Molecular Therapy
Review

The emerging regulatory roles of long non-coding RNAs implicated in cancer metabolism

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Compared to normal cells, cancer cells exhibit specific metabolic characteristics that facilitate the growth and metastasis of cancer. It is now widely appreciated that long non-coding RNAs (lncRNAs) exert extensive regulatory effects on a spectrum of biological processes through diverse mechanisms. In this review, we focus on the rapidly advancing field of lncRNAs and summarize the relationship between the dysregulation of lncRNAs and cancer metabolism, with a particular emphasis on the specific roles of lncRNAs in glycolysis, mitochondrial function, glutamine, and lipid metabolism. These investigations reveal that lncRNAs are a key factor in the complexity of malignant cancer metabolism. Only through understanding the relevance between lncRNAs and cancer metabolic reprogramming can we open a new chapter in the history of carcinogenesis, one that promises to alter the methods of cancer diagnosis and treatment.

INTRODUCTION

Energy metabolism refers to the set of substances and chemical transformations via enzyme-catalyzed reactions within the cells of organisms.[1] The process of metabolism can be divided into anabolism and catabolism, which focus either on using energy to make basic molecules or on harvesting energy from the breakdown of molecules. Compared with normal cells, the metabolic ecology of cancer cells is more complex. To satisfy the requirements of tumor growth and metastatic dissemination, cancer cells can reprogram metabolism, which is regarded as a hallmark of cancer.[2,3] There are some cancer-associated metabolic changes including excessive glucose and/or glutamine uptake, alterations in lipid metabolism, and increased dependence on aerobic glycolysis.[4] Accumulating evidence implies that cancer metabolism can be impacted by signaling pathways and eventually lead to the inactivation of tumor suppressor genes or activation of oncogenes, such as TP53, Myc, and hypoxia inducible factor-1 (HIF-1).[5,6] However, we are still far from a comprehensive understanding of cancer-associated metabolic reprogramming, and thus, elucidation of the molecular mechanisms underlying metabolic reprogramming is of great importance.

With rapid advancements in transcriptome sequencing technology and bioinformatics, an increasing number of non-coding RNAs (ncRNAs) have been annotated and investigated. According to size, these ncRNAs can be broadly grouped into two major classes. Long ncRNAs (lncRNAs) contain RNA transcripts longer than 200 nucleotides (nt) with no or limited protein coding potential.[3,7] It is important to note that lncRNAs are broadly defined and can be subclassified into several classes, including intergenic transcripts, enhancer RNAs, and exonic or intronic transcripts in either the antisense or sense orientation (Figure 1).[8] Analogous to mRNAs, many identified lncRNAs are transcribed by RNA polymerase II (RNA pol II) and undergo 5′ end capping and 3′ end polyadenylation.[9,10]

lncRNAs are diverse and numerous. In many instances, lncRNAs are located within cytosolic or nuclear fractions.[11] Compared with mRNA, the half-lives of lncRNAs appear to be more important during biological processes because of their limited protein coding potential. In 2012, Marcel E. Dinger and John S. Mattick[12] performed a genome-wide analysis of lncRNA stability by custom microarrays. They revealed that lncRNA half-lives vary over a wide range. *cis*-antisense or intergenic lncRNAs are more stable than those transcribed from introns. According to some reports, factors such as exosomes and microRNAs (miRNAs) degrade lncRNAs.[13,14] Recently, studies

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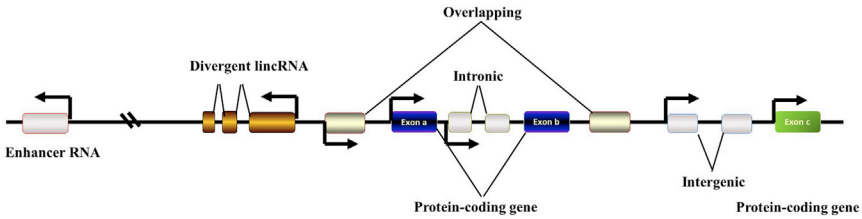

Figure 1. Classification of lncRNAs
lncRNAs can be further subclassified into divergent, overlapping, intronic, and intergenic lncRNAs on the grounds of their intersection with protein-coding genes.

have reported that RNA or ribosome-binding patterns can also affect lncRNA stability.[15,16] For example, lncRNA-highly expressed in GBC (HGBC) specifically binds to the RNA-binding protein HuR and is stabilized by HuR. In addition, RNA methylation has also been revealed to be associated with RNA metabolic processes. Chen and colleagues[17] found that ALKBH5-mediated m^6A modification contributes to the stability of PVT1. Consistently, another study identified that NSUN2-mediated m^5C modification of H19 lncRNA can increase its stability.[18] However, the underlying regulatory pathways affecting lncRNA stability remain largely undefined.

