Long non-coding RNAs, lipid metabolism and cancer (Review)

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Abstract. Cancer has emerged as the most common cause of death in China. The change in lipid metabolism has been confirmed to have a role in several tumor types, such as esophageal, gastric, colorectal and liver cancer. Cancer cells use lipid metabolism for energy and then rapidly proliferate, invade and migrate. The main pathway by which cancer cell lipid metabolism influences cancer progression is increased fatty acid synthesis. Long non-coding (lnc)RNAs are important ncRNAs that were indicated to have significant roles in the development of human tumors. They are considered potential tumor biomarkers. Increased lipid synthesis or uptake due to deregulation of lncRNAs contributes to rapid tumor growth. In the present review, current studies on the relationship between lncRNAs, lipid metabolism and the occurrence and development of tumors were collated and summarized, and their mechanism of action was discussed. The review is expected to provide a theoretical basis for tumor treatment and prognosis evaluation based on the effective regulation of lncRNAs and lipid metabolism.

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Abbreviations: ACSL1, long-chain acyl CoA synthetase 1; ATGL, adipose tissue TG lipase; CASC15, cancer susceptibility candidate 15; ceRNA, competing endogenous RNA; CRC, colorectal cancer; CoA, coenzyme A; DAG, diacylglycerol; EC, esophageal cancer; EMT, epithelial-mesenchymal transition; FA, fatty acid; FENDRR/FOXF1-AS1, fetal-lethal non-coding developmental regulatory RNA; FFA, free FA; GC, gastric cancer; HCC, hepatocellular carcinoma; HULC, highly up-regulated in liver cancer; ICC, intrahepatic cholangiocarcinoma; LINC00514, long intergenic non-protein coding RNA 00514; lncRNA HAGLROS, HAGLR opposite strand long non-coding RNA; lncRNA NEAT1, long non-coding RNA nuclear paraspeckle assembly transcript 1; LUCAT1/SCAL1, lung cancer associated transcript 1; mTOR, mammalian target of rapamycin; PA, palmitic acid; PI3K-γ, phosphatidylinositol 3-kinase γ isoform; PPARα, peroxisomal proliferator-activated receptor α; RXRA, RXR-α; SNHG16, small nucleolar RNA host gene 16; SREBP, sterol regulatory element-binding protein; TAMs, tumor-associated macrophages; TG, triglyceride; TME, tumor microenvironment

Key words: long non-coding RNA, lipid metabolism, cancer, signal transduction, therapy

Contents

1. Introduction

In spite of extensive efforts and progress in the field of cancer research, the mortality rate due to tumors remains high (1). According to the recently published official data from the National Bureau of Statistics of China, in 2018-2020, malignant tumors ranked first for the constituted ratio of deaths from diseases in cities and towns in China, and the death rate due to malignant tumors consistently ranked second or third in rural areas of China (2). Therefore, in-depth study of the mechanisms of the occurrence and development of tumors and the search for novel therapeutic targets and prognostic biomarkers are of great significance to reduce the mortality rate and improve the survival rate of patients with tumors. Long non-coding RNAs (lncRNAs) are a crucial class of RNA molecules and an increasing number of lncRNAs have been demonstrated to have important roles in the development and progression of tumors. They may serve as diagnostic or prognostic biomarkers and therapeutic targets for cancer (3). Dysregulated lipid metabolism is a prominent metabolic alteration in cancer, and increased synthesis or uptake and storage of lipids occur in tumors, promoting rapid cancer cell growth and tumor formation (4,5). lncRNAs can reprogram cancer lipid metabolism pathways and are important factors regulating abnormal lipid metabolism in cancer (6). In the present review,

the progress in understanding the mechanisms of lncRNA action and lipid metabolism in cancer were summarized.

2. Overview of lncRNAs

lncRNAs are RNA molecules transcribed from the mammalian genome with a length of >200 nucleotides (7). Although they are void of any protein-coding function and the roles of most lncRNAs have remained to be elucidated, they are newly discovered functional ncRNAs that may exert a wide range of regulatory effects through several mechanisms of action and are important regulators in gene expression networks (8-10). lncRNAs are widely known for their key role in human cancer progression (11). With the development of molecular biology and genomics, lncRNAs have emerged as promising biomarkers for cancer and individual lncRNAs have different characteristics in different cancers (12). Certain lncRNAs are involved in important biological processes in cancer development through the regulation of target genes, including DNA methylation, histone modification and chromatin remodeling (13), and have considerable roles in the processes of proliferation, migration and invasion in a variety of tumors, which are closely related to treatment strategies and prognoses of these patients. For instance, lncRNA hypoxia-inducible factor 1α-antisense 2 (AS2) is an oncogenic KRAS-inducible lncRNA and its high expression may promote lung cancer cell proliferation and tumor metastasis (14). Therefore, lncRNAs may be potential therapeutic and prognostic targets for tumors (15-18).

