

Role and mechanisms of noncoding RNAs in the regulation of metabolic reprogramming in bladder cancer (Review)

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Abstract. Bladder cancer (BLCA) is the most common type of urothelial cancer. The role of metabolic reprogramming in tumors is gradually gaining more attention and being investigated. Recent studies have shown that noncoding RNAs (ncRNAs) are strongly related to BLCA metabolic reprogramming. ncRNAs are able to directly regulate the expression and function of metabolic enzymes, or indirectly regulate them through a number of important pathways to regulate metabolism in BLCA cells. The mechanism of the development of BLCA has not yet, to the best of the authors' knowledge, been studied and identifying how ncRNAs act in metabolic reprogramming in BLCA may assist with developing BLCA treatments. In the present review, a summary of the ncRNAs participating in the metabolic reprogramming of BLCA was provided. The regulation of ncRNAs in glucose, lipid and amino acid metabolism was also detailed. Furthermore, the molecular mechanisms underlying the regulation of ncRNAs in the metabolic reprogramming of BLCA and potential

treatment strategies that track cancer cell metabolism by regulating the expression of particular ncRNAs were discussed.

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1. Introduction

Bladder cancer (BLCA) is one of the top 10 most common cancers worldwide, with an annual incidence rate of >500,000 individuals and an annual mortality rate of >200,000 individuals (1,2). In the process of tumor development, the metabolism of tumor cells also changes, which is now referred to as metabolic reprogramming. Similarly, metabolic reprogramming serves a crucial role in the development and progression of BLCA. To some extent, BLCA is also a metabolic disease. Glucose is mainly metabolized by glycolysis in tumor cells (3,4), whether or not they are well oxygenated and this has prompted continued exploration and research into the role of metabolism in tumorigenesis (5). When cells are hypoxic, BLCA cells can adapt their own glucose metabolism in the oxidative phosphorylation pathway into glycolysis, a phenomenon called the Warburg effect (6). This metabolic switch meets the needs of tumor cells to absorb nutrients and provides sufficient energy supply for tumor progression. The growth and membrane synthesis of BLCA cells also require lipid function and the growth of cells under hypoxia is also inseparable from the modification of lipid metabolism, which allows bladder tumor cells to continue to survive cellular hypoxia and chemotherapeutic drugs (7). Amino acid metabolism also serves an important role in the proliferation of tumor cells and the maintenance of oxidative homeostasis. In conclusion, metabolic reprogramming of BLCA cells will become an important metabolic marker of bladder carcinogenesis through changes in metabolic patterns.

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Abbreviations: BLCA, bladder cancer; ncRNAs, noncoding RNAs; circRNAs, circular RNAs; lncRNA, long non-coding RNA; miRNA, microRNA; snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; piRNA, piwi-interacting RNA; siRNA, small interfering RNA; srpRNA, signal recognition particle RNA; PNPT 1, polyribonucleotide nucleotidyltransferase 1; HK2, hexokinase2; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase; TME, tumor microenvironment; TCA cycle, tricarboxylic acid cycle; GLS, glutaminase; ROS, reactive oxygen species; GLS1, glutaminase 1; GLS2, glutaminase 2

Key words: bladder cancer, metabolic reprogramming, noncoding RNA, long noncoding RNA, microRNA, circular RNA

Noncoding RNA (ncRNAs) have not been evaluated because they do not encode proteins. They were previously considered to be noise generated during transcription and to have no biological function (8). In the human genome, genes encoding proteins are only ~2% of the total, and the remaining fraction is transcribed to ncRNA. Therefore, a number of researchers hypothesize that ncRNAs serve an important role in biological processes. As more research has begun to focus on ncRNAs in BLCA, a number of studies have showed their role and function (9-13). For example, miR-183-5p has low expression in BLCA and enhances cisplatin-induced apoptosis in BLCA cells by regulating PNPT 1 (14). miR-665 is downregulated by upstream methylation in BLCA and suppresses epithelial-stromal transformation in BLCA via the SMAD3/zinc finger protein SNAIL axis (15). miR-125a-5p inhibits BLCA progression by targeting fucosyltransferase 4 (16). miR-125b-5p inhibits BLCA progression by targeting hexokinase (HK)2 and inhibiting the PI3K/AKT pathway (17). Aberrant expression of long ncRNAs (lncRNAs) is also critical in the metabolic process of BLCA. For example, lncRNA RP11-89 promotes tumorigenesis and iron death resistance via sponging miR-129-5p through pro 2-activated iron export in BLCA (18). Exosomal lncRNA LNMAT2 promotes lymphatic metastasis of BLCA (19). As a target and coactivator of E2F transcription factor 1, lncRNA-SLC16A1-AS1 induces metabolic reprogramming during BLCA progression (20). lncRNA BLACAT2 promotes BLCA-related lymphangiogenesis and lymphatic metastasis (21). In addition, a large number of dysregulated circular RNAs (circRNAs) have been found in BLCA. A recent study showed that circFAM13B is dysregulated in BLCA and inhibits glycolysis via the IGF2 mRNA binding protein 1/pyruvate kinase M2 (PKM2) pathway, increasing immunotherapy sensitivity in BLCA (22). Another study found that circRNA_0071196 promotes BLCA proliferation and migration through the miRNA-19b-3p/CIT axis (15). Exosome-derived circTRPS1 promotes the malignant phenotype and CD8⁺ T cell exhaustion in the BLCA microenvironment (23). circ0008399 interacts with WT1 associated protein to promote the assembly and activity of the m6A methyltransferase complex and promotes cisplatin resistance in BLCA (24).