Over the past several years, multiple studies have begun to advance the idea that lncRNAs are not just "junk products" of transcription but crucial supplements to proteins and other effectors in complex regulatory networks.[19] Given that lncRNAs show strict biological regulation and participate in a spectrum of cellular processes, misregulated lncRNA expression can cause various human diseases and cancers.[20,21] lncRNAs exhibit complex modulatory roles via various mechanisms, including functioning as scaffolds for chromatin-protein interactions and regulating mRNA splicing, protein translation, miRNA sequestration, and so on.[22] Notably, although miRNA "sponges" have been a hot area of research for several years,[23] the competing endogenous RNA (ceRNA) hypothesis remains controversial. The *in vivo* data of Denzler et al.[24] indicated that modulation of miRNA target abundance is unlikely to lead to significant effects on gene expression through a ceRNA effect.[25] Recent studies have discovered a novel regulatory connection between miRNAs and their target genes, named as target-directed miRNA degradation (TDMD). Extended base pairing with a target can expose the 3′ end of the miRNA from the argonaute (AGO) PAZ domain or AGO proteolysis through the ubiquitin-proteasome pathway, resulting in miRNA degradation.[26–29] lncRNA CYRANO mediates miRNA (miR)-7 degradation through TDMD.[30] Owing to the major transcriptional and post-transcriptional regulatory ability of lncRNAs in cell proliferation, metastasis, and survival, it is now well recognized that lncRNAs are emerging stars in development and progression.[31] In this review, we will discuss in detail the pivotal roles of lncRNAs in the regulation of cancer metabolism.

THE OVERVIEW OF CANCER METABOLISM AND lncRNAs

Carcinogenesis is a multifactor and multistage process. During this process, cancer cells must overcome the biosynthetic demands for proliferation and metastasis. As a result, the absence of sufficient metabolic resources might have disastrous consequences for the cell if there is an attempt to grow rapidly. To avoid this, the aberrant loss of tumor suppressors and/or activated oncogenes has an impact on signaling pathways, which result in metabolic reprogramming, particularly in the hypoxic microenvironment.[32,33] Metabolic reprogramming allows cancer cells to maintain unlimited proliferation and metastasis potential by supplying materials and corrupting the surrounding microenvironment.[4] Emerging evidence favors the hypothesis that some cancer-related lncRNAs are key players in enabling cancer cells to overcome metabolic stress and complete metabolic reprogramming.[34] In Table 1 and Figure 2, we provide an overview of how lncRNAs control the cancer metabolism.

lncRNAs REGULATE GLUCOSE METABOLISM IN CANCER

The preference for glycolysis over oxidative phosphorylation to generate energy regardless of oxygen availability, which is a unique metabolic phenotype that characterizes cancer cells, has been defined as "aerobic glycolysis" or the "Warburg effect."[68,69] Compared with mitochondrial oxidative phosphorylation, glycolysis produces low levels of ROS (reactive oxygen species) that can cause apoptosis in cancer cells.[70,71] Additionally, glycolysis generates substrates and intermediates fulfilling the biosynthetic demands needed for rapid cell proliferation, such as acetyl-CoA.[72] Glucose metabolic alterations often lead to enhanced lactate excretion and low pH values in the microenvironment, which drives malignant progression and is related to poor prognosis in human cancer.[73] Hence, glucose metabolic reprogramming is an optimized approach in which cancer cells deal with cellular stress. Glucose transporters (GLUTs), multiple enzymes, and several signaling pathways may be involved in the glucose metabolism.[74] To date, it has been reported that numerous lncRNAs can affect genes and pathways forming complex regulatory networks of glucose metabolism regulation.[70]

Regulation of glucose uptake

Malignant cells are famous for the avid uptake of glucose to meet energy and substance demands. What drives cancer cells to internalize more glucose than normal cells? Normally, GLUTs and Na^+-glucose-linked transporters (SGLTs) are two important transmembrane proteins that facilitate glucose uptake into the eukaryotic cytoplasm.[75] Hox transcript antisense intergenic RNA (HOTAIR) is one of the most studied lncRNAs involved in genome modification.[76] It is transcribed from the opposite direction of the HOXC gene and represses transcription from the HOXD gene by recruiting PRC2 in fibroblasts.[77] Further study showed that HOTAIR promotes

