Long non-coding RNAs: Key regulators involved in metabolic reprogramming in cancer (Review)

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Abstract. Metabolism is defined as the biochemical processes that produce or consume energy in living organisms. Otto Warburg suggested that cancer is a metabolic disease, thus metabolic reprogramming is widely considered as an emerging hallmark of cancer cells. Long non-coding RNAs (lncRNAs), which are defined as transcripts >200 nucleotides with limited protein coding potential, are involved in cancer metabolism. lncRNAs can control pathophysiological processes of cancer by regulating gene expression at epigenetic, transcriptional and post-transcriptional levels. The process of tumorigenesis is usually accompanied by alterations in metabolic patterns, involving glycolysis, the tricarboxylic acid cycle, mitochondrial oxidative phosphorylation, the pentose phosphate signaling pathway, glutamine metabolism and lipid metabolism, which is also known as metabolic reprogramming. The present review summarized the functions of lncRNAs in cancer metabolism and discussed how the dysregulation of lncRNAs contributed to metabolic reprogramming and tumorigenesis, which may provide novel therapeutic targets for cancer.

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Contents

1. Introduction

Long non-coding RNAs (lncRNAs) are defined as transcripts >200 nucleotides in length that display limited protein coding potential (1). Certain lncRNAs with open reading frames can be translated into peptides (2), and a previous study reported that certain non-coding RNA (ncRNA) genes could undergo active protein translation in mouse macrophages (3). The human genome project confirmed that <2% of genomes encode proteins, whereas >98% are transcribed into ncRNAs, of which 76% are lncRNAs (4,5). lncRNAs were initially considered to be the 'noise' of genomic transcription, lacking biological functions (6,7); however, with the development of sequencing technology, rapid progress has been made in the field of lncRNA research.

lncRNAs can be placed into one or more of the following categories: Sense, antisense, bidirectional, intronic and intergenic (8). Previous studies on well-characterized lncRNAs have demonstrated that lncRNAs can regulate gene expression at epigenetic, transcriptional and post-transcriptional levels by functioning as enhancers of their neighbouring genes, scaffolds for protein-protein interactions, guides for protein-DNA interactions, or decoys for proteins or microRNAs (miRs) to participate in various biological processes, including cell proliferation, differentiation, survival and migration (9-11). Moreover, dysregulation of lncRNAs impacts different human diseases, including cancer (12). lncRNAs are also involved in

DNA damage repair, cell cycle regulation, metabolism and other physiological or pathological processes that contribute to regulating the occurrence and development of cancer (1,13-15). Therefore, lncRNAs have become a research hotspot in the field of life science.

Metabolism is defined as biochemical processes that produce or consume energy in living organisms (16). Otto Warburg suggested that cancer is a metabolic disease (17). Increasing evidence has demonstrated that the process of tumorigenesis is typically accompanied by alterations in metabolic patterns, including glycolysis, the tricarboxylic acid (TCA) cycle, mitochondrial oxidative phosphorylation (OXPHOS), the pentose phosphate pathway (PPP), glutamine metabolism and lipid metabolism, which is also known as metabolic reprogramming (18-23). At present, metabolic reprogramming is considered as an emerging hallmark of cancer cells (24). Under aerobic conditions, the majority of differentiated cells metabolize glucose to carbon dioxide and GTP via the oxidation of pyruvate produced by glycolysis. Pyruvate is converted into acetyl Coenzyme A (CoA), which then enters the TCA cycle of aerobic oxidation, which is also known as the citric acid cycle or Krebs cycle. It is only when oxygen is unavailable that differentiated cells produce ATP via glycolysis. By contrast, cancer cells typically obtain energy from glycolysis rather than relying on mitochondrial OXPHOS, even in the presence of oxygen, a phenomenon known as the Warburg effect or aerobic glycolysis, which was first reported by Otto Warburg in the 1920s (25).

Another important aspect of altered energy metabolism in cancer cells is glutamine addiction, which is characterized by enhanced uptake and utilization of glutamine. In addition to glucose, glutamine is another major source of energy for tumor cells, as it can function as a substrate for the TCA cycle, but can also serve as a nitrogen donor for nucleic acid synthesis and as a precursor for protein and glutathione biosynthesis (26). Abnormal lipid metabolism is also a hallmark of tumor metabolic reprogramming, which is characterized by abnormal fatty acid (FA) metabolism and lipolysis (26). As important regulators, lncRNAs have attracted increasing attention for their role in regulating tumor metabolic reprogramming and their potential clinical application. The present review discussed the current understanding of the roles of lncRNAs in the metabolic reprogramming of cancer cells and summarized the mechanisms underlying lncRNA-mediated regulation of chemoresistance via metabolic pathways. In addition, the present review discussed the drugs that are currently in clinical use or clinical trials, as well as a number of potential challenges associated with targeting metabolic reprogramming.

2. Glucose metabolism

As an important energy substance, glucose is also essential for the occurrence and development of tumors (27). Glucose is taken up by cells via glucose transporters (GLUTs) and then enters three pathways for further oxidative decomposition, including the glycolysis pathway to produce lactic acid, the PPP to produce nicotinamide adenine dinucleotide phosphate (NADPH) and nucleic acids, and the TCA cycle and the OXPHOS pathway to produce oxygen and ATP (28). lncRNAs primarily regulate the process of glucose metabolism by directly regulating the enzymes and transporters involved in the aforementioned pathways or by indirectly regulating the associated transcription factors (Fig. 1 and Table I) (20,29-33).

