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REVIEW

Long non-coding RNAs involved in cancer metabolic reprogramming

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Abstract

Metabolic reprogramming has now been accepted as a hallmark of cancer. Compared to normal cells, cancer cells exhibit different metabolic features, including increased glucose uptake, aerobic glycolysis, enhanced glutamine uptake and glutaminolysis, altered lipid metabolism, and so on. Cancer metabolic reprogramming, which supports excessive cell proliferation and growth, has been widely regulated by activation of oncogenes or loss of tumor suppressors. Here, we review that long non-coding RNAs (lncRNAs) can affect cancer metabolism by mutual regulation with oncogenes or tumor suppressors. Additionally, the interaction of lncRNAs with crucial transcription factors, metabolic enzymes or microRNAs can also effectively modulate the processes of cancer metabolism. LncRNAs-derived metabolism reprogramming allows cancer cells to maintain deregulated proliferation and withstand hostile microenvironment such as energy stress. Understanding the functions of lncRNAs in cancer metabolic reprogramming that contributes to carcinogenesis and cancer development may help to develop novel and effective strategies for cancer diagnosis, prognosis and treatment.

Keywords Long non-coding RNA · Cancer · Metabolism

Introduction

Metabolism reprogramming is regarded as an emerging hallmark of cancer [1]. Cancers share a common trait of uncontrolled and fast cell proliferation, which drives reprogramming of cellular energy metabolism and macromolecules biosynthesis to satisfy the requirement of cancer expansion and dissemination. Reprogramming of cancer metabolism signifies cancer-specific metabolic alterations, including dysregulation of glucose and glutamine metabolism, alterations of lipid synthesis and decomposition, and rewiring of mitochondrial function [2–5]. These phenotypes of cellular metabolism reprogramming are direct and indirect consequences of oncogenic events (activation of oncogenes [6, 7] or loss of tumor suppressors [8, 9]) or constraints imposed by the tumor microenvironment (e.g., hypoxia [10] and nutrient scarcity [11]). As a primary feature during carcinogenesis, metabolic reprogramming contributes to the establishment and maintenance of the cancerogenic state [12, 13].

LncRNAs are defined as a group of transcripts longer than 200 nucleotides, with little or no protein-coding potential. Through interactions with cellular macromolecules including chromatin, protein or RNA, lncRNAs can regulate gene expression by controlling chromatin architecture, promoting the assembly of protein complexes or disrupting protein–protein interactions, sequestering miRNA away from target mRNA as competitive endogenous RNA, and affecting mRNA metabolism including mRNA splicing, stability, and translation, etc [14]. LncRNAs have been determined to be involved in many physiologic and pathologic processes including differentiation, development and disease [15–17]. Multiple evidence verified that lncRNAs are aberrantly expressed in various cancers where they act as oncogenes [18] or tumor suppressors [19], which qualifies their potential utilization for cancer diagnosis, monitoring, prognosis, and prediction for therapeutic responsiveness [14]. Although microRNAs (miRNAs), one class of small non-coding RNAs, have been well documented for their involvement in cancer metabolism [20, 21], the roles of lncRNAs in the regulation of metabolism and energy homeostasis remain largely unknown. Here, we review the recent findings on the functions of lncRNAs in cancer metabolism reprogramming, with particular emphasis on how lncRNAs regulate glucose,

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glutamine and lipid metabolism, as well as their response to energy stress in cancer cells.

Regulation of central metabolism by lncRNAs

Activation of oncogenes or loss of tumor suppressors promotes metabolism reprogramming in cancer and supports growth and survival of cancer cells [6–9]. The ability of oncogenes (e.g., c-*MYC* [22, 23] and *HIF-1α* [24, 25]) and tumor suppressors (e.g., *p53* [26] and *AMPK* [27]) to alter cellular metabolism have been well established. The oncogenic transcription factor c-Myc is a master regulator that not only controls glucose [28, 29], glutamine [30, 31] and lipid metabolism [32, 33] in cancer, but also supports nucleotide [34] and serine biosynthesis [35] and formation of new organelles, particular ribosomes [36] and mitochondria [37]. A amount of metabolic genes are activated by c-Myc, including *GLUT1*, *HK2*, *LDH-A* and *MCT* in glycolysis, *SLC1A5* and *GLS1* in glutaminolysis, as well as *ACLY*, *ACACA*, *FASN* and *SCD* in lipid synthesis [2, 38]. However, tumor suppressor p53 represses glucose transport [39], glycolysis [40] and lipid synthesis [41], and promotes fatty acid oxidation [42], glutaminolysis [43] and mitochondrial respiration [44]. Transcription, protein stability and functional activity of oncogenes or tumor suppressors can be regulated by multiple factors in cancer cells, leading to abnormal metabolism and further tumor progression or inhibition [22, 38, 45].