BLCA cells often vary because of genetic changes and changes in the surrounding microenvironment (20). During BLCA development, ncRNAs regulate metabolic pathways in cancer cells. With the study of metabolomics, researchers have gained a new understanding of metabolic reprogramming and developed new alternative treatments for BLCA (25,26). Therefore, how ncRNA functions in BLCA metabolism and its mechanism of action need to be studied in depth. In the present review, ncRNA classification, abnormal ncRNA expression in BLCA and ncRNAs involved in metabolic reprogramming in BLCA are summarized. In addition, the ncRNAs involved in glucose, lipid and amino acid metabolism in BLCA are discussed.

Classification of ncRNAs. RNAs were first identified some time ago and are classified into coding RNAs and ncRNAs based on whether they encode proteins (27,28). Coding RNA mainly refers to mRNA, while ncRNA encompasses

more types, such as microRNA (miRNA), lncRNA, small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), piwi-interacting RNA (piRNA), circRNA, small interfering RNA (siRNA) and signal recognition particle RNA (srpRNA) (29-33). According to their length, ncRNAs are divided into lncRNAs and small ncRNA (sncRNAs). lncRNAs are ncRNAs with nucleotide lengths >200 bp and sncRNAs are ncRNAs with nucleotide lengths <200 bp (34,35), including miRNAs, circRNAs, siRNAs, snRNAs, srpRNAs, snoRNAs and telomerase RNAs (11,36,37).

ncRNAs and metabolic reprogramming in BLCA. With increased research into ncRNAs, their various roles in cellular activities have been identified, such as substance metabolism, protein transport and translation and RNA splicing, modification and editing (38-40). In particular, the role of ncRNAs in tumor metabolism has been widely recognized (41-43). Studies have implicated ncRNAs in regulating metabolic reprogramming in BLCA, including miRNAs, such as miRNA-195-5p, miR-16, miRNA-21 and miR-210 (44-47). lncRNAs, such as lncRNA-SLC16A1-AS, lncRNA-P21, lncRNA-UCA1, lncDBET and lncRNA-TPRG1-AS1, have also been implicated in the metabolic reprogramming of BLCA (48-51).

With the further study of miRNAs and lncRNAs, another type of ncRNA has gradually gained attention: circRNAs, which have gradually become a research hot spot. circRNA is generated by mRNA or linear ncRNA 'reverse splicing'. It has a closed-loop structure, is stably expressed, is not susceptible to degradation, and is not influenced by RNA exonucleases (52). circRNAs generally exert their effects using sponge miRNAs to regulate protein function and translation (53-55). Numerous circRNAs have been discovered, but exactly how they perform their biological functions remains to be elucidated. However, a number of recent studies on circRNAs have focused on tumors and circRNA_0088036, circRIP2, circNCOR1, circRNA-ST6GALNAC6, circEHBP1, circRNA-ST6GALNAC6, hsa_circ_0014130 and circRNA_0071196 have been found to serve oncogenic or suppressor gene roles in the development of BLCA (15,56-61). Studies have also found that circ_0020394, circFAM13B and circANKHD1 are strongly linked to metabolic reprogramming in BLCA (22,62,63).

At present, studies on snoRNAs and piRNAs are relatively rare in research related to metabolic reprogramming in BLCA. snoRNA is an sncRNA of 60-300 nt in length that forms a snoRNP complex by binding to nucleolar ribonucleoproteins (64). snoRNAs are mainly involved in rRNA processing, transcription regulation, RNA splicing and oxidative stress (65). In previous studies, it has been found that Rpl13a, SNORD12B and SNORA73 are involved in BLCA metabolism (66-68). piRNAs are sncRNAs 24-31 nt in length and have been found in up to 15,000 species (69). piRNA complexes are formed by binding to piwi proteins, which mainly regulate translocon expression in mammalian germ cells (70,71). piRABC regulates bladder function (72). However, there have been no relevant studies on the piRNAs involved in BLCA metabolism. In conclusion, various ncRNAs serve important roles in the metabolic reprogramming of BLCA.