Glycolysis. In aerobic glycolysis, there is an excessive conversion of pyruvate to lactate rather than acetyl CoA, which only produces 2 ATPs per molecule of glucose. By contrast, the complete OXPHOS of one molecule of glucose produces up to 36 ATPs (28). Therefore, an interesting question is why cancer cells utilize a less efficient metabolic pathway, at least for the production of ATP. One possible explanation is that aerobic glycolysis can produce intermediate metabolites for further *de novo* nucleotide and lipid synthesis. In addition, compared with mitochondrial OXPHOS, aerobic glycolysis reduces reactive oxygen species (ROS) production, as ROS are a by-product of electron transport (34). Moreover, the acidic microenvironment caused by aerobic glycolysis is also beneficial for cancer cell migration and invasion (35,36). For example, the bloodstream has a higher oxygen concentration compared with most other tissues, yet leukemic cells are highly dependent on aerobic glycolysis, which is beneficial to cell migration (37,38). Furthermore, aerobic glycolysis requires fewer steps, thus it provides energy at a faster rate for tumor proliferation. Therefore, cancer cells tend to obtain energy from aerobic glycolysis.

lncRNAs influence glucose uptake by regulating the expression of GLUTs. GLUTs are membrane proteins that serve a pivotal role in glucose metabolism in cancer cells by transporting glucose into cells. At present, 14 members of the GLUT family have been identified, among which GLUT1 GLUT3 and GLUT4 are closely associated with glucose metabolism in cancer (39,40). lncRNA-p23154 can interact with the promoter region of miR-378a-3p, which inhibits miR-378a-3p transcription. miR-378a-3p targets the 3'-untranslated region (UTR) of GLUT1, leading to downregulation of GLUT1 expression. Thus, the ability of lncRNA-p23154 to promote oral squamous metastasis is mediated by GLUT1 (41). lncRNA HOX transcript antisense intergenic RNA (HOTAIR) also regulates GLUT1 expression by activating mTOR signaling in hepatocellular carcinoma (HCC) (23). Similarly, lncRNA colorectal neoplasia differentially expressed (CRNDE) positively modulates GLUT4 expression and glucose uptake in colorectal cancer (CRC). High CRNDE expression promotes glucose uptake and leads to an enhanced Warburg effect (42). Furthermore, the dysregulation of lncRNAs that regulate GLUT expression promotes the proliferation and metastasis of other tumors, including osteosarcoma and lung cancer (LC) (19,43,44). In addition to directly regulating the expression of GLUTs, lncRNAs can also modulate the distribution of GLUTs, thereby regulating their capacity to transport glucose. MACC1 antisense RNA 1 (MACC1-AS1) is the cognate antisense lncRNA of the oncogene MET transcriptional regulator MACC1 (MACC1). Under metabolic stress, lncRNA MACC1-AS1 is induced, which promotes MACC1 mRNA stability via the 5'AMP-activated protein kinase (AMPK)/lin-28 homolog A signaling pathway, further enhancing the distribution of GLUT1 to the cell membrane and promoting glucose absorption (45).