PCGEM1, an androgen-induced prostate-specific lncRNA, is the first lncRNA that has been identified to function as a master regulator of metabolic reprogramming in cancer [46]. Although PCGEM1 facilitates androgen-induced metabolic gene expression through the activation of androgen receptor, it is c-Myc that predominantly mediates the regulation of metabolic genes by PCGEM1. By directly interacting with c-Myc and functioning as a c-Myc coactivator, PCGEM1 enhances c-Myc transactivation potency and facilitates the recruitment of c-Myc to the chromatin target sites, therefore, controlling expression profiles of multiple key metabolic pathways [46]. On the one hand, PCGEM1 overexpression in prostate cells enhances glucose uptake and lactate production, indicating an increased aerobic glycolysis. On the other hand, elevated cellular levels of citrate, G6PD activity, and NADPH in PCGEM1-overexpressing cells demonstrate increased biosynthesis of fatty acid, nucleotide and redox control by PCGEM1 [46]. The correlation of PCGEM1 with high-risk prostate cancer patients [47] and its specific role in tumor metabolism [46] makes it a promising therapeutic target for prostate cancer. Another lncRNA, colorectal neoplasia differentially expressed transcript (CRNDE), has also been reported to regulate genes involved in central metabolism [48]. Transcripts from the *CRNDE* gene locus comprise of two categories of lncRNAs: transcripts retaining intronic sequences localized in the nucleus and transcripts lacking intronic sequences enriched in the cytoplasm [48]. Nuclear CRNDE are specifically downregulated by insulin and IGF1/2 in colorectal cancer cells. It appears to regulate genes at both transcriptional and post-transcriptional levels [49], and many of these genes are involved in glucose and lipid metabolism [48].

Regulation of glucose metabolism by lncRNAs

Glucose is a major cellular energy source, providing energy mostly in the form of adenosine triphosphate (ATP). After being imported into cells by transporters, glucose is broken down via glycolysis, generating energy and building blocks for cell growth and proliferation [2, 29]. Owing to an accelerated glucose uptake or undergoing aerobic glycolysis other than oxidative phosphorylation in mitochondria, cancer cells usually exhibit a higher rate of glucose metabolism than normal cells [50]. HOTAIR, a highly expressed lncRNA in hepatocellular carcinoma cells and tissues, promotes cell proliferation by regulating glucose metabolism, partly through inducing glucose transporter 1 (GLUT1) expression via activating the mTOR pathway, or through interacting with GLUT1 directly [51] (Fig. 1a). As a lncRNA overexpressed in osteosarcoma cells and tissues, PVT1 not only promotes uptake of glucose but also enhances production of lactate by acting as a molecular sponge of miR-497, which directly targets and suppresses the expression of the rate-limiting glycolytic enzyme hexokinase 2 (HK2) [52] (Fig. 1b). Another study showed that lncRNA UCA1 promotes glycolysis in bladder cancer cells by activating the mTOR pathway, which mediates the regulation of UCA1 to HK2 through activation of STAT3 and repression of miR-143 [53] (Fig. 1c). Although all above lncRNAs play important roles in regulating glucose metabolism reprogramming in cancer, the studies are limited to in vitro observations.

However, several other lncRNAs have been demonstrated to regulate glucose metabolism and affect cancer development both in vitro and in vivo. LincRNA-p21, a class of large intergenic non-coding RNAs, has been reported to be induced by hypoxia and is essential for hypoxia-enhanced glycolysis [54]. Under conditions of hypoxia, HIF-1α is induced and activates lincRNA-p21 at the transcriptional level. LincRNA-p21 in return stabilizes HIF-1α by disrupting the VHL-HIF-1α interaction, which mediates HIF-1α ubiquitination and degradation (Fig. 1d). As a result, HIF-1α is accumulated and promotes glycolysis under hypoxia. Additionally, validation of lincRNA-p21 in promoting tumor growth by mouse xenograft models indicates lincRNA-p21