Table I. Regulates ncRNAs related to glucose metabolism and their functions and mechanisms.

First author, year	Name of ncRNA	Expression	Function	Target	(Refs.)
Guo, 2019	miR-204-3p	Down	Inhibit proliferation and promote apoptosis	LDHA	(75)
Yang, 2015	miR-21	Down	Inhibit proliferation	PTEN, AKT, mTOR	(76)
Wu, 2022	miR-4792	Down	Inhibit proliferation and reduce aerobic glycolysis	FOXCl, c-Myc	(77)
Yuan, 2017	miR-200c	Down	Inhibition of glycolysis and inhibition of proliferation and invasion	LDHA	(78)
Logotheti, 2020	lncRNA SLC16A1-AS1	Up	Increase in glycolysis and promote invasion	E2F1	(20)
Cai, 2022	lncRNA CCDC183-AS1	Up	Promote the proliferation, invasion and migration	miR-4731-5p/TCF7L2	(79)
Wang, 2020	lncRNA HULC	Up	Promote proliferation and inhibit apoptosis	LDHA, PKM2, FGFR1	(80)
Chen, 2022	lncRNA UCA1	Up	Promote glycolysis and promote proliferation	hnRNPs, GPT2	(92)
Li, 2014	lncRNA UCA1	Up	Promote glycolysis and promote proliferation	STAT3, miR-143, mTOR, HK2	(82)
Du, 2022	circ_0020394	Down	Inhibit glycolysis, inhibit proliferation and invasion and promote apoptosis	miR-328-3p/NRBP1	(62)
Lv, 2013	circFAM13B	Down	Suphibit immune escape and enhance immune sensitivity	IGF2BP1/PK M2	(22)
Wei, 2019	has-circRNA-403658	Up	Promote glycolysis and promote proliferation	LDHA	(83)

lncRNA, long non-coding RNA; miR, microRNA; LDHA, lactate dehydrogenase A; PTEN, phosphatase and tensin homolog; FOXCl, Forkhead box C1; E2F1, E2F transcription factor 1; TCF7L2, transcription factor 7-like 2; PKM1/M2, pyruvate kinase isozymes M1/M2; FGFR1, fibroblast growth factor receptor 1; hnRNPs, heterogeneous nuclear ribonucleoproteins; GPT2, glutamic-pyruvic transaminase 2; HK2, hexokinase 2; NRBP1, nuclear receptor binding protein 1; TME, tumor microenvironment.

2. ncRNAs and glucose metabolism in BLCA

Studies have found that multiple ncRNAs are closely associated with glucose metabolism in BLCA (73-79). The most common mode of participation is the promotion of the degradation of the mRNA or the inhibition of protein translation. Glucose metabolism mainly refers to glycolysis, the tricarboxylic acid (TCA) cycle and the pentose phosphate pathway. Bladder tumor cells rely on aerobic glycolysis-dependent metabolism (the Warburg effect) to promote their proliferation. Enhanced glycolytic metabolism generally promotes the increased production of pyruvate, alanine and lactate through the increased expression of its related genes, such as glucose transporter 1, lactate dehydrogenase (LDHA), hexokinase 1 and pyruvate kinase M (PKM) (78,81). In addition, the expression of genes related to the pentose phosphate pathway and fatty acid synthesis increases during BLCA metabolism, promoting tumor cell proliferation (73). Numerous studies have demonstrated that changes in tumor oncogenes and tumor suppressor genes influence metabolic reprogramming by regulating key metabolic enzymes (74-87). The role of ncRNAs in glucose metabolism is discussed in detail below.

Studies have indicated that the ncRNAs involved in glucose metabolism in BLCA are mainly miRNAs, lncRNAs and

circRNAs, with few studies on piRNAs and snoRNAs (75-84). miR-204-3p binds to the 3'-UTR of LDHA in BLCA to reduce its mRNA and protein expression. Glucose depletion and lactate formation are depleted in BLCA cells after overexpression of miR-204-3p (75). Enhanced growth inhibition and apoptosis of BLCA cells induced by miR-204-3p are restored by LDHA overexpression (Table I). miR-204-3p can inhibit BLCA cell growth by regulating LDHA-mediated glycolysis (75). Low expression of miR-21 in BLCA cells leads to reduced tumor aerobic glycolysis and reduced glucose uptake and lactate production, which increases the expression of phosphatase and tensin homologue, inhibits phosphorylated AKT and inactivates mTOR to regulate aerobic glycolysis in BLCA cells (76). Low expression of miR-4792 in BLCA tissues and its overexpression in BLCA cells inhibits the expression levels of Forkhead box C1 and c-Myc, inhibits cell proliferation and decreases aerobic glycolysis and lactate content (77). miR-200c can inhibit glycolysis, cell growth and invasion of BLCA cells by targeting LDHA in BLCA cells (78).