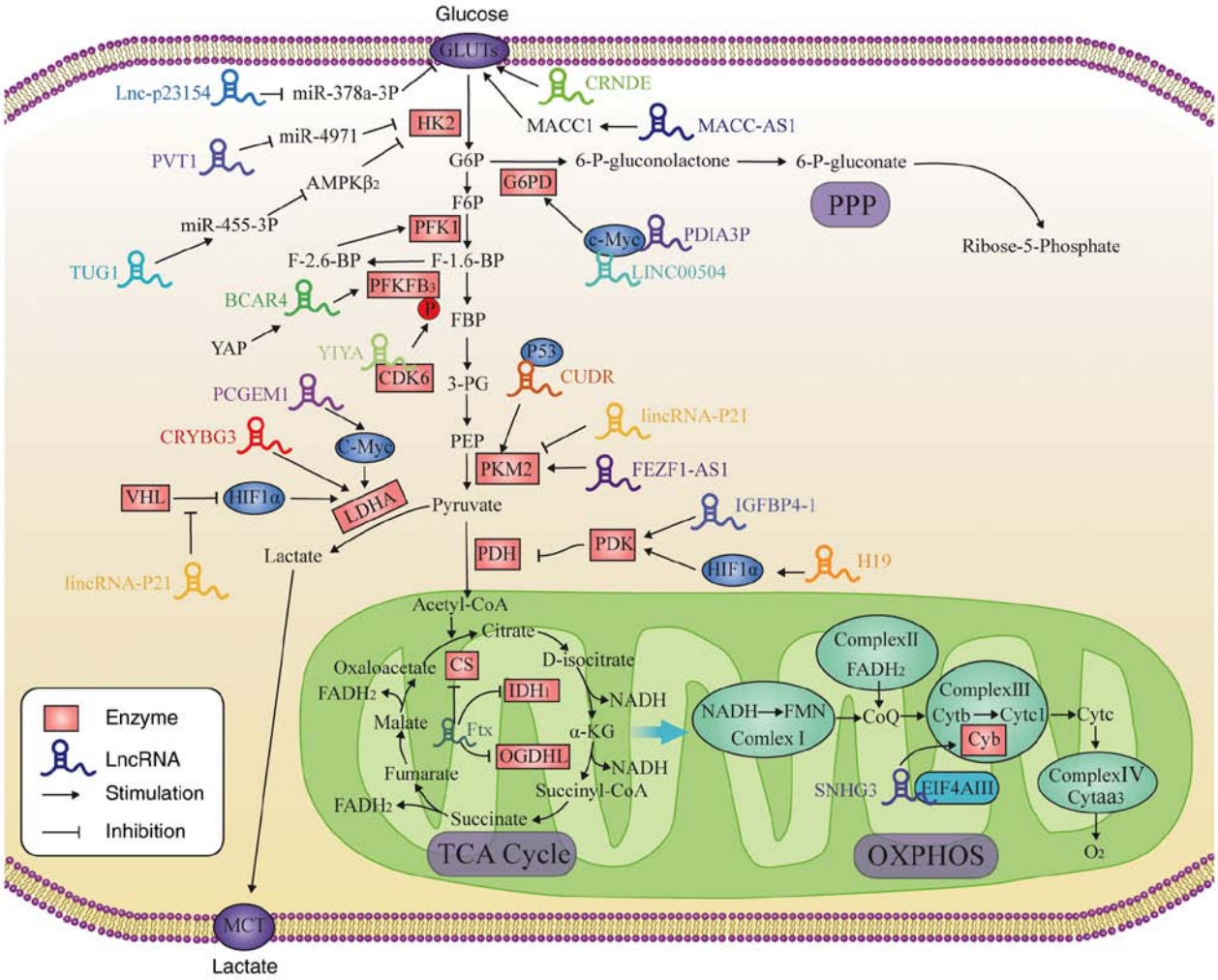

Figure 1. lncRNAs regulate glucose metabolism in cancer cells. lncRNAs modulate glucose uptake and glycolytic flux by modulating GLUTs, metabolism-related enzymes and key transcription factors. lncRNA, long non-coding RNA; GLUT, glucose transporters.

lncRNAs can affect glucose metabolism by regulating the expression or stability of key enzymes or kinases in glycolysis. Hexokinase 2 (HK2) is a key enzyme in glycolysis that catalyses the conversion of glucose to glucose-6-phosphate (G6P) (46). In osteosarcoma, lncRNA Pvt1 oncogene (PVT1) can promote glycolysis and tumor progression by serving as a molecular sponge to suppress miR-497, and miR-497 can downregulate HK2 expression. Therefore, PVT1 regulates tumor progression via the miR-497/HK2 axis (47). Another study demonstrated that lncRNA can affect the stability of HK2. lncRNA taurine-upregulated gene 1 (TUG1) can upregulate the expression of miR-455-3p, and miR-455-3p can regulate the expression of AMPKβ2 via binding to AMPKβ2 3'UTR at positions 54-61. TUG1 affects HK2 stability via modulating the p21/miR-455-3p axis, promoting HCC cell migration (48). Phosphofructo-1-kinase (PFK1) catalyzes the conversion of G6P to fructose-1,6-bisphosphate, which is the rate-limiting step of glycolysis. 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) catalyzes the conversion of G6P to fructose-2,6-bisphosphate, which can increase the activity of PFK1. Thus, PFKFB3 can indirectly promote glycolysis (29). A previous study suggested that lncRNA long intergenic non-protein coding RNA (LINC)00538 can associate with CDK6 and F-box and WD repeat domain containing 7 (FBXW7) to promote the association between CDK6 and cyclin D3, further enhancing the phosphorylation of PFKFB3, and ultimately promoting glucose consumption and lactate production (29). In addition to direct involvement in the modulation of glycolytic enzymes, lncRNAs can also be involved in various cancer-related signaling pathways to indirectly regulate glycolytic enzymes. A previous study reported that lncRNA breast cancer anti-estrogen resistance 4 (BCAR4) participates in the regulation of glycolysis via the Hippo/Yes-associated protein (YAP) signaling pathway. YAP can promote the transcription of BCAR4 via directly binding to the BCAR4 promoter region. BCAR4 can activate HK2 and PFKFB3 transcription by recruiting p300, which promotes the acetylation of histones marked by H3K27ac (49).

To date, four members of the pyruvate kinase (PK) family have been identified: L, R, M1 and M2 types, among which the abnormal expression of pyruvate kinase M2 (PKM2) is the most common in tumor cells (50-52). LINC-p21 can function as a tumor-suppressive lncRNA, as LINC-p21 knockdown upregulates the expression of PKM2 via the PTEN/AKT/mTOR cascade (30). In addition, lncRNAs can regulate not only the expression of enzymes, but also the stability of enzymes via modulating the degradation pathway of enzymes. FEZF1 antisense RNA 1 can bind to PKM2 protein to inhibit the

Table I. lncRNAs and their targets in the regulation of metabolic reprogramming in cancer.