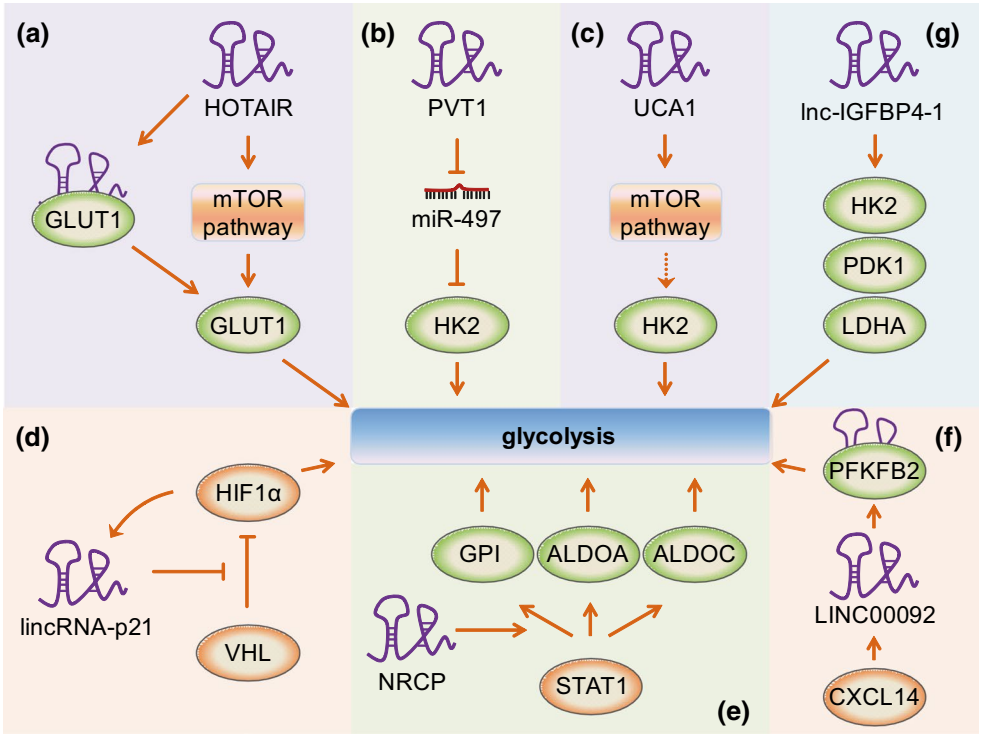

Fig. 1 Regulation of glucose metabolism by lncRNAs. **a** HOTAIR enhances GLUT1 expression through activating the mTOR pathway, or through interacting with GLUT1 directly. **b** PVT1 acts as a molecular sponge of miR-497, which directly targets and suppresses the expression of HK2. **c** UCA1 promotes glycolysis by activating the mTOR pathway, which regulates the expression of HK2. **d** Under conditions of hypoxia, HIF-1α activates the transcription of lincRNA-p21. In return, lincRNA-p21 stabilizes HIF-1α by inhibiting VHL-mediated HIF-1α ubiquitination and degradation. **e** NRCP promotes glycolysis by enhancing the regulation of STAT1 to its downstream target genes, including *GPI*, *ALDOA*, and *ALDOC*. **f** LINC00092 is induced by CXCL14 and enhances glycolysis by interaction with PFKFB2. **g** Lnc-IGFBP4-1 enhances glycolysis by upregulating the expression of metabolic enzyme genes, including *HK2*, *PDK1*, and *LDHA*. Please see more detail in the text. "down arrow" indicates a promotion effect, but "perpendicular sign" indicates an inhibition effect. Solid line indicates a direct effect, but dashed line indicates an indirect effect. *HOTAIR* HOX transcript antisense intergenic RNA, *GLUT1* glucose transporter 1, *PVT1* plasmacytoma variant translocation 1, *HK2* hexokinase 2, *UCA1* urothelial cancer-associated 1, *NRCP* long non-coding RNA ceruloplasmin, *GPI* glucose-6-phosphate isomerase, *ALDOA* aldolase, fructose-bisphosphate A, *ALDOC* aldolase, fructose-bisphosphate C, *PFKFB2* 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase, *PDK1* pyruvate dehydrogenase kinase 1, *LDHA* lactate dehydrogenase A