Table 1. lncRNAs associated with cancer metabolism

Metabolic process	lncRNA	Tumor	Molecular mechanism	The level of evidence	Ref.
Glucose metabolism	HOTAIR	hepatocellular carcinoma	increases GLUT1 expression by activating mTOR signaling	*in vitro*	35
	ANRIL	nasopharyngeal carcinoma	increases GLUT1 expression by activating mTOR signaling	*in vitro*	36
	SLC2A1-AS1	hepatocellular carcinoma	represses GLUT1expression by inhibiting the STAT3/FOXM1 pathway	*in vivo*	37
	lnc-p23154	oral squamous cell carcinoma	increases GLUT1 expression by interacting with miR-378a-3p	*in vitro* and *in vivo*	38
	LINC00174	glioma carcinogenesis	increases GLUT1 expression by interacting with miR-152-3p	*in vitro*	39
	UCA1	cervical cancer and pediatric AML	regulates hexokinase 2 (HK2)	*in vitro*	40,41,42
	PVT1	osteosarcoma and gallbladder cancer	regulates HK2 by regulating miR-497 and miR-143	*in vitro*	43,44
	UCA1	esophageal cancer	increases HK2 expression by interacting with miR-203	*in vitro*	45
	TUG1	hepatocellular carcinoma	regulates HK2 by miR-455-3p	*in vitro*	46
	LINC00092	ovarian cancer	interacts with PFKFB2	*in vitro*	47
	HOXB-AS3	colon cancer	binds to hnRNP A1 and regulates PKM splicing	*in vitro*	48
	AC020978	non-small cell lung cancer	directly interacts with PKM2 and enhances its protein stability	*in vitro*	49
	GLCC1	colorectal cancer	binds to HSP90 and stabilizes c-Myc protein	*in vitro*	50
	FILNC1	renal cell carcinoma	represses c-Myc protein level through sequestering AUF1	*in vitro*	51
	PDIA3P	multiple myeloma	interacts with c-Myc directly and binds to the promoter of G6PD	*in vitro*	52
	lincRNA-p21		decreases HIF-1α ubiquitination and accumulation of HIF-1α	*in vitro*	53
Glutamine metabolism	CCAT2	colorectal cancer	secondary structure	*in vitro* and *in vivo*	54
	lincRNA-p21	bladder cancer	regulates GLS level	*in vitro*	55
	HOTAIR	glioma	regulates GLS level by interacting with miR-126-5p	*in vitro*	56
	AK123493.1	pancreatic cancer	regulates GLS level via ADAR/Dicer-dependent RNA interference	*in vitro*	57
	UCA1	bladder cancer	regulates GLS2 level by miR-16	*in vitro*	58
	TUG1	intrahepatic cholangiocarcinoma	stabilizes Sirt3 mRNA by binding to miR-145	*in vitro*	59
Lipid metabolism	LINC01138	ccRCC	stabilizes SREBP-1 protein by interacting with PRMT5	*in vitro*	60
	lncRNA SNHG16	pancreatic cancer	modulates SREBP-2 expression by directly targeting miR-195	*in vitro*	61
	lncRNA SNHG16	colorectal cancer	Wnt signaling	*in vitro*	62
	HULC	hepatocellular carcinoma	upregulates PPARA and activates ACSL1	*in vitro*	63
	NEAT1	hepatocellular carcinoma	binds to miR-124-3p	*in vitro*	64
Mitochondrial oxidative metabolism	UCA1	bladder cancer	binds to miR-195 and induces ARL2	*in vitro*	65
	SAMMSON	melanomas	sequesters XRN2	*in vitro*	66,67

hepatocarcinogenesis partially through increasing GLUT1 expression by activating mammalian target of rapamycin (mTOR) signaling or by binding GLUT1 directly in hepatocellular carcinoma (HCC) cells.[35] Analogously, CDKN2B antisense RNA1 (lncRNA ANRIL) also upregulated GLUT1 via activation of the mTOR signaling pathway, resulting in nasopharyngeal carcinoma (NPC) cell glucose metabolism reprogramming.[36] In addition to the mTOR signaling pathway, SLC2A1-AS1 suppresses HCC metastasis and aerobic