lncRNA SLC16A1-AS1 promotes ATP production by increasing aerobic glycolysis and mitochondrial respiration and through fatty acid β -oxidation. In addition, complex formation of lncRNA-SLC16A1 by E2F1-induced AS1 with its transcription factors promotes cancer metabolic

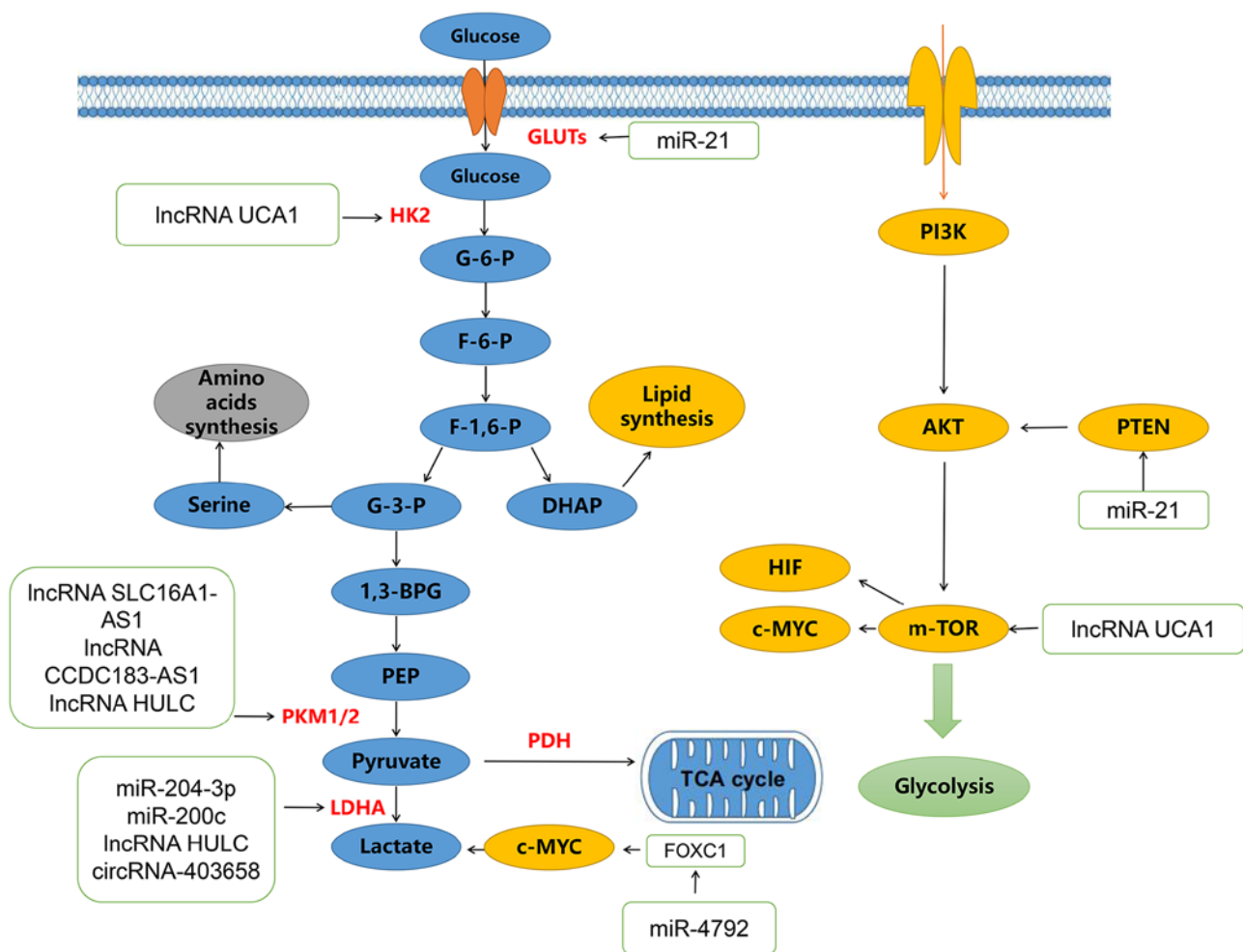


Figure 1. ncRNAs promote aerobic glycolysis in bladder cancer cells by regulating key enzymes and signaling pathways that regulate glucose metabolism processes. The major metabolites are in blue and the major metabolic enzymes in red, major metabolic pathways are shown in yellow. IncRNA, long non-coding RNA; miRNA, microRNA; G-6-P, glucose-6-phosphate; F-6-P, fructose-6-phosphate; F-1,6-P, fructose-1,6-bisphosphate; G-3-P, glyceraldehyde 3-phosphate; DHAP, dihydroxy acetone phosphate; 1,3-BPG, 1,3-bisphosphoglyceric acid; PEP, phosphoenolpyruvate; GLUT, glucose transporter; HK2, hexokinase 2; PDH, pyruvate dehydrogenase; LDHA, lactate dehydrogenase A; PKM1/M2, pyruvate kinase isozymes M1/M2; PTEN, phosphatase and tensin homolog; HIF, hypoxia-inducible factor; FOXC1, Forkhead box C1; TCA, tricarboxylic acid.

reprogramming and increases oxidative phosphorylation and glycolysis to promote BLCA invasion (20). The IncRNA CCDC183-AS1 serves an oncogenic role in BLCA by increasing aerobic glycolysis (79). The IncRNA HULC can bind to key enzymes of glycolysis, LDHA and PKM2, to enhance the binding of fibroblast growth factor receptor type 1, thus, increasing the phosphorylation levels of these two enzymes and promoting glycolysis (80). Ho *et al* (81) identified a group of glycolysis-related IncRNAs using The Cancer Genome Atlas database and found that these molecular-related BLCA patients had a poor prognosis and high immune infiltration, while epithelial mesenchymal transition was activated to promote tumor progression. The IncRNA UCA1 can bind to heterogeneous nuclear ribonucleoprotein (hnRNP), promote its binding to the glutamate transaminotransferase (GPT)2 promoter, enhance the expression of glutamine-derived carbon in the TCA cycle and affect glycolysis, the TCA cycle, glutamine metabolism and proliferation in BLCA (49). Another study on IncRNA UCA1 found that it could regulate hexokinase2 (HK2) to promote glycolysis in BLCA cells by activating STAT3, inhibiting miRNA143

and activating mTOR, revealing a new relationship between IncRNAs and glucose metabolism in BLCA (82).