Author, year	lncRNA	Target genes	Expression	Type of cancer	Mechanism	(Refs.)
Wang *et al*, 2018	lnc-p23154	GLUT1	Up	OSCC	Inhibits miR-378a-3p	(41)
Ellis *et al*, 2014	CRNDE	GLUT4	Up	CRC	Not mentioned	(42)
Zhao *et al*, 2018	MACC1-AS1	GLUT1	Up	GC	AMPK/Lin28 signaling pathway	(45)
Song *et al*, 2017	PVT1	HK2	Up	Osteosarcoma	Suppresses miR-497	(47)
Lin *et al*, 2018	TUG1	HK2	Up	HCC	Suppresses miR-455-3p	(48)
Xing *et al*, 2018	YIYA	PFKFB3	Up	Breast cancer	Associates with CDK6	(29)
Zheng *et al*, 2017	BCAR4	HK2, PFKFB3	Up	Breast cancer	Hedgehog signaling pathway	(49)
Wang *et al*, 2017	LINC-p21	PKM2	Down	Prostate cancer	PTEN/AKT/mTOR	(30)
Bian *et al*, 2018	FEZF1-AS1	PKM2	Up	CRC	Binds with PKM2	(53)
Yang *et al*, 2017	lnc-IGFBP4-1	HK2, PDK1, LDHA	Up	Lung cancer cell	Negatively regulates IGFBP4 gene	(54)
Chen *et al*, 2018	CRYBG3	LDHA	Up	Lung cancer cell	Interacts with LDHA	(58)
Rupaimoole *et al*, 2015	NRCP	GPI, ALDOC	Up	Ovarian tumor	Enhances the interaction of STAT1 and RNA pol II	(59)
Zhang *et al*, 2016	lncRNA-MIF	c-MYC	Not mentioned	HeLa cells	Acts as a molecular sponge	(31)
Hung *et al*, 2014	PCGEM1	c-MYC	Up	Prostate cancer	Binds to c-MYC	(62)
Peng *et al*, 2018	lncRNA H19	HIF1α, PDK1	Up	Breast carcinoma	Serves as an endogenous sponge of let7	(66)
Su *et al*, 2017	CASC9	HIF1α	Up	Nasopharyngeal carcinoma	Increases the stability of HIF1α	(67)
Yang *et al*, 2014	LINC-p21	HIF1α	Not mentioned	HeLa cells	Increases the stability of HIF1α	(18)
Lin *et al*, 2016	LINK-A	HIF1α	Up	Breast cancer	Interacts with BRK and LRRK2	(32)
Malakar *et al*, 2019	MALAT1	TCF7L2	Up	HCC	Modulates the translation of TCF7L2	(72)
Li *et al*, 2016	UCA1	PKM2	Up	Liver cancer	Binds to mutant P53	(33)
Yang *et al*, 2018	PDIA3P	G6PD	Up	Multiple myeloma	Binds to c-Myc	(20)
Li *et al*, 2019	LINC00184	COMPLEX II, III, IV and V subunits	Up	Esophageal cancer	Recruits DNMT1 to promote the promoter methylation of PTEN	(21)
Li *et al*, 2018	Ftx	GLUT1, GLUT4, IDH1, CS, OGDH	Up	HCC	Activates the PPARγ signalingpathway	(19)
Deng *et al*, 2019	GLS-AS	GLS	Up	Pancreatic cancer	Regulates the stability of Myc protein	(91)
Li *et al*, 2015	UCA1	GLS2	Up	Bladder cancer	Binds to the 3'UTR of GLS2 mRNA	(88)
Redis *et al*, 2016	CCAT2	GLS	Up	Colon cancer	Regulates the alternative splicing of GLS	(22)
Cui *et al*, 2015	HULC	PPARA/ACSL1	Up	HCC	Downregulates the expression of miR-9	(102)
Liu *et al*, 2018	NEAT1	ATGL	Up	HCC	Binds to miR-124-3p	(110)
Shang *et al*, 2018	LNMICC	FABP5	Up	Cervical cancer	Recruits the nuclear factor NPM1 to the promoter of FABP5	(111)

lncRNA, long non-coding RNA.

ubiquitin-proteasome signaling pathway and increase its stability, promoting activation of STAT3 signaling and the Warburg effect (53).

Pyruvate dehydrogenase kinase (PDK) phosphorylates and negatively modulates pyruvate dehydrogenase, inhibiting pyruvate entry into the TCA cycle. In human cells, four PDK isoenzymes (1-4) have been identified. In LC cells, a novel lncRNA, insulin-like growth factor binding protein 4-1 (IGFBP4-1), has been reported to upregulate the expression of HK2, PDK1 and lactate dehydrogenase (LDH)A (54).

LDH catalyzes the last step of aerobic glycolysis, the conversion of pyruvate to lactate. To date, four members of the LDH family have been identified: LDHA, LDHB, LDHC and LDHD (55). Increasing evidence has demonstrated that LDHA is overexpressed and correlated with the poor prognosis of several types of tumors (56,57). The novel lncRNA crystalline βγ domain containing 3 has been reported to promote glycolysis via directly interacting with LDHA and further promote the LC cell proliferation (58).

In addition to the aforementioned enzymes, other enzymes can also be regulated by lncRNAs (59-61). Although numerous studies on these enzymes have been conducted, the regulatory mechanisms underlying lncRNA-mediated regulation of these enzymes are not completely understood. Therefore, further investigations should be conducted to explore additional specific mechanisms for the molecular targeted treatment of tumors.

Transcription factors involved in glycolysis. In addition to regulating glycolytic enzymes, lncRNAs can also regulate the expression and stability of transcription factors associated with glycolysis, or be regulated by these transcription factors, thereby regulating the occurrence and development of tumors (32,62). The primary transcription factors associated with lncRNAs in glycolysis are c-Myc, hypoxia-inducible factor 1α (HIF1α), transcription factor 7 like 2 (TCF7L2) and p53. MYC is a potent oncogene that can promote tumorigenesis in multiple tissues (63). Under normoxic conditions, aerobic glycolysis is commonly driven by c-Myc, a protein product of MYC. lncRNA-Myc inhibitory factor (MIF) can serve as a molecular sponge for miR-586 to attenuate the inhibitory effect of miR-586 on FBXW7, thereby upregulating FBXW7 expression. FBXW7 is a E3 ubiquitin ligase, and c-Myc and c-Jun are the substrates of FBXW7. Thus, lncRNA-MIF can decrease c-Myc and c-Jun expression to inhibit aerobic glycolysis. Furthermore, c-Myc can activate lncRNA-MIF transcription via binding to the promoter and intronic region of the lncRNA-MIF gene, thus forming a positive feedback loop between c-Myc and lncRNA-MIF (31). In addition, lncRNA prostate cancer gene expression marker 1 (PCGEM1) can increase the transactivation activity of c-Myc, promoting aerobic glycolysis. Mechanistically, PCGEM1 can recruit c-Myc to metabolic gene promoters and enhance histone hyper-acetylation on the majority metabolic genes, thereby upregulating the expression of these target genes (62).