3. Role of lncRNAs in tumor development

The pathogenesis of cancer involves precancerous lesions, gene mutations, oncogenic activation and tumor-suppressor gene inactivation, which is a complex process. Aberrant expression of multiple lncRNAs has been implicated in the development of cancer and is associated with various biological behaviors of cancer cells, including enhanced metastasis, upregulation of proliferation, inhibition of apoptosis and altered cell cycle (19). Both overexpression of certain lncRNAs with oncogenic functions and inactivation of lncRNAs with tumor-suppressor properties may promote tumor development. lncRNAs are able to regulate the activity and expression of oncogenes by targeting tumor-related genes or signaling pathways, thereby affecting downstream processes of autophagy, proliferation and migration of tumor cells (20). lncRNAs may be utilized as biomarkers for the effectiveness of therapies for the treatment of patients with tumors, such as immunotherapy, chemotherapy and surgery (21). For instance, lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) was observed to have an important role in patients with tumors treated with immune checkpoint inhibitors, and those with high NEAT1 expression had good treatment outcomes (22).

lncRNAs with oncogenic effects

LOC100133669. LOC100133669 is an lncRNA with a length of 831 nt. An experimental study indicated that LOC100133669 is mainly localized in the cytoplasm and upregulated in esophageal cancer (EC) tissues, as evidenced by an RNA *in situ* hybridization assay (23). High LOC100133669 expression promotes the progression of EC, indicating poor prognosis of patients with EC. The LOC100133669 gene promotes EC cell proliferation and cell cycle progression, whereas knocking down LOC100133669 had the opposite effect. LOC100133669, as a novel oncogene of EC, is a potential diagnostic marker and therapeutic target for EC.

Lung cancer-associated transcript 1 (LUCAT1 or SCAL1). LUCAT1 is a novel lncRNA (24). Chi *et al* (25) reported that the expression of LUCAT1 in human gastric cancer (GC) tissues was significantly higher than that in adjacent tissues by assessing human GC tissues and paracancerous tissues resected from 98 patients with GC. LUCAT1 knockdown inhibited the proliferation, migration and invasion of cancer cells. The relationship between LUCAT1 and microRNA (miR)-134-5p in GC was predicted using the miRDB database and the expression levels of LUCAT1 and miR-134-5p were negatively correlated (25). In conclusion, LUCAT1 is an oncogenic factor in GC and both LUCAT1 overexpression and miR-134-5p downregulation promote the occurrence and development of GC. Zhou *et al* (26) examined colorectal cancer (CRC) tissues and adjacent normal tissues obtained from patients with CRC by surgical resection and found that LUCAT1 was upregulated in human CRC tissues and downregulated in normal tissues. Upregulated LUCAT1 expression significantly increased the proliferation, apoptosis, migration and invasion of CRC cells compared with that in the normal cells. Knocking down LUCAT1 induced p53 expression at the protein level but not at the mRNA level, suggesting that LUCAT1 may affect p53 stability. A bioinformatics analysis suggested that low LUCAT1 expression was closely related to the p53 signaling pathway and inhibition of LUCAT1 combined with ubiquitin A-52 residue ribosomal protein fusion product 1 (UBA52) and activation of the UBA52/MDM2/p53 pathway induced cell-cycle arrest and apoptosis of CRC cells. LUCAT1 upregulation in CRC tissues was associated with a poor prognosis of patients with CRC. Xing *et al* (24) pointed out that LUCAT1 has an important role in the occurrence and development of liver cancer and the migration and invasion of liver cancer cells. LUCAT1 was able to promote the proliferation, migration and invasion of liver cancer cells, and further accelerate tumor cell growth and metastasis. Upregulated LUCAT1 expression was inversely associated with the survival rate of patients with liver cancer, and patients with high LUCAT1 expression in liver cancer tissues had poor survival and poor prognosis. In conclusion, LUCAT1 may serve as a potential therapeutic target and prognostic molecular marker for GC, CRC and liver cancer.