glycolysis *in vivo* by repressing GLUT1 expression by inhibiting the STAT3/FOXM1 pathway.[37] Moreover, lncRNAs can antagonize miRNA regulation of GLUT1 expression. For instance, by interacting with the miR-378a-3p promoter and repressing its transcription, lncp23154 increases GLUT1 expression, thus increasing glucose uptake and participating in metastasis of oral squamous cell carcinoma (OSCC) cells *in vitro* and *in vivo*.[38] In addition, LINC00174 promotes glioma carcinogenesis, which was verified by a nude mouse-transplanted tumor model and further facilitates glycolysis by regulating miR-152-3p, which leads to GLUT1 (SLC2A1) expression upregulation.[39] LINC00346 regulates cell proliferation and glycolysis in breast cancer by interacting with miR-148a/b and increasing GLUT1 expression.[78] These findings indicate that lncRNAs can affect glucose uptake in cancer cells by regulating GLUT1 expression through a wide range of mechanisms.

Regulation of glycolytic enzymes

In addition to regulating glucose uptake, lncRNAs have been identified to impact glycolysis by activating the transcription of key enzymes directly or indirectly. During the glycolysis process, four regulatory enzymes play an important role in the Warburg effect, namely, hexokinase (HK), glucokinase, pyruvate kinase (PK), and phosphofructokinase.[79] lncRNA urothelial carcinoma-associated 1 (UCA1) plays an oncogenic role, and its abundance is associated with therapeutic resistance in several malignancies. In cervical cancer and pediatric acute myeloid leukemia (AML), lncRNA UCA1 promotes glycolysis and radioresistance (cervical cancer) or chemoresistance (pediatric AML) by upregulating HK2, which is a crucial determining enzyme in the first irreversible step of the glycolysis process.[40,41,42] Moreover, several lncRNAs have been found to regulate HK2 expression via affecting miRNAs of target genes. For instance, PVT1 can influence miR-497 and miR-143 and thereby upregulate HK2 expression in osteosarcoma and gallbladder cancer,[43,44] whereas UCA1 regulates miR-203 to increase HK2 expression in esophageal cancer.[45] In addition, a subsequent study demonstrated that HK2 can be impacted by TUG1 in HCC by miR-455-3p binding[46]. Fructose-2,6-bisphosphatase (PFKFB2) and PKM2 are also key enzymes in the process of glycolysis and can also be regulated by lncRNAs. Rather than interacting with miRNAs, LINC00092 can directly interact with PFKFB2 to induce the glycolytic phenotype and metastasis *in vivo* cancer, which mediates the features of cancer-associated fibroblasts (CAFs) in ovarian cancer.[47] Under normal conditions, PKM2 is mainly expressed in stem or embryonic cells, whereas PKM1 is expressed in most differentiated tissues. HOXB-AS3 (HOXB cluster antisense RNA 3) can encode a conserved 53-amino acid small peptide that can competitively bind to hnRNP A1 and act as a switch in the conversion of PKM1 to PKM2, thereby suppressing the formation of PKM2 and subsequent glucose metabolism reprogramming in colon cancer cells.[48] AC020978 can directly interact with PKM2, enhance its stability, and promote the nuclear translocation of PKM2 in non-small cell lung cancer.[49] In addition to the molecular mechanisms we mentioned above, lncRNAs can also influence these key enzymes in other ways, such as impeding catalytic activity.

Regulation of related genes or signaling pathways

Several other lncRNAs have been reported to regulate glucose metabolism and cancer progression through some cancer-related genes or signaling pathways. Notably, c-Myc is a critical transcription factor that is increased in numerous human cancers and regulates genes either directly or indirectly involved in glycolysis.[80] Accumulating evidence has revealed that lncRNAs can regulate c-Myc expression or interact with c-Myc to affect the underlying pathway via multiple mechanisms. For example, glycolysis-associated lncRNA of colorectal cancer (GLCC1) binds to heat shock protein (HSP)90 (HSP90AA1) directly and further stabilizes c-Myc protein from ubiquitination degradation, thus increasing its target gene expression level, especially lactate dehydrogenase (LDHA), in colorectal cancer cells.[50] In addition, FoxO-induced lncRNA 1 (FILNC1) is specifically expressed in the kidney and can repress c-Myc protein levels by sequestering AUF1 from interacting with c-Myc mRNA under glucose starvation conditions. Thus, low FILNC1 levels promote glycolysis and are associated with poor patient survival outcomes in renal cell carcinoma (RCC).[51] Moreover, in multiple myeloma, lncRNA protein disulfide isomerase family A member 3 pseudogene 1 (PDIA3P) upregulates G6PD expression and pentose phosphate pathway flux by interacting with c-Myc directly and recruiting it to the promoter of G6P.[52]