The transcription factor HIF1α is another important regulator of glycolysis that is upregulated in hypoxia (64,65). In breast carcinoma, lncRNA H19 imprinted maternally expressed transcript can increase HIF1α expression by serving as an endogenous sponge of let7, which further enhances PDK1 expression and leads to increased glycolysis in hypoxia (66). In nasopharyngeal carcinoma (NPC), lncRNA cancer susceptibility candidate 9 interacts with HIF1α to increase its stability, promoting NPC cell glycolysis and tumorigenesis (67). Prolyl hydroxylases (PHDs) are oxygen sensors that hydroxylate HIF1α under normoxia, leading to the degradation of HIF1α via the von-Hippel-Lindau (VHL)-mediated ubiquitin-proteasome signaling pathway. However, PHD activity is inhibited under hypoxia, causing HIF1α accumulation (68). LINC-p21 is a hypoxia-responsive lncRNA. In hypoxia, HIF1α associates with the chromatin fragments corresponding to hypoxia response elements within the LINC-p21 gene to promote transcription of LINC-p21. Conversely, LINC-p21 can then increase HIF1α stability by disrupting the interaction between VHL and HIF1α, which protects HIF1α from being degraded via the VHL-mediated ubiquitin-proteasome signaling pathway (18). However, a previous study demonstrated that lncRNAs can increase HIF1α stability under normoxic conditions. lncRNA LINC for kinase activation is a cytoplasmic lncRNA that can interact with protein tyrosine kinase 6 and leucine rich repeat kinase 2, subsequently phosphorylating Tyr565 and Ser797 of HIF1α, respectively. Tyr565 phosphorylation represses pro 564 hydroxylation, which stabilizes HIF1α in normoxia, whereas Ser797 phosphorylation enhances its transcriptional activity, leading to increased glycolysis and breast cancer progression (32). In line with the aforementioned studies, a recent study also confirmed that a novel hypoxia-induced lncRNA G077640 can bind to H2A.X variant histone to enhance the stability of HIF1α, leading to enhanced hypoxia-related glycolysis, which ultimately promotes esophageal squamous cell carcinoma cell proliferation and migration (unpublished data).

Similar to HIF1α and c-Myc, TCF7L2 is also a metabolic transcription factor. TCF7L2 is a member of the TCF family that is involved in the formation of β-catenin/TCF, a key regulator of the canonical Wnt signaling pathway (69). Additionally, the Wnt signaling pathway has been reported to serve a crucial role in metabolic reprogramming (70,71). lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) can regulate the expression of TCF7L2 at the post-transcriptional level via splicing oncoprotein serine and arginine rich splicing factor 1 in HCC cells. In addition, MALAT1 can promote glycolysis and inhibit gluconeogenesis by modulating the translation of TCF7L2 (72).

p53, a tumor suppressor, can downregulate GLUT1 and GLUT4 expression and regulate multiple metabolism-related enzymes (73,74). Increasing evidence has demonstrated that p53 mutations can promote tumorigenesis (75,76). Mutant p53 (N340Q/L344R) can bind to lncRNA urothelial cancer associated 1 (UCA1) to form a complex, which then binds to the promoter regions of PKM2 to promote the expression and phosphorylation of PKM2, accelerating liver cancer cell proliferation. Thus, UCA1 serves a crucial role in the p53-mediated regulation of glycolysis (33).

lncRNAs involved in the PPP. Alterations in the PPP often occur during tumor metabolic reprogramming, and large amounts of NADPH and ribose-5-phosphate can be produced via this pathway, which can maintain the reduction-oxidation status of cells and provide the raw material for the synthesis of various substances, respectively (77). The conversion of G6P

to 6-phosphogluconate is catalyzed by G6P dehydrogenase (G6PD), which is the first key enzyme in the PPP (62). Using nuclear magnetic resonance spectroscopy, a previous study reported that lncRNA protein disulfide isomerase family A member 3 pseudogene 1 (PDIA3P) can increase the PPP flux and NADPH level via enhancing the expression and activity of G6PD. Mechanistically, PDIA3P can bind to c-Myc to increase its transactivation activity and binding to the G6PD promoter (20). Similarly, lncRNA LINC00504 was also reported to modulate G6PD activity by interacting with c-Myc and increasing its transactivation activity (78). In addition, lncRNA PCGEM1 can also regulate the PPP via regulating the expression and activity of G6PD (62).

lncRNAs involved in the TCA cycle and OXPHOS pathway. The abnormal expression of lncRNAs is often accompanied by alterations in OXPHOS during the regulation of glycolysis. Increased glycolysis is sometimes accompanied by either decreased or increased OXPHOS (19,21,79). Although the reasons for this phenomenon are unclear, these adaptive alterations are ultimately intended to promote the tumorigenesis and progression of cancer. A recent study demonstrated that lncRNA LINC00184 can recruit DNA methyltransferase 1 to promote promoter methylation of PTEN, leading to increased Akt phosphorylation and promoting glycolysis, as well as reducing the expression of mitochondrial COMPLEX II, III, IV and V subunits and the ATP level (21). lncRNA FTX transcript, XIST regulator (Ftx) was also reported to increase the expression of GLUT1 and GLUT4, and decrease isocitrate dehydrogenase (IDH)1, citrate synthase and oxoglutarate dehydrogenase expression by activating the peroxisome proliferator-activated receptor (PPAR)γ signaling pathway, indicating that lncRNA Ftx might promote glycolysis and inhibit the TCA cycle in HCC cells (14). By contrast, lncRNA small nucleolar RNA host gene 3 can simultaneously upregulate the expression of PKM, IDH2 and cytochrome b reductase 1 via binding eukaryotic translation initiation factor 4A3 (79).