Regulated by puerarin, circ_0020394 inhibits glycolysis and promotes apoptosis in BLCA cells (62). circFAM13B is present in low levels in BLCA and is associated with glycolysis and CD8+ T cell activation. circFAM13B can promote the function of CD8+ T cells, weaken glycolysis in BLCA cells and reverse the acidic tumor microenvironment (TME) (22). Inhibition of the acidic TME inhibits immune evasion and enhances immunotherapy sensitivity. Has-circRNA-403658 is highly expressed in BLCA cells under hypoxia and silencing its expression inhibits BLCA cell proliferation by inhibiting LDHA-mediated aerobic glycolysis (83). In conclusion, ncRNAs are associated with the metabolic reprogramming of BLCA cells in multiple ways (Fig. 1).

3. ncRNAs and lipid metabolism in BLCA

Unlike glucose metabolism, there have been few reports on lipid metabolism in BLCA; however, with the gradual understanding of fatty acid metabolism, the importance of

Table II. Regulatory ncRNAs related to lipid metabolism and their functions and mechanisms.

First author, year	Name of ncRNA	Expression	Function	Target	(Refs.)
Liu, 2022	lncDBET	Up	Promote lipid metabolism and promote proliferation	PPAR, FABP5	(50)
Logotheti, 2020	lncRNA SLC16A1-AS1	Down	Promote lipid metabolism and promote invasion	E2F1, PPARG	(20)

ncRNA, non-coding RNA; lncRNA, long non-coding RNA; PPAR, peroxisome proliferators-activated receptor; FABP5, fatty acid binding protein 5; E2F1, E2F transcription factor 1.

Table III. Regulatory ncRNAs related to amino acid metabolism and their functions and mechanisms.

First author, year	Name of ncRNA	Expression	Function	Target	(Refs.)
Yang, 2022	circTRPS1	Down	Inhibit proliferation and promote apoptosis	miR141-3p/GLS1	(23)
Chen, 2022	lncRNA UCA1	Up	Promote proliferation	hnRNP I/L, GPT2	(92)
Li, 2015	lncRNA UCA1	Up	Promote glutamate metabolism and promote proliferation	miR-16, GLS2	(45)
Zhou, 2019	lncRNA-p21	Down	Inhibition of both proliferation and invasion	GLS, α -KG	(48)

ncRNA, non-coding RNA; circ, circular RNA; lncRNA, long non-coding RNA; miR, microRNA; GLS, glutaminase; hnRNP, heterogeneous nuclear ribonucleoprotein; GPT, glutamate transaminotransferase; α -KG, α ketoglutarate.

reprogramming lipid metabolism in cancer cells is being increasingly appreciated (84). Lipids are primarily comprised of triglycerides, phospholipids, sphingolipids and cholesterol (85). Lipids serve important roles in cellular metabolism, including energy storage, fatty acid synthesis, biofilm formation and signal transmission (86). In tumor cells, migration is mainly promoted through lipid synthesis, storage and metabolism. For example, cholesterol lipids are synthesized from acetyl-CoA and NADPH through the TCA cycle and the pentose phosphate pathway (87).