Generally, it is widely accepted that the microenvironment of cancer cells has a shortage of glucose and oxygen supply owing to delayed tumor angiogenesis during the rapid growth of solid tumors.[72,81] Interestingly, several lncRNAs have been found to be involved in the HIF-1 pathway that is activated by hypoxic stress and have gained widespread attention, including lincRNA-p21 and AC020978. lincRNA-p21, a direct transcriptional target of HIF-1, is able to disrupt the von Hippel-Lindau disease (vHL)-HIF-1α complex interaction, leading to a decrease in HIF-1α ubiquitination and accumulation of HIF-1α.[53] As a consequence, a positive-feedback loop between lincRNA-p21 and HIF-1α is established and promotes glycolysis under conditions of hypoxia. Unlike lincRNA-p21, lncRNA-AC020978 can bind to PKM2 directly, thereby stabilizing PKM2 protein from ubiquitination degradation, and translocation to the nucleus, resulting in enhanced transcription of HIF-α.[49] Collectively, these findings suggest that lncRNAs are vital players in Warburg effect regulation and highlight therapeutic targets for glucose metabolic reprogramming.

lncRNAs IN GLUTAMINE METABOLISM

Glutamine, another kind of principal growth-supporting substrate, provides not only carbon but also a reduced nitrogen source required for the biosynthesis of various nitrogen-containing compounds.[82] Once taken up into the cytoplasm, glutamine can be converted to glutamate by glutaminase (GLS) and then catalyzed into alpha-ketoglutarate (α-KG) via transaminases or glutamate dehydrogenase (GLUD/GDH). Since α-KG is an important intermediate product of the tricarboxylic acid (TCA) cycle, to sustain rapid proliferation, cancer cells demand α-KG.[83,84] In addition, glutamine has also been reported to facilitate the import of essential amino acids.[4] Hence,