would be a valuable therapeutic target for cancer [54]. NRCP is a non-coding splice variant of ceruloplasmin-coding gene with deletion of exon 11 and several nucleotide variations in the 3′ end exons [55]. Rupaimoole et al. have observed that NRCP is a top-upregulated lncRNA in ovarian tumor samples compared with normal ovarian tissues [55]. Additionally, in Kaplan–Meier survival analyses, patients with high tumoral NRCP expression have significantly worse overall survival. Furthermore, they revealed that NRCP promotes glycolysis and tumor progression by functioning as an intermediate binding partner between STAT1 and RNA polymerase II, which results in enhanced expression of downstream target genes, including glucose-6-phosphate isomerase (GPI), ALDOA, and ALDOC (Fig. 1e). Together with the finding that NRCP silencing reduced tumor growth and metastasis in vivo in an orthotopic mouse model of ovarian cancer [55], their study highlights the potential for targeting NRCP in the treatment of this kind of cancer. Another lncRNA LINC00092 was also reported to be upregulated and involved in the alteration of glycolysis in ovarian cancer [56]. *LINC00092* is induced upon stimulation by CXCL14, which is a premetastatic factor secreted by cancer-associated fibroblasts (CAFs) in ovarian cancer and promotes ovarian cancer metastasis in vitro and in vivo. By directly interacting with 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB2), a glycolytic enzyme, LINC00092 enhances glycolysis, promotes metastasis, and sustains the local supportive function of CAFs within tumor microenvironment [56] (Fig. 1f). Recently, one study reported that lnc-IGFBP4-1 was a significantly up-regulated lncRNA in lung cancer tissues compared to corresponding non-tumor tissues [57]. It increases ATP production and enhances aerobic glycolysis by upregulating the expression of metabolic enzymes, including HK2, PDK1, and

LDHA (Fig. 1g). Possibly through reprogramming tumor cell energy metabolism, lnc-IGFBP4-1 plays a positive role in cell proliferation and metastasis. This study suggests lnc-IGFBP4-1 may be a potential biomarker or therapeutic target for lung cancer [57].

Regulation of glutamine metabolism by lncRNAs

As another kind of important cellular energy source, glutamine is also essential for the survival and proliferation of most cancer cells [58]. Through providing nitrogen and carbon, glutamine metabolism is critical for many fundamental cell functions in cancer cells, including energy generation, macromolecular synthesis, activation of cell signaling, and maintenance of redox balance [59]. After being imported into cytoplasm via transporters, glutamine is first converted into glutamate by glutaminase (GLS/GLS2) that is the rate-limiting enzyme of glutaminolysis. Besides regulating glucose metabolism [53], UCA1 has also been reported to promote glutamine metabolism in human bladder cancer [60]. UCA1 and GLS2 were shown to be positively correlated in bladder cancer tissues and cell lines. By binding to miR-16 as a molecular sponge, UCA1 improves GLS2 expression through UCA1–miR-16–GLS2 axis, leading to increased glutaminolysis and repressed ROS formation in bladder cancer cells (Fig. 2a). Another recent study demonstrated that lncRNA HOTTIP was involved in GLS1-mediated glutaminolysis in hepatocellular carcinoma (HCC) [61] (Fig. 2b). MiR-192 and miR-204 are two miRNAs identified to suppress HOTTIP expression via the Argonaute 2-mediated RNA interference pathway. Ectopic expression of miR-192, miR-204 or HOTTIP siRNA significantly represses GLS1 expression, thereby interrupts glutaminolysis and inhibits HCC growth in vitro and in vivo [61]. Therefore, miR-192/-204-HOTTIP axis may be a potential target for prognostic and therapeutic implications in HCC.

Another lncRNA Colon Cancer-Associated Transcript 2 (CCAT2), whose coding gene locates at the highly conserved 8q24 region harboring cancer risk-associated rs6983267 SNP, not only boosts glycolysis but also regulates glutamine metabolism in an allele-specific manner in vitro and in vivo [62]. For the two alleles of the rs6983267 SNP, the CCAT2 G allele is related to greater colorectal cancer predisposition than the T allele [63]. Although both CCAT2 G and T allele enhance glucose uptake in colon cancer cells, it is CCAT2 G allele but not T allele that increases oxygen consumption and intracellular glutamate production [62]. Mechanistically, CCAT2 G allele preferentially binds CFIm25, the small 25 kDa subunit of the Cleavage Factor I (CFIm) complex, which binds to UGUA sequences within intron 14 of GLS pre-mRNA. Whereas CCAT2 T allele prefers

