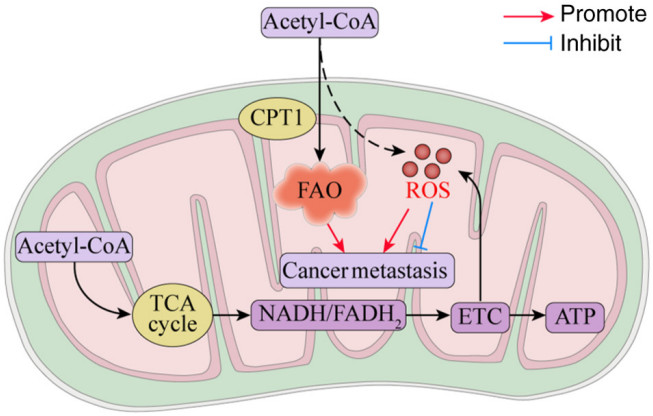

Figure 3. Oxidative phosphorylation and fatty acid β-oxidation in mitochondria. Long-chain fatty acids are transported into mitochondria via CPT1, where they undergo FAO to generate acetyl-CoA and a small amount of ROS. The acetyl-CoA then enters the TCA cycle for complete oxidation, producing NADH and $FADH_2$. These reducing equivalents are transferred to the ETC, driving proton pumping to establish a transmembrane proton gradient. This gradient ultimately powers ATP synthesis through oxidative phosphorylation, facilitating cellular energy conversion. CPT1, carnitine palmitoyltransferase 1; FAO, fatty acid oxidation; ROS, reactive oxygen species; TCA, tricarboxylic acid; ETC, electron transport chain.

inherently generates ROS as metabolic byproducts. Although FAO is recognized as a tumor-promoting process, the metabolic crosstalk triggered by FAO-derived ROS requires further mechanistic exploration. However, when mtROS accumulation becomes excessive and surpasses the cellular antioxidant defense capacity, it induces severe oxidative stress, triggering cell death, necrosis and ferroptosis, resulting in tumor-suppressive effects (106). For example, CST1 promotes gastric cancer metastasis by recruiting OTUB1 to alleviate GPX4 ubiquitination, thereby enhancing GPX4 protein stability, reducing ROS accumulation, and consequently inhibiting ferroptosis (107). Therefore, strategies aimed at leveraging ROS to block tumor metastasis have emerged as a promising therapeutic approach in oncology.

6. Conclusions and perspectives

In recent years, metabolism in tumor metastasis has attracted more attention. However, cancer cell metabolism is a complex matter. The present review discusses, primarily based on evidence from *in vitro* studies, several metabolic alterations commonly found in cancer cells, including glycolysis, FAO, amino acid metabolism and alterations in mitochondria. This review systematically synthesizes evidence on how key genes target metabolic enzymes or related signaling pathways to drive tumor invasion and metastasis. It aims to establish the correlation between tumor metastasis and cellular metabolism, and to identify suitable targets at the intersection of metabolic pathways to selectively disrupt metabolic networks and prevent tumor metastasis (108,109). For instance, 2-deoxy-d-glucose can inhibit glycolysis and induce cell death (110). However, monotherapy targeting tumor progression still requires further exploration.

Digestive system neoplasms metastasis is one of the leading causes of tumor-related mortality worldwide. The present review identified common features in metabolic

reprogramming across gastrointestinal cancers. Beyond the classical Warburg effect, metabolic alterations such as enhanced fatty acid β-oxidation, elevated mitochondrial oxidative phosphorylation, and increased ROS levels all contribute to varying degrees to tumor progression. Furthermore, during the invasion or migration of digestive system tumors, the expression levels of certain key metabolic enzymes are upregulated; for instance, HK expression is increased in HCC (75), colorectal cancer (76), PC (77) and GC (80). However, metabolic specificity also exists among different gastrointestinal tumors, primarily stemming from differences in tissue origin and the TME. For example, enhanced bile acid metabolism promotes the progression of liver cancer: Treatment with T-CDCA was reported to markedly increase the proliferative capacity of HCC HepG2 cells, and downregulate the expression of the tumor suppressor protein CEBPα in HCC (111). Additionally, metabolic dysregulation mediated by gut microbiota serves a crucial role in CRC, involving species such as *Streptococcus bovis*, *Helicobacter pylori* and *Escherichia coli* (112).

Targeting a single metabolic pathway presents notable challenges, whereas a combination of therapies simultaneously targeting multiple tumor metabolites or metabolic enzymes may enhance therapeutic efficacy. Studies have demonstrated that mitochondria generate ATP through multiple pathways, serving as the primary energy source for tumor metastasis. Precise targeting of cancer-specific mitochondria can impair their capacity for de-differentiation, proliferation and metastasis, thereby contributing to improved treatment outcomes and overall prognosis (113). As a result, the individualized role of mitochondria in cancer should receive more attention. The tumor metabolic microenvironment *in vivo* is complex, and the present review summarizes only a part of the complex events of cancer development. Therefore, researching the function that mitochondrial metabolism serves in the TME can lead to novel therapeutic approaches for cancer, including targeted medication development.

Although preliminary progress has been made in research on tumor metabolic reprogramming, notable knowledge gaps and insufficient investigation remain regarding the role of metabolic crosstalk in tumor metastasis, necessitating further in-depth exploration: i) Most current studies rely on *in vitro* cell models, which fail to fully recapitulate the complexity and dynamic nature of the TME *in vivo*. Consequently, conclusions derived from *in vitro* experiments exhibit certain limitations; ii) tumor metabolism demonstrates high heterogeneity, not only between primary and metastatic sites but also within different regions of a single tumor. To date, systematic studies on metabolic dynamics are still lacking; and iii) although the present review summarizes several metabolic enzymes and metabolites that regulate tumor cell metastasis, the understanding of transcriptome-genome-metabolome crosstalk patterns continues to evolve. Elucidating the mechanisms of metabolic crosstalk in tumor cells will provide new opportunities for effectively combating cancer.

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Competing interests

The authors declare that they have no competing interests.

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