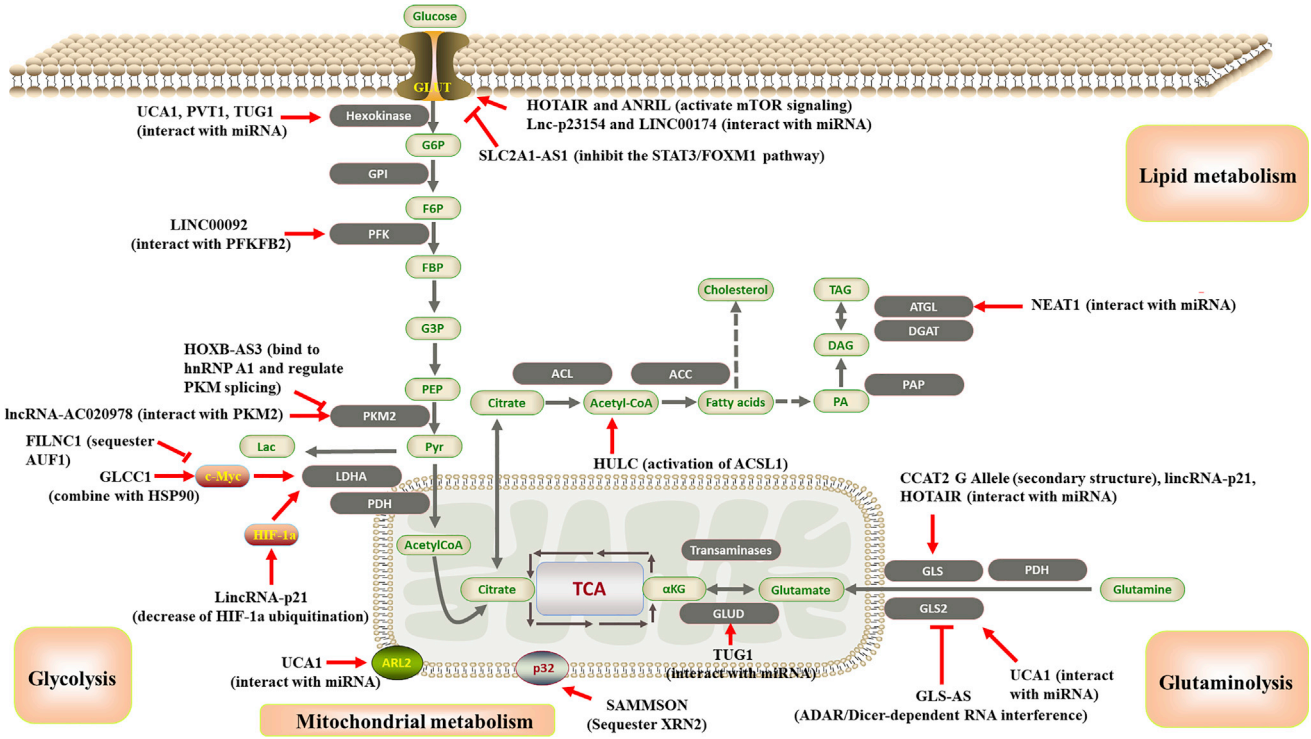

Figure 2. Schematic illustration of lncRNAs involved in the metabolic rearrangement of cancer metabolism by targeting metabolism-related molecules or pathways

Detailed mechanisms of these lncRNAs are described in the main text.

glutamine internalization and metabolism are critical for a spectrum of biological processes in cancer cells, including the maintenance of redox balance and ROS levels, energy production, and macromolecular synthesis[85].

GLS is the rate-limiting enzyme in the glutamine metabolism and has different functions depending on the isoform.[86] In mammals, GLS is encoded by two genes known as liver-type GLS (GLS2) and kidney-type GLS.[87,88] Of these two GLS enzymes, GLS can be further classified into GLS kidney isoform (KGA) and GLS isoform C (GAC) due to alternative splicing.[89] Interestingly, the GLS2 and two GLS isoforms also show differences in their regulation and activity by lncRNAs and other factors, such as colon cancer-associated transcript 2 (CCAT2). CCAT2 was originally identified in colorectal cancer, and its upregulation was related to high risks for multifarious malignancies.[90,91] Notably, Redis et al.[54] reported that CCAT2 regulates glutamine metabolism in an allele-specific manner. Through hyperpolarized magnetic resonance imaging, metabolic changes were also detected in nude mice after injection with CCAT2-overexpressing HCT116 cells. Mechanistic studies showed that the rs6983267 SNP (G/T) altered the secondary structure of CCAT2, resulting in a transcript with the G allele preferentially interacting with CFIm25 instead of CFIm68. Through the complex and allele-specific regulatory mechanism, CCAT2 affects the alternative splicing of GLS and contributes to the preferential expression of the more aggressive splice isoform.

In addition to CCAT2, research to date has revealed other lncRNAs involved in the glutamine metabolism by regulating GLS. As discussed previously, lincRNA-p21 is well known to be involved in the glucose metabolism; interestingly, lincRNA-p21 also contributes to the glutamine catabolism. Zhou et al.[55] found that the decrease in lincRNA-p21 in bladder cancer enhances glutamine catabolism and accelerates the growth of cancer cells by upregulating GLS levels. Nonetheless, the accurate molecular regulatory mechanisms between lincRNA-p21 and GLS remain unknown. In contrast, by miRNA binding, HOTAIR can modulate GLS expression by interacting with miR-126-5p.[56] In addition, AK123493.1, a nuclear-enriched antisense lncRNA of GLS (GLS-AS), can form double-stranded RNA with GLS premessenger RNA (premRNA) via adenosine deaminase RNA-specific (ADAR)/Dicer-dependent RNA interference (RNAi) in pancreatic cancer.[57] Further investigation showed that deprivation of glutamine and glucose can induce the downregulation of GLS-AS at the transcriptional level by Myc, thereby reducing the interaction of GLS-AS and GLS premRNA and upregulating GLS expression. Remarkably, the stability and level of Myc protein can also be decreased by GLS-AS, which implies that there is a reciprocal feedback loop between GLS-AS and Myc when pancreatic cancer cells respond to nutrient stress.[57]

In addition, GLS2 is also pivotal for the glutamine metabolism reprogramming in cancer cells, especially in redox balance

maintenance, and the elimination of excessive ROS levels.[92] A recent study conducted by Li et al.[58] revealed a positive relationship between the expression levels in UCA1 and GLS2 mRNA or protein in bladder cancer. Mechanistically, it was proposed that UCA1 binds with miR-16, promoting the expression of GLS2 to inhibit ROS formation and protect cells from oxidative toxicity in bladder cancer. In addition to UCA1, TUG1 could also interact with miR-145 and protect Sirt3 mRNA from degradation, allowing Sirt3 to positively regulate GDH levels and α-KG production in intrahepatic cholangiocarcinoma.[59]

Overall, the multiple lines of evidence favor the viewpoint that the glutamine metabolism is crucial for tumorigenesis. lncRNAs related to the metabolism of glutamine might be an attractive therapeutic target against cancer. Therefore, further studies are required to explore the potential therapeutic roles of lncRNAs, especially in specific *in vivo* models.