3. Glutaminolysis

Although glutamine is a nonessential amino acid that can be synthesized from glucose, cancer cells also display an increased dependence on glutamine to feed the TCA cycle. Moreover, certain cancer cells display a sensitivity to glutamine starvation, which is known as glutamine addiction (80,81). In 1950, Harry Eagle (71) reported that HeLa cells require excess glutamine compared with other amino acids present in the culture medium. In addition, it has been reported that tumors consume glutamine faster than surrounding healthy tissues (82) and the level of blood glutamine is increased in patients with advanced cancer (83). Glutamine is transferred into cells via the solute carrier (SLC) family members, including SLC1, SLC6, SLC7 and SLC38 members. When in the cell, glutamine is deaminated by glutaminase (GLS)1 and GLS2 to produce glutamate. Glutamine dehydrogenase, glutamate oxaloacetate transaminase or glutamine pyruvate transaminase can further catalyze glutamate to α-ketoglutarate to fuel the TCA cycle (84). Alternatively, glutamate can be further oxidized to glutathione by glutathione cysteine ligase, which can neutralize mitochondrial ROS (85). Under certain circumstances, reduced acetyl CoA entering the TCA cycle may also promote the compensatory oxidation of glutamine to further fuel the TCA cycle and OXPHOS in mitochondria (86).

GLSs are the rate-limiting enzymes in glutamine metabolism, which are encoded by the human genes GLS1 and GLS2, and have been reported to be involved in the development of numerous malignant tumors (87-90). GLS-antisense (AS) can repress GLS expression at the post-transcriptional level via adenosine deaminases acting on RNA/dicer-dependent RNA interference. Under nutrient stress circumstances, Myc can bind to the promoter region of GLS-AS to inhibit the transcriptional activity of GLS-AS. Furthermore, GLS and GLS-AS can also regulate Myc protein stability. Therefore, there is a feedback loop between GLS-AS and Myc, leading to reduced expression, which increases GLS expression and promotes pancreatic cancer progression (91). UCA1 expression is positively correlated with GLS2. UCA1 can bind to miR-16, and miR-16 can further regulate the expression of GLS2 via directly binding to the 3'UTR of GLS2 mRNA. Thus, UCA1 can bind to miR-16 to repress the inhibitory effect of miR-16 on GLS2, leading to increased GLS2 expression, glutamine uptake and reduced ROS production (88). Similarly, lncRNAs HOTAIR, HOXA distal transcript antisense RNA and OIP5 antisense RNA 1 have also been reported to affect glutaminolysis by regulating GLS (92-94).

In addition to the aforementioned effects, lncRNAs have been reported to regulate the alternative splicing of GLS. Single nucleotide polymorphisms (SNPs) in lncRNAs have been identified to be associated with susceptibility to numerous types of cancer (95-97). lncRNA colon cancer-associated transcript 2 (CCAT2) harboring the rs6983267 SNP could modulate cancer metabolism via binding the cleavage factor I complex, which can regulate the alternative splicing of GLS. Compared with control cells, CCAT2 T allele- or G allele-overexpression HCT116 cells both display enhanced GLS activity. However, compared with T allele-overexpression HCT116 cells, G allele-overexpression HCT116 cells display higher enzymatic activity. Therefore, the aforementioned results revealed an allele-specific regulatory mechanism underlying glutamine metabolism in colon cancer (Fig. 2 and Table I) (22).

4. Abnormal lipid metabolism

Abnormal lipid metabolism is characterized by abnormal FA metabolism and abnormal lipolysis. The majority of healthy cells obtain FA primarily via the exogenous pathway. However, 90% of FA obtained by tumor cells is derived via *de novo* synthesis. FA β oxidation can provide energy to meet the needs of rapid tumor cell proliferation and growth, and lipids are the major components of cell membranes (98).

With respect to the modulation of lipid metabolism in tumor cells, three regulatory mechanisms should be taken into consideration: i) Regulation of the expression of the enzymes in the lipid synthesis pathway, including acetyl CoA carboxylase, fatty acid synthase (FASN), acetyl CoA synthase (ACS), malonyl-CoA decarboxylase and ATP citrate lyase (ACLY); ii) regulation of the expression of the enzymes in lipolysis, including adipose triacylglyceride lipase (ATGL), hormone-sensitive lipase and monoacylglycerol lipase; and iii) regulation of related transcription factors, including sterol regulatory element-binding