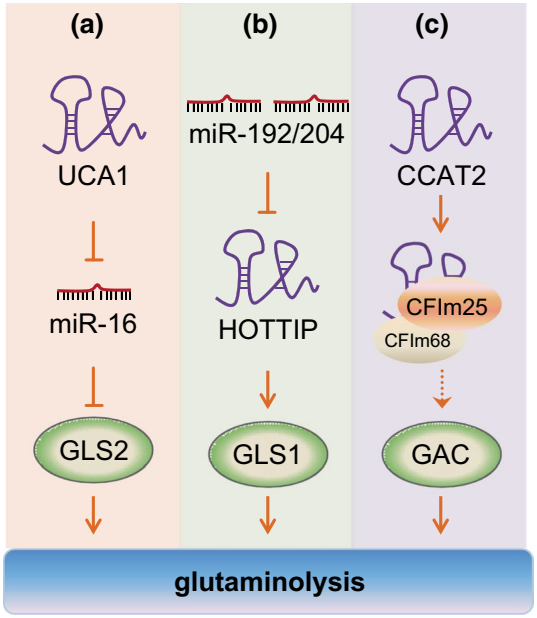

Fig. 2 Regulation of glutamine metabolism by lncRNAs. **a** UCA1 functions as a molecular sponge of miR-16 and releases the expression of its target GLS2, which converts glutamine into glutamate. **b** HOTTIP, a target of both miR-192 and miR-204, is involved in glutaminolysis through its downstream gene *GLS1*. **c** CCAT2 alleles bind the CFIm complex, regulate the alternative splicing of *GLS*, and induce the production of GAC, which promotes the cancer progression. Please see more detail in the text. *GLS* glutaminase, *HOTTIP* HOXA transcript at the distal tip, *CCAT2* colon cancer-associated transcript 2, *CFIm* cleavage factor I, *GAC* glutaminase isoform C

to bind CFIm68, the larger 68 kDa subunit of the CFIm complex. The interaction between CCAT2 G allele and the CFIm complex regulates alternative splicing of glutaminase (GLS) by selecting the poly(A) site in intron 14 of the GLS pre-mRNA, inducing the production of GAC splice isoform (glutaminase isoform C) other than KGA (glutaminase kidney isoform) (Fig. 2c). For reason of possessing a higher enzymatic activity than KGA, GAC is a more aggressive splicing variant of glutaminase and promotes in vitro cell proliferation and migration and in vivo metastases [62]. This is the first example that a lncRNA serves as a regulator of glutamine metabolism by controlling alternative splicing of glutaminase.

Regulation of lipid metabolism by lncRNAs

In addition to aberrant glucose and glutamine metabolism, dysregulation of lipid metabolism has also been identified as one character of cancer metabolic reprogramming [2]. Lipid metabolic network contains import of exogenous lipids or cholesterol, catabolic pathways of lipids (fatty acid oxidation), de novo synthesis pathways including

lipogenesis and cholesterol synthesis, as well as storage in lipid droplets and export of high-density lipoproteins into circulations [64, 65]. Fatty acids need to be transformed to acyl-CoA before they enter into the subsequent anabolism or catabolism. Acyl-CoA synthetases, which catalyze the conversion of fatty acids to fatty acid-CoA, are classified into very long-chain acyl-CoA synthases (ACSVL), long-chain acyl-CoA synthases (ACSL), medium-chain acyl-CoA synthases (ACSM) and short-chain acyl-CoA synthases (ACSS) according to the carbon chain length of the targeted fatty acid [66]. Highly upregulated in liver cancer (HULC) is the first lncRNA identified to be specifically upregulated in hepatocellular carcinoma [67]. Cui et al. revealed that HULC facilitates the deregulation of lipid metabolism through miR-9/PPARA/ACSL1 pathway in hepatoma cells [68] (Fig. 3a). HULC downregulates miR-9 by inducing methylation of CpG islands in its promoter, then releases the inhibition of PPARA by miR-9. Next, the transcriptional factor PPARA activates *ACSL1*. ACSL1 can catalyze the initial step in cellular long-chain fatty acid metabolism in mammals and participate in the formation of triglycerides and cholesterol in the liver. Furthermore, HULC-modulated abnormal lipid metabolism promotes tumor growth in vivo [68].