How ncRNAs regulate lipid metabolism was detailed in a recent study. In BLCA, the m6A-related enzyme methyltransferase-like 14 promotes lncDBET expression through methylation modification and activates the peroxisome proliferators-activated receptor (PPAR) signaling pathway, promoting lipid metabolism in BLCA cells by directly interacting with fatty acid binding protein 5, thus, promoting the malignant progression of BCa *in vitro* and *in vivo* (50). lncRNA SLC16A1-AS1 promotes ATP production through the β -oxidation of fatty acids in BLCA, accompanied by changes in the expression of the SLC16A1-AS1:E2F1 response gene PPARG, which is critical for fatty acid β -oxidation (Table II). E2F1-induced lncRNA-SLC16A1-AS1 forms a complex with its transcription factors, promoting metabolic reprogramming of BLCA and increasing BLCA invasion (20). In summary, the ncRNA and lipid metabolism in BLCA are closely related (Fig. 2).

4. ncRNAs and amino acid metabolism in BLCA

In cells, amino acid metabolism mainly includes anabolism and catabolism. Anabolism is primarily the supply of peptides,

proteins and other nitrogenous substances to the human body. Catabolism involves the breakdown of alpha-keto acids, glutamate by transamination, deamination, or carbon dioxide. The alpha-keto acids generated by amino acid metabolism can also be transformed into sugars or lipids, or resynthesized into a number of nonessential amino acids. They can also release energy from the TCA cycle to form carbon dioxide and water (88,89). With the development of current understanding of amino acid metabolism, the role of ncRNAs in amino acid metabolism in BLCA has gained greater attention (90). Glutamine is a type of free nonessential amino acid. It participates in the anabolism of BLCA cells by converting glutaminase (GLS) to glutamate and is also an energy source for tumor cell proliferation (91).

As an important type of ncRNA, circRNAs are involved in amino acid metabolism (23). Exosome-derived circTRPS1 from BLCA cells can regulate reactive oxygen species (ROS) balance and CD8⁺ T cell depletion in BLCA cells through the circTRPS1/miR141-3p/glutaminase (GLS)1 axis (23). Metabolomics and RNA sequencing data have shown that GLS1-mediated glutamine metabolism participates in circTRPS1-mediated changes and suppresses the malignant phenotype of BLCA cells. lncRNAs are also involved in glutamine metabolism in BLCA. The lncRNA UCA1 serves an important role in glutamine metabolism in BLCA through its interaction with hnRNPI/L and UCA1 promotes the expression of glutamic-pyruvic transaminase 2 (GPT2) at the transcriptional level. Inhibition of either UCA1, hnRNPI/L, or GPT2 significantly reduces the growth of BLCA tumors and inhibits tumor progression in mouse models (92). A positive correlation between lncRNA UCA1 and RNA levels of GLS2