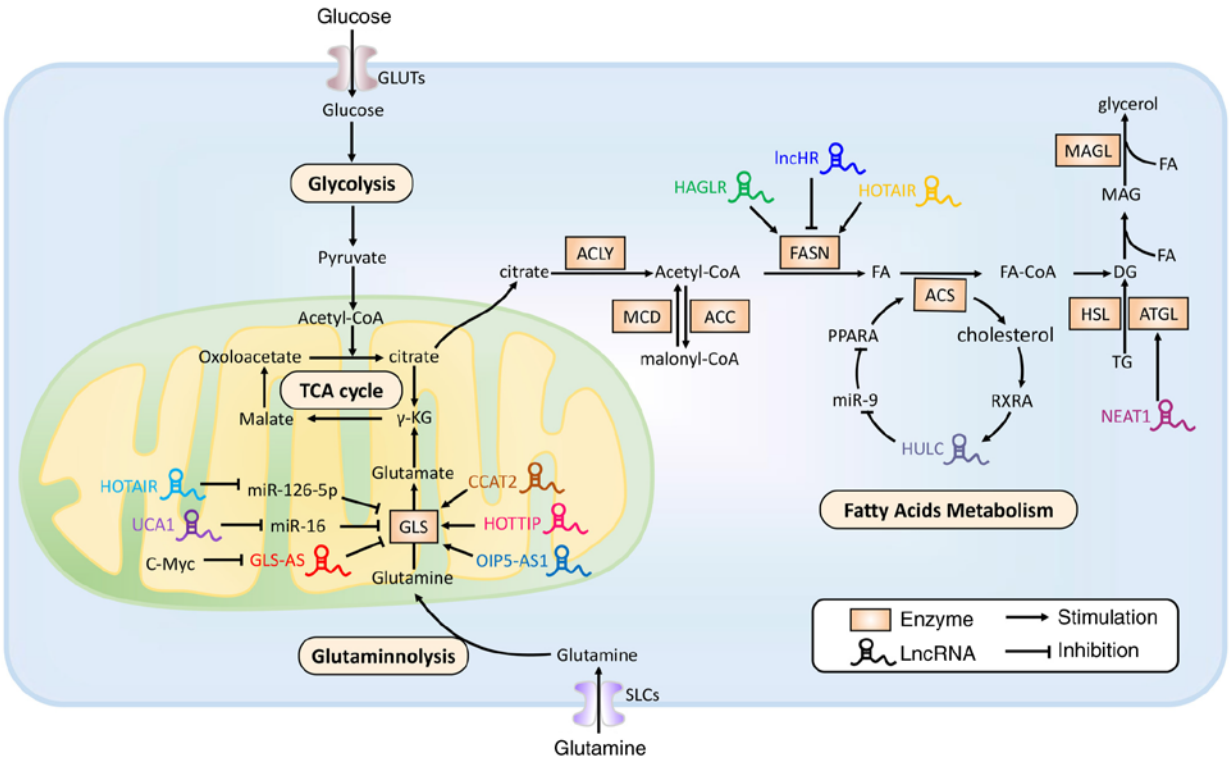

Figure 2. lncRNAs regulate glutaminolysis and lipid metabolism in cancer cells. lncRNAs function via modulating enzymes and transcription factors related to glutaminolysis and lipid metabolism. lncRNA, long non-coding RNA.

protein 1 (SREBP-1), liver X-activated receptor, retinoid X receptors (RXRs) and PPAR-α (Fig. 2) (99,100). ACS long chain family member 1 (ASCL1) is a member of the ACSL family that can catalyze the first step in FA metabolism and can be activated by the transcription factor PPAR-α in the liver (99). A study has demonstrated that highly upregulated lncRNA in liver cancer (HULC) can downregulate miR-9 expression levels by inducing methylation of CpG islands in its promoter, and miR-9 can downregulate PPAR-α expression by directly binding to the 3'UTR of PPAR-α. Therefore, HULC can upregulate the level of ACSL1. By contrast, the cholesterol product of ACSL1 can upregulate HULC expression by activating RXRA, a member of the RXR family, which serves a crucial role in the control of various physiologic processes and can be activated by sterol (101), thereby forming a positive feedback loop between HULC/miR-9/PPAR-α/ACSL1/cholesterol/RXRA/HULC in hepatoma cells (102). snoRNA host gene 16 (SNHG16) is highly expressed and regulated by the Wnt signaling pathway and c-Myc in CRC. SNHG16 regulates the genes involved in lipid metabolism potentially via a competitive endogenous (ce)RNA-related mechanism and serves an oncogenic role in CRC (103).

FASN is the key enzyme that catalyzes the final step of *de novo* FA synthesis (100). FASN is upregulated in multiple tumor types and is associated with a poor prognosis and resistance to cancer therapy (104-106). Interestingly, HOXD antisense growth-associated long non-coding RNA (HAGLR) knockdown downregulates FASN expression and decreases cellular free FA levels in non-small cell LC cells (107). Similar to the role of HAGLR, lncRNA HOTAIR promotes NPC cell proliferation and invasion by upregulating FASN expression (108).

Nuclear paraspeckle assembly transcript 1 (NEAT1) is an lncRNA that is primarily located in cytoplasm and can also promote the formation of nuclear paraspeckles by serving as a scaffolding factor. ATGL is a primary enzyme of lipolysis that can hydrolyze triglyceride (TAG) into diacylglycerol (DAG) and free fatty acid (FFA) during TAG metabolism (109). A previous report demonstrated that NEAT1 can regulate ATGL expression via binding to miR-124-3p to disrupt the lipolysis of hepatoma cells, leading to elevated levels of DAG and FFA. In addition, NEAT1 can also regulate PPAR-α expression. Thus, NEAT1 can modulate HCC cell proliferation via the miR-124-3p/ATGL/DAG+FFA/PPAR-α signaling pathway (110).

Lymph node (LN) metastasis indicates poor prognosis of patients with cancer, but the mechanism underlying this process is not completely understood. lncRNA associated with LN metastasis in cervical cancer (LNMICC) upregulation was observed in patients with cervical cancer with LN metastasis. LNMICC can recruit the nuclear factor nucleophosmin 1 to the promoter of fatty acid binding protein 5, a fatty acid binding protein that is indispensable for FA uptake and transport, to activate fatty acid metabolism, further promoting LN metastasis and accelerating lipogenesis *in vitro* and *in vivo*. However, this effect can be suppressed by miR190, which can directly bind to LNMICC (111).

SREBP-1c is a transcriptional factor that can regulate hepatic lipid homeostasis. The novel human specific lncRNA HCV regulated 1 can negatively modulate SREBP-1c and FASN expression, thereby inhibiting oleic acid-induced triglyceride and lipid droplet accumulation in Huh7 cells (112). Thus, lncRNAs can affect cellular lipid metabolism by regulating the associated enzymes and transcription factors (Fig. 2 and Table I).