Recently, Andersen's research group reported lncRNA SNHG16 was involved in lipid metabolism [69]. Their study found that SNHG16 was up-regulated in colorectal adenomas and all stages of adenocarcinomas when compared to adjacent normal colon mucosa samples. The mechanism behind SNHG16 deregulation in colorectal cancer (CRC) may be attributed to the transcriptional activation of the SNHG16 locus by the Wnt signaling pathway-regulated transcription factors, including c-Myc (Fig. 3b). Knockdown of SNHG16 suppresses growth, increases apoptotic death, and decreases migration in vitro. This evidence indicates that SNHG16 plays an oncogenic role in CRC. By binding to AGO and HuR, SNHG16 may function as a microRNA sponge and relieve miRNA-mediated repression of targets, including genes involved in fatty acid biosynthesis, such as fatty acid desaturase family member stearoyl-CoA desaturase (SCD) [69]. Another recent study reported that lncRNA LNMICC, a direct target of miR-190, is upregulated in cervical cancer with lymph node metastasis and associated with poor prognosis [70]. Mechanistically, LNMICC recruits NPM1 to the promoter region of *FABP5* and enhance transcription of *FABP5*, thereby modulates reprogramming of fatty acid metabolism (Fig. 3c). Moreover, through FABP5-mediated fatty acid metabolism, LNMICC facilitate lymph node metastasis of cervical cancer. This study highlight LNMICC as a candidate prognostic biomarker and therapeutic target in cervical cancer.

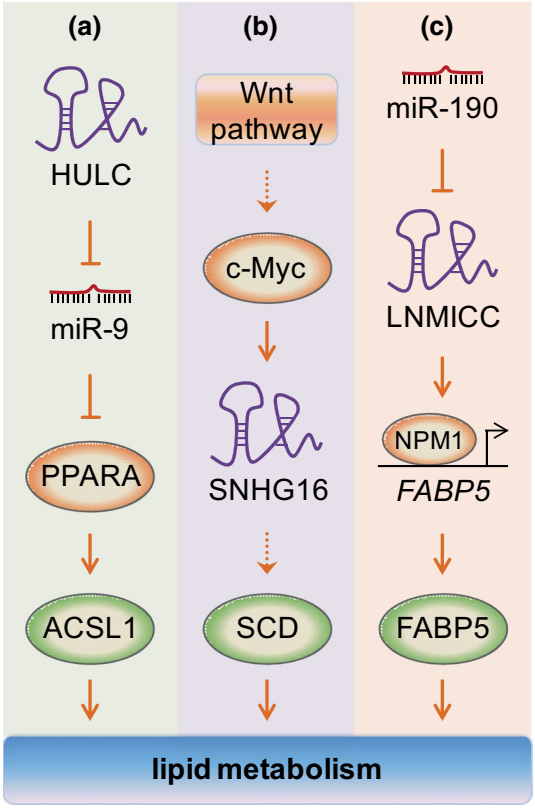

Fig. 3 Regulation of lipid metabolism by lncRNAs. **a** HULC modulates lipid metabolism by miR-9/PPARA/ACSL1 pathway in hepatoma cells. **b** SNHG16, which is activated by the Wnt pathway/c-Myc axis in colorectal cancer, promotes the expression of genes involved in fatty acid biosynthesis, such as SCD. **c** LNMICC, a target of miR-190, induces binding of NPM1 to the promoter of *FABP5* and activates its expression in cervical cancer. Consequently, FABP5 regulates the reprogramming of fatty acid metabolism. Please see more detail in the text. *HULC* highly upregulated in liver cancer, *PPARA* peroxisome proliferator activated receptor alpha, *ACSL1* acyl-CoA synthetase long chain family member 1, *SNHG16* snoRNA host gene 16, *SCD* stearoyl-CoA desaturase, *LNMICC* lncRNA associated with lymph node metastasis in cervical cancer, *NPM1* nucleophosmin 1, *FABP5* fatty acid binding protein 5

Response of lncRNAs to energy stress

Metabolic composition of the extracellular environment around cancer cells is usually altered for their rapid proliferation, which results in tumor microenvironment with characters of hypoxia, downregulated pH, increased redox stress, and nutrient depletion [71]. Tumor cells always ingeniously scheme out various strategies to adapt to the harsh environment, such as energy stress [72–74]. A key signaling pathway involved in energy stress adaptation is the liver kinase B1 (LKB1)–AMP–activated protein kinase (AMPK) pathway [75]. Energy stress strikingly induces phosphorylation of AMPKα by LKB1 and activates AMPK. Then, AMPK phosphorylates a number of downstream targets to