Cancer susceptibility candidate 15 (CASC15). CASC15 is highly expressed and has an oncogenic role in lung cancer, breast cancer, GC, CRC, hepatocellular carcinoma (HCC) and cervical cancer. Furthermore, aberrant expression of CASC15 is associated with tumorigenesis, progression and patient prognosis through the regulation of several target genes and signaling pathways (27). Wu *et al* (28) found significantly elevated CASC15 expression in GC tissues, and high expression of CASC15 promoted the proliferation, migration and epithelial-mesenchymal transition (EMT) of GC cells. lncRNAs contribute to EMT and promote GC progression by regulating cell cycle progression and affecting the downstream

signaling pathways to promote GC progression through mechanisms involving competing endogenous RNA (ceRNA). High expression of CASC15 is associated with poor prognosis (poor survival) of patients with GC and by analyzing The Cancer Genome Atlas data, expression of CASC15 was found to be negatively correlated with the overall survival of patients with GC and positively correlated with tumor size and TNM stage (29). The findings suggest that CASC15 has a relatively powerful prognostic value for patients with GC, a molecular marker with potential oncogenic effects in GC, and a promising therapeutic target.

LncRNA H19. lncRNA H19, an lncRNA originally described as an oncofetal transcript, functions in most tumors as an oncogene. H19 is aberrantly upregulated in GC and promotes GC cell proliferation by inactivating p53 or inhibiting the expression of the tumor suppressor gene RUNX family transcription factor 1 (RUNX1) through miR-675. H19 may inhibit RUNX1 expression by miR-675, further activating the AKT/mammalian target of rapamycin (mTOR) pathway and having a key role in gastric carcinogenesis (30,31). The results of a study on patients with primary CRC indicated that the expression of H19 was significantly upregulated, while that of miR-29b-3p was significantly reduced in CRC tissues compared to adjacent normal tissues (32). Thus, the expression of H19 is negatively correlated with that of miR-29b-3p and H19 targets miR-29b-3p to inhibit its expression. Since the expression of H19 is associated with the risk of CRC recurrence, detecting H19 levels after surgery is a method to predict the prognosis of patients, as CRC cells with high expression of H19 and low expression of miR-29b-3p have poor differentiation, and the prognosis of these patients is poor. The following situation also arises when H19 expression is upregulated: The expression of α-SMA increases, the expression of E-cadherin is inhibited and the transformation of epithelial marker keratin to mesenchymal marker vimentin occurs. Cell metastasis and EMT appear to indicate the aggravation of the condition of patients with CRC. MiR-29b-3p targets granulin precursor (PGRN) and reduces its expression, thus altering downstream Wnt signaling, resulting in a significant regulation of the EMT process. The miR-29-3b/PGRN/Wnt signaling pathway may be involved in the occurrence and development of EMT in CRC, which may facilitate the identification of new diagnostic markers and therapeutic targets for CRC.

LncRNAs with tumor-suppressor effects

Fetal-lethal non-coding developmental regulatory RNA [FENDRR; also known as forkhead box (FOX)F1-AS1]. FENDRR is a novel lncRNA that is significantly downregulated in EC and CRC cells, inhibits their proliferation, migration and invasion, and serves as a prognostic marker for patients with CRC (33). Luo *et al* (34) performed high-throughput sequencing of tumor tissues obtained from six patients with diffuse GC, analyzed the expression patterns of transcriptomes from matched adjacent tissues and identified a group of representative lncRNAs that were potentially associated with gastric carcinogenesis. Furthermore, a co-expression network for dysregulated lncRNAs and mRNAs was constructed and FENDRR was found to be significantly downregulated in GC, thus inhibiting its development.

Maternally expressed 3 (MEG3). lncRNA MEG3 is able to inhibit cell growth and induce apoptosis (35). Yang *et al* (36) determined that MEG3 overexpression inhibited melanoma cell proliferation, migration and tumor formation through *in vitro* and *in vivo* experiments. By comparing the expression of MEG3 in GC tissues and adjacent normal tissues, Soghala *et al* (37) found that the expression level of MEG3 in GC tissues was lower than that in adjacent normal tissues. Therefore, MEG3 may be an indicator of the prognosis of patients with GC, with high MEG3 expression indicating a good prognosis.