lncRNAs AND LIPID METABOLISM IN CANCER

In addition to the established role of lncRNAs in the glucose and glutamine metabolism, participation in the lipid metabolism is another essential role of lncRNAs in energy metabolism. In particular, lncRNAs have been proposed to be crucial regulators of fatty acids, adipogenesis, phospholipid metabolism, and transport.[93] Multiple studies have verified that aberrant lncRNA expression can cause various metabolism-related diseases and disorders, including dyslipidemia, obesity, and atherosclerosis.[94] Abnormal alterations in lipid metabolism have also been observed in cancerous tissue. The distinctive changes in lipid metabolism in cancer cells include *de novo* lipid synthesis, storing lipids, and converting cholesterol esters to free cholesterol. Herein, we focus on the molecular mechanisms mediated by lncRNAs leading to lipid abnormalities in human cancer.

Sterol regulatory element-binding proteins (SREBPs) are considered the most important regulatory factors in the processes of lipid homeostasis. There are three isoforms of SREBPs, named SREBP-1a, SREBP-1c, and SREBP-2. Among them, SREBP-1a and SREBP-1c mainly promote fatty acid synthesis, whereas SREBP-2 seems to be essential for *de novo* lipogenesis and cholesterol synthesis, and therefore, they might be potential drug targets for cancer treatment.[95] Recently, Dong et al.[96] revealed crucial roles for SREBP-1 in lipid desaturation through regulation of nuclear factor κB (NF-κB) signaling in clear cell RCC (ccRCC). Subsequently, research has shown that LINC01138 is located at chromosome 1q21.2 and correlated with poor ccRCC patient survival. *In vitro* assays showed that the ectopic expression of LINC01138 strongly increased the ratios of unsaturated/saturated lipids in ccRCC cells and promoted ccRCC cell proliferation. This effect was attributed to the increase in SREBP-1 protein stability by interacting with PRMT5.[60] Moreover, SNHG16 has been proven to modulate the SREBP-2 expression level by directly targeting miR-195 in pancreatic cancer.[61] Surprisingly, another study showed that SNHG16 is positively regulated by Wnt signaling and implicated in lipid metabolism of colorectal cancer depending on stearoyl coenzyme A (CoA) desaturas.[62] With the use of AGO-cross-linking and immunoprecipitation (CLIP) analysis, Claus L. Andersen[62] found that one-half of the unique miRNA families with high-confidence targets on SNHG16 also target the 3′ UTR of stearoyl CoA desaturase, which implies that SNHG16 alters lipid metabolism through diverse mechanisms in different malignant tumors.

Another lncRNA, a 500-nt lncRNA, involved in abnormal lipid metabolism is highly upregulated in liver cancer (HULC).[97] A recent study showed that HULC also contributes to the accumulation of intracellular triglycerides and cholesterol in hepatoma cells.[63] Acyl-CoA synthetase long-chain family members (ACSLs) are enzymes that catalyze the conversion of long-chain fatty acids to fatty acid-CoA in mammals.[98] ACSL1 is a member of the family and is transactivated by peroxisome proliferator-activated receptor (PPAR)α. In hepatoma cells, HULC inhibits miR-9 transcription by eliciting the methylation of CpG islands in its promoter, resulting in the upregulation of PPARα and activation of ACSL1. Of particular note, the cholesterol product of ACSL1 promotes HULC expression, in turn, by activating the transcription factor retinoid X receptor A (RXRA). Similar to HULC, nuclear paraspeckle assembly transcript 1 (NEAT1) can also modulate abnormal lipolysis to drive HCC proliferation but through a different mechanism. By directly binding to miR-124-3p, NEAT1 regulates adipose triglyceride lipase (ATGL), diacylglycerol (DAG), and free fatty acid (FFA) levels, which finally activate the PPARα signaling pathway and induce HCC cell growth.[64] Taken together, lipid metabolism is obviously supervised by complex lncRNA regulation networks, and studying these networks could allow us to develop novel strategies or therapies for human cancers.