inactivate ATP-consuming anabolic processes, such as mammalian target of rapamycin complex 1 (mTORC1)-regulated protein synthesis [76]. AMPK also promotes autophagy and cell survival under energy stress through direct phosphorylation of ULK1, the mammalian autophagy-initiating kinase [77, 78]. Liu et al. reported lincRNA neighbour of BRCA1 gene 2 (NBR2) was involved in metabolic stress response by regulating the function of AMPK [79] (Fig. 4a). Under the condition of energy stress such as glucose starvation, NBR2 expression was induced through the LKB1–AMPK pathway. However, NBR2 depletion attenuated glucose starvation-induced AMPK activation and mTORC1 inactivation. Mechanistically, NBR2 regulates AMPK activity under energy stress by interaction with its kinase domain AMPKα, which is the catalytic subunit of AMPK. Therefore, the functional effects of NBR2 are partially mediated by AMPK, which may serve to explain the phenomena that

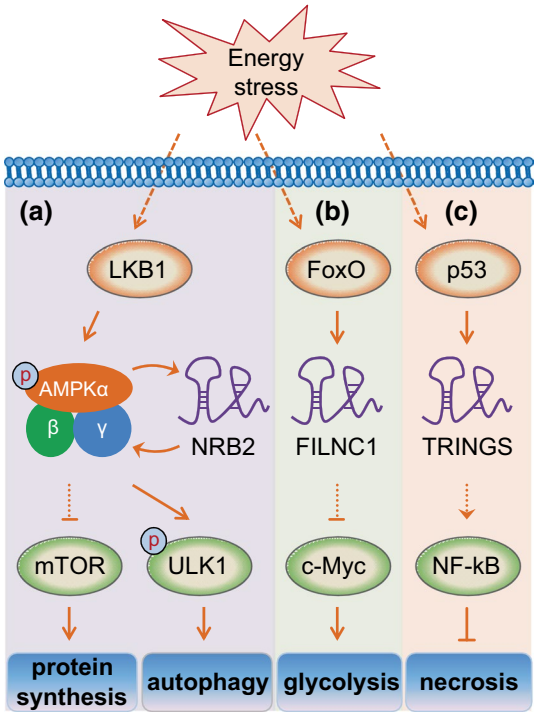

Fig. 4 Response of lncRNAs to energy stress. Under the condition of energy stress such as glucose starvation, the expression of lncRNAs NBR2, FILNC1, and TRINGS are activated by LKB1–AMPK pathway, p53, and FoxO, respectively. **a** NBR2 enhances AMPK activity under energy stress by interaction with its kinase domain AMPKα. On the one hand, AMPK inhibits mTOR signaling that mediates protein synthesis. On the other hand, AMPK directly phosphorylates and activates the autophagy regulator ULK1. **b** FILNC1 suppresses the protein level of c-Myc, a master regulator of glycolysis. **c** NF-kB signaling is promoted by TRINGS and protect cancer cells from necrosis. Please see more detail in the text. *NBR2* neighbour of BRCA1 gene 2, *FILNC1* FoxO-induced long non-coding RNA 1, *TRINGS* Tp53-regulated inhibitor of necrosis under glucose starvation

NBR2 deficiency leads to increased apoptosis and decreased autophagy in response to energy stress [79].

Additionally, FoxO-induced long non-coding RNA 1 (FILNC1), another lncRNA, was reported to repress c-Myc-mediated energy metabolism under energy stress in renal cancer [80] (Fig. 4b). In response to energy stress such as glucose starvation, FoxO transcription factors enhanced the expression of FILNC1. Furthermore, glucose starvation also induced the interaction of FILNC1 with AUF1, which can bind to AU-rich elements within 3′ UTR of c-Myc mRNA and promote c-Myc translation without affecting c-Myc mRNA level. As a result, AUF1 was sequestered from binding to c-Myc mRNA, resulting in downregulated protein level of c-Myc, a master transcription factor regulating most of the glycolytic enzymes [2, 38]. Consistently, FILNC1 deficiency increased the expression of various genes involved in glucose uptake, glycolysis, and lactate secretion under glucose starvation condition, thereby led to enhanced glucose uptake and lactate production [80]. Therefore, FILNC1 controls energy metabolism reprogramming under energy stress conditions by repressing c-Myc protein level via a post-transcriptional regulation. Recently, Wu's research group revealed that lncRNA TRINGS was induced by p53 and protected cancer cells from necrosis induced by glucose starvation [81] (Fig. 4c). p53 activated TRINGS by physically interacting with p53 response elements in the promoter region of *TRINGS*. As a consequence of p53 up-regulation under glucose starvation, TRINGS was significantly induced in cancer cells and protected cancer cells from necrotic cell death. Mechanistically, glucose starvation-induced TRINGS impairs the interaction between STRAP and GSK3β by competitive binding to STRAP, leading to increased GSK3β phosphorylation at serine 9 that inhibited GSK3β activity [81]. Therefore, inhibition of NF-kB signaling by GSK3β is released to protect cancer cells from necrosis [82]. Taken together, TRINGS promotes cell survival under glucose starvation through the STRAP–GSK3β–NF-kB axis [81].