4. Overview of lipid metabolism

Lipids are a group of highly complex biomolecules that not only constitute the structural basis of biological membranes but also function as signaling molecules and energy sources (38). Lipids or lipid metabolites promote the proliferation and invasion of cancer cells by assisting in the synthesis of biofilms and the production of cholesterol lipids (39). Lipid metabolism has been a hot spot of research in recent years and reprogramming lipid metabolism has an important role in the proliferation and migration of cancer cells. Lipid metabolites also alter the tumor microenvironment (TME). For instance, the progression of CRC is accompanied by substantial changes in the cellular lipidome, including changes in the composition of fatty acids (FAs), phospholipids and sphingolipids in CRC tissues (40). Lipid metabolism is a complex process. Altered lipid metabolism in cancer cells affects numerous cellular functions, such as autophagy, apoptosis, necrosis, growth, proliferation, differentiation and chemotherapy drug resistance (41). Therefore, elucidating the molecular mechanism by which lipid metabolism regulates tumor immunity is of great value for understanding tumor cell immune escape and targeting lipid metabolism, along with developing novel and promising anticancer treatment regimens (42-44).

5. Relationship between abnormal lipid metabolism and cancer

A long-term follow-up of patients with EC who had undergone radical esophagectomy was performed to investigate the association between recurrence and lipid metabolism after curative esophagectomy. The results indicated that an earlier time of postoperative recurrence was associated with higher serum total cholesterol levels in patients, suggesting that hyperlipidemia is a high-risk factor for postoperative recurrence of EC. It was demonstrated that high and low serum total cholesterol levels have a certain prognostic value for patients with EC (45).

An experimental study by Luo *et al* (46) indicated that tumor-associated macrophages (TAMs) contain several lipids and TAMs in patients with GC are rich in lipids. Phagocytosis of TAMs with high lipid content is low and lipid accumulation in TAMs is mainly through the uptake of more extracellular lipids by tumor cells, which leads to high expression of phosphatidylinositol 3-kinase γ isoform (PI3K-γ). By contrast, targeting PI3K-γ reverses the tumor growth-promoting function of lipid TAM, thereby inhibiting the proliferation of GC cells. This suggests that targeting the PI3K-γ signaling pathway in macrophages may be a novel potential method to prolong the

overall survival and determine the prognosis of patients with GC. Sterol regulatory element-binding protein (SREBP) is an endoplasmic reticulum-binding transcription factor that has a central role in lipid metabolism. SREBP is able to regulate lipid synthesis or genes involved in lipid metabolism. Three types, including SREBP-1a, SREBP-1c and SREBP-2, have been identified in mammalian cells (47). Abnormal expression of SREBP frequently leads to dysregulation of lipid metabolism (48). It has been indicated that palmitic acid (PA), an FA with significantly downregulated expression in GC tissues, specifically inhibits the proliferation, migration and invasion of GC cells at high concentrations (49). SREBP-1c, a central transcription factor regulating lipid metabolism, is a key lipogenic transcription factor that is activated in human GC tissues, leading to upregulation of the expression of genes involved in FA synthesis, including stearoyl CoA desaturase-1 and FA synthase, which in turn reduce PA levels and promote GC cell growth and metastasis. Therefore, high SREBP-1c expression is closely associated with poor prognosis of patients with GC, and its knockdown inhibited the proliferation, migration and invasion of GC cells. In conclusion, PA has a certain effect on the treatment of GC at high concentrations, and SREBP-1c is an important biomarker for the treatment of GC. Peroxisomal proliferator-activated receptor α (PPARα) is another key transcription factor regulating lipid metabolism, and its expression is associated with FA oxidation and tumor development. Pascual *et al* (50) investigated the enhancing action of dietary palmitic acid on metastatic processes of tumors and demonstrated that dietary PA is able to promote metastasis in oral cancer and melanoma. Through *in vitro* cellular and *in vivo* animal experiments, Zhang *et al* (51) confirmed that PA promotes melanoma-cell metastasis and this involves the Toll-like receptor 4/Toll/IL-1 receptor domain-containing adaptor-inducing IFN-β/Pellino1-phosphorylated NF-κB pathway. It is clear from the aforementioned results that dietary PA may aggravate the development of melanoma, and thus, a reduction in dietary PA may be needed to reduce metastasis and the recurrence rate of melanoma, and to improve prognosis (50).