THE ROLE OF lncRNAs IN CANCER MITOCHONDRIAL OXIDATIVE METABOLISM

Mitochondria are the metabolic factories and primary powerhouses in human cells. Mitochondria are responsible for multiple biological processes, such as oxidative phosphorylation and cytosolic biosynthetic precursor synthesis.[99,100] Warburg originally hypothesized that mitochondrial function is impaired in tumor cells.[72] However, subsequent evidence indicates that tumor cells possess functional mitochondria and can carry out oxidative phosphorylation.[4] Notably, some tumor cells are more reliant on mitochondrial metabolism. Accordingly, the exploration of the roles that lncRNAs play in mitochondrial metabolism is pivotal for understanding cancer progression, particularly cancer cell metabolism.

As mentioned above, UCA1 not only is involved in glutamine and glucose metabolism but can also execute regulatory roles in mitochondria. In bladder cancer, UCA1 interacts with miR-195 and induces ADP-ribosylation factor-like 2 (ARL2) expression, thereby elevating mitochondrial function.[65] Previous data showed that ARL2 is located on the mitochondrial membrane and functions as an activator of ATP/ADP transporters.[101] Thus, studies on the roles and underlying mechanisms of UCA1 in metabolic rearrangement demonstrate its potential applications in novel antitumor therapies. In addition to UCA1, another lncRNA, designated survival-associated mitochondrial melanoma-specific oncogenic noncoding RNA

(SAMMSON), that is located in the cytoplasm and mitochondria, prevents the exoribonuclease XRN2 from binding to the RNA-binding protein CARF by forming a complex containing the CARF and p32 proteins.[66] This favors the nuclear localization of XRN2 and mitochondrial localization of p32. As a result, SAMMSON alters ribosomal RNA (rRNA) maturation and protein synthesis in the cytosol and mitochondria to promote cell growth. Given that SAMMSON is highly, selectively expressed in melanomas, these data identify SAMMSON as an attractive biomarker and therapeutic target of melanoma.[67] In summary, lncRNAs function as essential regulators of mitochondrial metabolism and function through different mechanisms. Further studies are needed to identify other mitochondria-related lncRNAs and to study their roles in cancer mitochondrial oxidative metabolism.

THE FUNCTIONS OF lncRNAs IN NORMAL CELL METABOLISM

Currently, intensive research efforts are underway to better understand the moderating effect of lncRNAs on cancer metabolism. Of note, recent studies report that lncRNAs are also involved in the control of normal cell metabolism, such as adipogenesis and adipose tissue differentiation. Sun et al.[102] demonstrated 175 lncRNAs that are significantly and specifically abnormally expressed during adipogenesis in 2013. Among them, lncRAPs (lncRNAs regulated in adipogenesis) were enriched within adipose tissues, and the functional roles of lncRAPs were further explored through RNAi. Additionally, lncRNA steroid receptor RNA activator (SRA), a well-known lncRNA that fulfills its activation function (AF) through the AF-1 domain of nuclear receptors, is implicated in the differentiation of adipose tissues and regulation of insulin sensitivity.[103] Thus, there is strong interest in the regulation of cell metabolism under physiological and pathological conditions.

CONCLUSIONS AND PROSPECTS

Altered cellular metabolism is a well-established hallmark of cancer cells.[4] Cumulative evidence shows that many factors are involved in this process. In this review, we have highlighted lncRNAs as an important class of regulators in cancer metabolism. The encouraging results from functional studies demonstrate the potential applications of lncRNAs in tumor diagnosis and therapies. However, compared with miRNA and protein-coding genes, our knowledge of lncRNAs in cancer metabolism is still limited. Notably, the majority of insights concerning the metabolic functions and regulatory mechanism of lncRNAs was inferred from *in vitro* studies. To convincingly assess the role of lncRNAs in the control of metabolism, further *in vivo* models through lncRNA knockdown or overexpression are needed. Fortunately, thanks to the success of oligo-based and RNAi-based drugs, some clinical trials with ncRNAs have begun.[104,105] lncRNAs were inhibited via approaches such as antisense oligonucleotide (ASO) technology *in vivo*, and the stability of lncRNA-targeting ASOs can be increased by specific chemical modifications, such as locked nucleic acid (LNA).[106] To date, some lncRNA-targeting drugs are currently undergoing preclinical studies. For example, lncRNA MALAT1 depletion by ASO can impact the growth and metastasis of breast and lung cancer cells in murine models.[107,108] It is expected that lncRNA-based diagnostics and therapeutics involved in cancer metabolism will one day be beneficial for cancer patients, even though the clinical applications of lncRNAs are still at an early stage.

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AUTHOR CONTRIBUTIONS

Y.X., M.Q., M. Shen, S.D., and G.Y. retrieved the related literature and drafted the manuscript. X.S. and M. Shu participated in the design of the review and drafted the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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