Conclusions

Carcinogenesis and cancer development are dependent on the reprogramming of cellular metabolism, which is precisely controlled by the activation of oncogenes and inactivation of tumor suppressors. The metabolic reprogramming enables cancer cells acquire increased nutrient and biosynthesis and escape hostile environment, which facilitates cancer development [83–85]. We summarize here that on the one hand, lncRNAs in cancer can be regulated by oncogenes (e.g., *c-Myc* [69]) or tumor suppressors (e.g., *p53* [81]). On the other hand, lncRNAs can also affect the expression or function of oncogenes (e.g., *HIF-1α* [54] and *c-Myc* [46, 80]), tumor suppressors

Table 1 Long non-coding RNAs involved in regulation of cancer metabolic reprogramming

	LncRNAs	Target	Cancer type	References
Central metabolism	PCGEM1	c-Myc	Prostate cancer	[46]
	CRNDE	Multiple metabolic genes	Colorectal cancer	[48]
Glucose metabolism	HOTAIR	mTOR pathway, GLUT1	Hepatocellular carcinoma	[51]
	PVT1	miR-497/HK2 axis	Osteosarcoma	[52]
	UCA1	mTOR pathway	Bladder cancer	[53]
	lincRNA-p21	HIF-1α	Ovarian cancer	[54]
	NRCP	STAT1	Ovarian cancer	[55]
	LINC00092	PFKFB2	Ovarian cancer	[56]
	lnc-IGFBP4-1	HK2, PDK1 and LDHA	Lung cancer	[57]
Glutamine metabolism	UCA1	miR-16-GLS2 axis	Bladder cancer	[60]
	HOTTIP	GLS1	Hepatocellular carcinoma	[61]
	CCAT2	CFIm-GLS axis	Colon cancer	[62]
Lipid metabolism	HULC	miR-9/PPARA/ACSL1 axis	Hepatocellular carcinoma	[68]
	SNHG16	Multiple miRNAs	Colorectal cancer	[69]
	LNMICC	FABP5	Cervical cancer	[70]
Energy stress	NBR2	AMPK	Renal cancer	[79]
	FILNC1	AUF1	Renal cancer	[80]
	TRINGS	STRAP	Osteosarcoma	[81]

(e.g., *AMPK* [79]), metabolic enzyme genes [48, 57, 61], as well as transcription factors [70] and signaling pathway [51, 53] (Table 1). Additionally, the interaction of lncRNAs with crucial transcription factors [55, 80], metabolic enzymes [56] or miRNAs [52, 60] can effectively regulate their function or activity, modulate the processes of cancer metabolism, and influence cancer progression. Through acting as oncogenes or tumor suppressors, lncRNAs drive metabolic reprogramming that allows cancer cells to maintain deregulated proliferation, withstand metabolic challenges of poor oxygen and nutrient limitation, and sustain the surrounding microenvironment suitable for tumor growth and dissemination.

Recently, Natalya Pavlova and Craig Thompson have organized known cancer-associated metabolic changes into six hallmarks, including deregulated uptake of glucose and amino acids, increased demand for nitrogen, metabolic interactions with the microenvironment, and so on [71]. In this review, we have highlighted lncRNAs as an important class of regulators in cancer metabolism. Nevertheless, function and species of lncRNAs, which are involved in affecting hallmarks of cancer metabolic reprogramming, remain far from being clarified and need to be further discovered. Comprehensive understanding of which and how lncRNAs mediate regulation of metabolism reprogramming in tumor cells may facilitate the development of lncRNA inhibitors. Consequently, investigation on the functional roles and action mechanisms of lncRNAs in regulating cancer metabolism would help to develop lncRNAs as valuable targets for the diagnosis, prognosis, or treatment of human cancers.

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