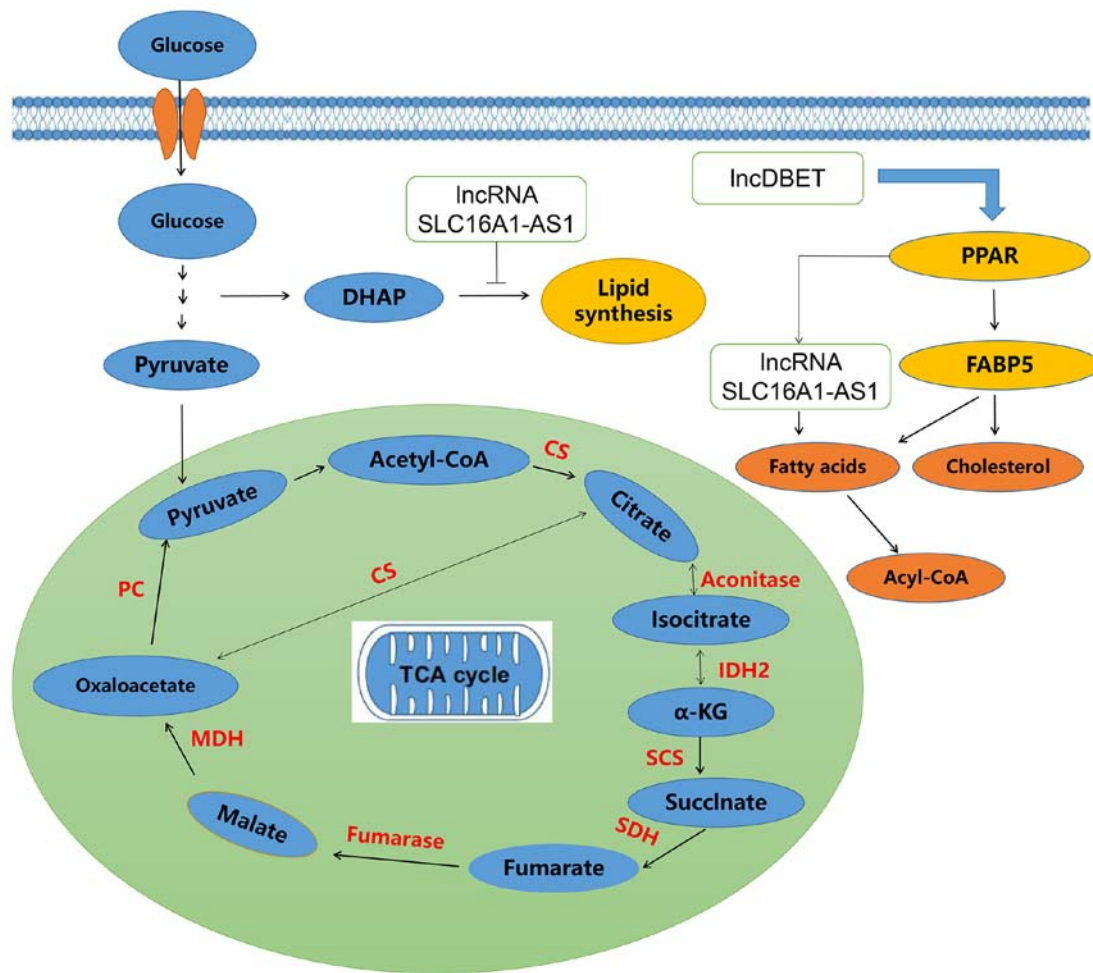


Figure 2. ncRNAs promote lipid synthesis, storage and use of cholesterol lipid metabolism in bladder cancer cells by regulating key enzymes and signaling pathways that regulate lipid metabolic processes. The major metabolites are in blue and the major metabolic enzymes in red. IncRNA, long non-coding RNA; ncRNA, non-coding RNA; DHAP, dihydroxy acetone phosphate; α-KG, α-ketoglutarate; PC, phosphoenolpyruvate carboxykinase; CS, citrate synthase; IDH, isocitrate dehydrogenases; MDH, malate dehydrogenase; SDH, succinate dehydrogenase; SCS, succinyl coenzyme A synthetase; PPAR, peroxisome proliferators-activated receptor; FABP5, fatty acid binding protein 5; Acyl-CoA, Acyl coenzyme A.