5. lncRNAs involved in chemoresistance via metabolic reprogramming signaling pathways

Chemotherapy is one of the primary treatment strategies for multiple types of tumors, and the major hurdle of chemotherapy is chemoresistance. A number of different mechanisms lead to chemoresistance, including cancer stem cells (113), mitochondrial alteration (114), epithelial-mesenchymal transition (115), DNA repair (116) and autophagy (117). Recent studies have confirmed that metabolic reprogramming is involved in the regulation of lncRNAs in the chemoresistance of multiple tumors, including glycolysis, lipid synthesis and FA oxidation (FAO) (118-120). Elevated glycolysis rates were observed in cisplatin-resistant colon cancer cells. lncRNA differentiation antagonizing non-coding RNA (DANCR) is upregulated in colon cancer tissues, cells and cisplatin-resistant colon cancer cells. DANCR can regulate miR-125b-5p expression via a ceRNA mechanism, and miR-125b-5p can bind to HK2 to modulate glycolysis, further leading to enhanced cisplatin resistance. Thus, DANCR can modulate cisplatin resistance via the miR-125b-5p/HK2 axis (118). Similarly, lncRNA-suppressing androgen receptor in renal cell carcinoma can improve the sensitivity of osteosarcoma cells to cisplatin via targeting HK2 to regulate miR-143-mediated glycolysis (121). In addition to glycolysis, lipid metabolism is also involved in the regulation of lncRNAs on chemoresistance. lncRNA TINCR ubiquitin domain containing (TINCR) can bind to ACLY to protect it from ubiquitin degradation, leading to increased cellular acetyl CoA levels and further promoting NPC cisplatin resistance. Mechanistically, TINCR regulates NPC cisplatin resistance via the peptidyl arginine deiminase 1/MAPK/matrix metallopeptidase 2/9 signaling pathway (119). FAO regulates drug resistance in breast cancer stem cell (122). In gastric cancer cells, lncRNA MACC1-AS1, induced by mesenchymal stem cells-derived TGF-β1, can promote FAO-dependent chemoresistance by antagonizing miR-145-5p (120). Therefore, targeting these lncRNAs and associated signaling pathways may serve as an effective strategy to increase the sensitivity of tumors to chemotherapy.

6. Conclusions and future perspectives

The occurrence of tumors is due to abnormal cell growth and proliferation, which requires the materials for cell construction, including nucleic acids, proteins and lipids, as well as the energy for tumor cell proliferation. As aforementioned, glucose, glutamine and lipid metabolism are not independent in tumor cells; they cooperate with one another to allow tumor cells to rapidly proliferate. lncRNAs, as important regulators of metabolic reprogramming, do not serve singular roles. Certain lncRNAs have only been reported to regulate glycolysis, such as the aforementioned lncRNA IGFBP4-1 and LINC00538 (29,54). However, it is possible that lncRNAs can also regulate other metabolic processes because metabolic processes are not independent and may display feedback mechanisms. Certain lncRNAs have been reported to simultaneously regulate multiple metabolic pathways. For example, CCAT2 can enhance glutamine metabolism and glycolysis (22), lncRNA Ftx can promote glycolysis and inhibit the TCA cycle (19), and PCGEM1 can regulate multiple metabolic pathways, including glucose metabolism, glutamine metabolism, and nucleotide and fatty acid biosynthesis (62). Similarly, lncRNA HOTAIR has been reported to regulate glutaminolysis, the expression of FASN and glucose metabolism in different experiments (23,92,108). Metabolic pathways are not independent, which makes it difficult to target metabolic pathways for tumor therapy due to the possible compensatory effects of other pathways.

Tumor-associated alterations in metabolism involve numerous molecules and pathways that are potential targets of tumor therapy. Therefore, targeting metabolism is an effective strategy as the heterogeneity in the genetic landscape of tumors is greater than the metabolic heterogeneity. The first small-interfering RNA (siRNA) drug, Patisiran, was approved by the Food and Drug Administration in 2018, which might aid in the development of siRNA drugs targeting lncRNAs or other genes involved in metabolic reprogramming (123). Notably, some inhibitors or RNA interference-mediated inhibition of enzymes and transcription factors involved in metabolic reprogramming have been demonstrated to inhibit the proliferation of tumor cells, some of which are entering clinical evaluation or currently undergoing clinical evaluation. PKM2 and GLS inhibitors have been reported to inhibit gastric cancer cell proliferation (89). Similarly, a report demonstrated that a GLS inhibitor, Bis-2 (5-p henylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide, displayed antitumor efficacy in several tumor models both *in vitro* and *in vivo* (124,125). Moreover, antisense oligonucleotide-targeting HIF-1a, EZN-2968, can bind to HIF-1a mRNA and reduce HIF-1a protein expression levels. In addition, the study demonstrated that EZN-2968 can be safely used in patients with advanced solid tumors (126). However, whether these inhibitors are toxic to healthy cells requires further investigation. For example, the glycolysis pathway is also widely used by immune cells to provide energy. In addition, the compensatory expression of other genes after the administration of inhibitors is also unclear. Therefore, further studies of metabolic reprogramming should provide additional options for targeted therapy in patients with tumors.

Although lncRNAs were previously believed to not encode proteins, a previous study demonstrated that certain ncRNA genes can undergo active protein translation in mouse macrophages (3). lncRNAs perform complex biological functions in various tumors, and further studies should be conducted to understand how lncRNAs regulate tumorigenesis for the identification of novel therapeutic targets for cancer treatment and biomarkers for prognostic assessment.

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Authors' contributions

CL and HL confirm the authenticity of all the raw data. CL and HL drafted the review. FC and XZ assisted with developing the tables and graphs. RX and QW revised the review with regard to grammar, text format and framework, revised the manuscript for important intellectual content and collated the references. SY and TL revised the manuscript. SL and ML provided the direction and ideas for the writing, made repeated revisions to the review and provided guidance throughout the process. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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