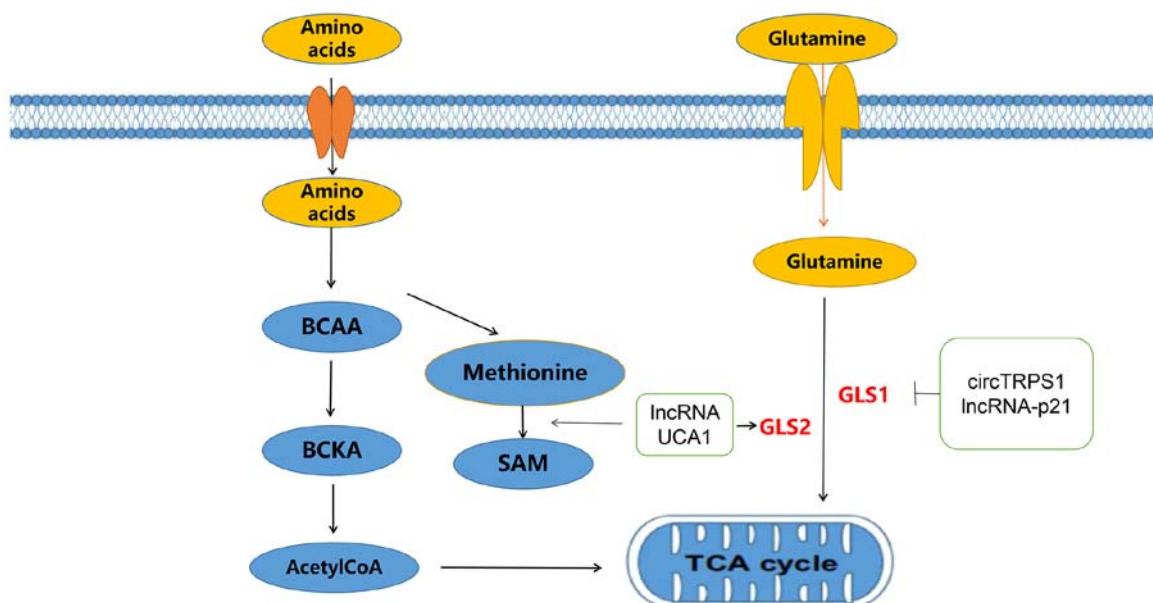


Figure 3. ncRNAs Regulation of amino acid metabolism in bladder cancer. The ncRNA regulates the metabolism of various amino acids and glutamine. The major metabolites are in blue and the major metabolic enzymes in red. ncRNA, non-coding RNA; BCAA, branched-chain amino acid; BCKA, branched-chain keto acid; SAM, sadenosyl-L-methionine; GLS1, glutaminase 1; GLS2, glutaminase 2; Acyl-CoA, Acyl coenzyme A; circ, circular RNA; IncRNA, long non-coding RNA.

in BLCA tissues and cell lines as well as the expression of GLS2 are regulated by miR-16 (Table III). Following UCA1 overexpression, the expression of both GLS2 mRNA and protein increases, whereas the expression is decreased after knockdown of UCA1 (45). UCA1 decreases ROS production and promotes mitochondrial glutamine lysis in human BLCA cells. Low expression of lincRNA-p21 in BLCA cells by negatively regulating GLS expression, intracellular glutamate and α -ketoglutaric acid and the expression abundance of lincRNA-p21 and GLS, determines the sensitivity to bis-2-(5-phenylacetyl-1,2,4-thiadiazole-2-based) ethylsulfide treatment (48). In addition, glutamine metabolism is associated with tumor drug resistance and it has been shown that lncRNAs can participate in glutamate metabolism through amino acid transporters and glutamine-metabolizing enzymes (93). lncRNAs dysregulate glutamine in cancer cells to promote tumor proliferation and metastasis by increasing chemotherapy and radiation tolerance (94). ncRNAs Play an important role in amino acid metabolism in bladder cancer (Fig. 3).

5. Conclusion and future prospects

As metabolism has become an important research topic, the participation of ncRNAs in tumor metabolic reprogramming has received extensive attention in the fields of biology and oncology. Numerous studies have shown that ncRNAs are closely related with BLCA metabolism (49,50,77,83). Metabolic reprogramming has become an important aspect of malignancy. ncRNAs affect the progression of BLCA, such as proliferation, invasion and metastasis, by participating in the metabolism of BLCA cells. Thus, these key ncRNAs involved in BLCA metabolism could serve as potential biomarkers for BLCA.

However, there are still some limitations in the current metabolic reprogramming of bladder cancer. For example, what are the causes of metabolic abnormalities? How can we treat bladder cancer by affecting the metabolic reprogramming of cancer cells? What is the mechanism of action in the metabolic reprogramming of bladder cancer? Furthermore, we lack the ncRNA knockout in animal models to study metabolic reprogramming in bladder cancer and have not investigated this model in metabolic reprogramming in bladder cancer. These are the problems to be solved by future research. An ncRNA knockout mouse model will help identify the key molecules that regulate the metabolic reprogramming of bladder cancer and provide a rationale for clinical applications.

ncRNAs regulate the metabolic reprogramming of BLCA in various ways; however, a large number of ncRNA functions and mechanisms of action still require further study, as metabolic reprogramming of BLCA not only provides an energy source for tumor progression, but also creates suitable conditions for its development. Metabolic reprogramming acts mainly through metabolism-related enzymes, which are modulated by ncRNAs, offering new options for the treatment of BLCA (45,82,83). Current research on the metabolic reprogramming of lncRNAs in BLCA is relatively extensive and offers good theoretical support for preclinical studies; however, there remain a number of areas of uncertainty, such as the cause of

metabolic abnormalities. Extensive studies are needed to identify how treatment can be more directly targeted to BLCA and how ncRNA-based therapies can be applied clinically. This requires further study of the mechanism of ncRNAs in the metabolic reprogramming of BLCA as well as theoretical support for clinical treatments in the thriving field of precision medicine.

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Availability of data and materials

Not applicable.

Authors' contributions

ZB conceived and supervised the present study and wrote, reviewed and edited the original draft of the manuscript. YM wrote, reviewed and edited the manuscript. HY, HL and QP performed data curation. SF supervised the present study, project administration and funding. All authors read and approved the final manuscript. Data sharing is not applicable to this article.

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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