Adipose tissue triglyceride (TG) lipase (ATGL) is a novel CRC oncogene and upregulation of ATGL expression was indicated to promote the proliferation of CRC cells, and conversely, its knockdown inhibited the proliferation and promote apoptosis of CRC cells (52). ATGL is a key lipase for TG hydrolysis and CRC cells with high expression of ATGL have a greater lipolysis ability. ATGL may also enhance the proliferation of CRC cells by promoting lipolytic pathways [degradation of genes related to sphingolipid metabolism and coenzyme A (CoA) biosynthetic pathway]. ATGL levels are significantly inversely associated with overall survival of patients with CRC, and may thus represent a novel and valuable target for the treatment and prognostication of patients with CRC. Wen *et al* (53) found that increased lipogenesis mediated by SREBP may promote the rapid proliferation of colon cancer cells, along with the occurrence and development of colon cancer. Knockdown of SREBP-1 or SREBP-2 inhibited lipid synthesis in colon cancer cells, and the FA and cholesterol indices were consequently decreased, leading to inhibition of colon cancer cell proliferation and tumorigenesis. Therefore, targeting lipid synthesis by SREBP may provide a novel and promising therapeutic strategy for the treatment of colon cancer and prognosis of patients.

The liver is central to lipid metabolism, as this is where lipogenesis occurs (54). Liver cancer refers to a malignant tumor of the liver, generally referred to as primary liver cancer. According to the pathological classification, primary liver cancer may be divided into HCC and intrahepatic cholangiocarcinoma, among other types (55). HCC is the most common type of primary liver cancer (47), and is currently a hot spot of domestic and international research. Accumulating evidence suggests that alterations in lipid metabolism are involved in the occurrence and development of HCC and abnormal lipid metabolism is a potential target for the diagnosis and treatment of HCC (56). Long-chain acyl CoA synthetase 4 (ACSL4), a member of the acyl CoA synthetase 4 family, is a key regulator of lipid metabolism (57), an oncogene and a novel biomarker for HCC. HCC cells generate large amounts of FA through *de novo* synthesis, which promotes rapid tumor cell growth. ACSL4 is required for *de novo* FA synthesis in HCC cells and upregulates SREBP-1. The downstream lipogenic enzymes in HCC cells function through the c-Myc pathway, resulting in increased lipogenesis and rapid proliferation of HCC cells. Therefore, inhibition of ACSL4 and SREBP-1 overexpression may prolong the survival of patients with HCC. Thus, ACSL4 and SREBP-1 are promising biomarkers for HCC treatment and prognosis (58). Numerous studies have indicated that lipid metabolism has a key role in the occurrence and development of HCC, but the underlying mechanism has remained to be fully elucidated, which is also the focus of future research and may facilitate the development of new drugs for the treatment of liver cancer (59).

6. Role of lncRNAs and lipid metabolism in tumor development

Numerous studies have indicated that lncRNAs, in addition to regulating key lipid transcription factors, also alter lipid storage and FA oxidation by modulating *de novo* lipogenesis. lncRNAs reprogram a large portion of cancer lipid metabolism pathways, regulate lipid metabolism and are key regulators of abnormal lipid metabolism in cancer. lncRNAs and lipid metabolism are also involved in the expression of multiple signaling pathways in the process of tumor occurrence and development, leading to the activation of oncogenes or the inactivation of tumor suppressor genes, and promoting rapid growth of tumors (60,61).

LncRNAs affect tumor progression by regulating transcription factors related to lipid metabolism

SREBP-1. Li *et al* (62) found a novel human-specific lncRNA, lncHR1, which inhibited SREBP-1c levels, downregulated the expression of factor SREBP-1c and reduced lipogenesis by phosphorylating the pyruvate dehydrogenase kinase 1/AKT/FOXO1 axis to inhibit TG and lipid droplet accumulation in liver cancer cells (63).

SREBP-2. Small nucleolar RNA host gene 16 (SNHG16) is located at 17q25.1 and is an oncogenic lncRNA. It has been indicated that SNHG16 is aberrantly expressed in gastrointestinal tumors and associated with poor prognosis (64). An

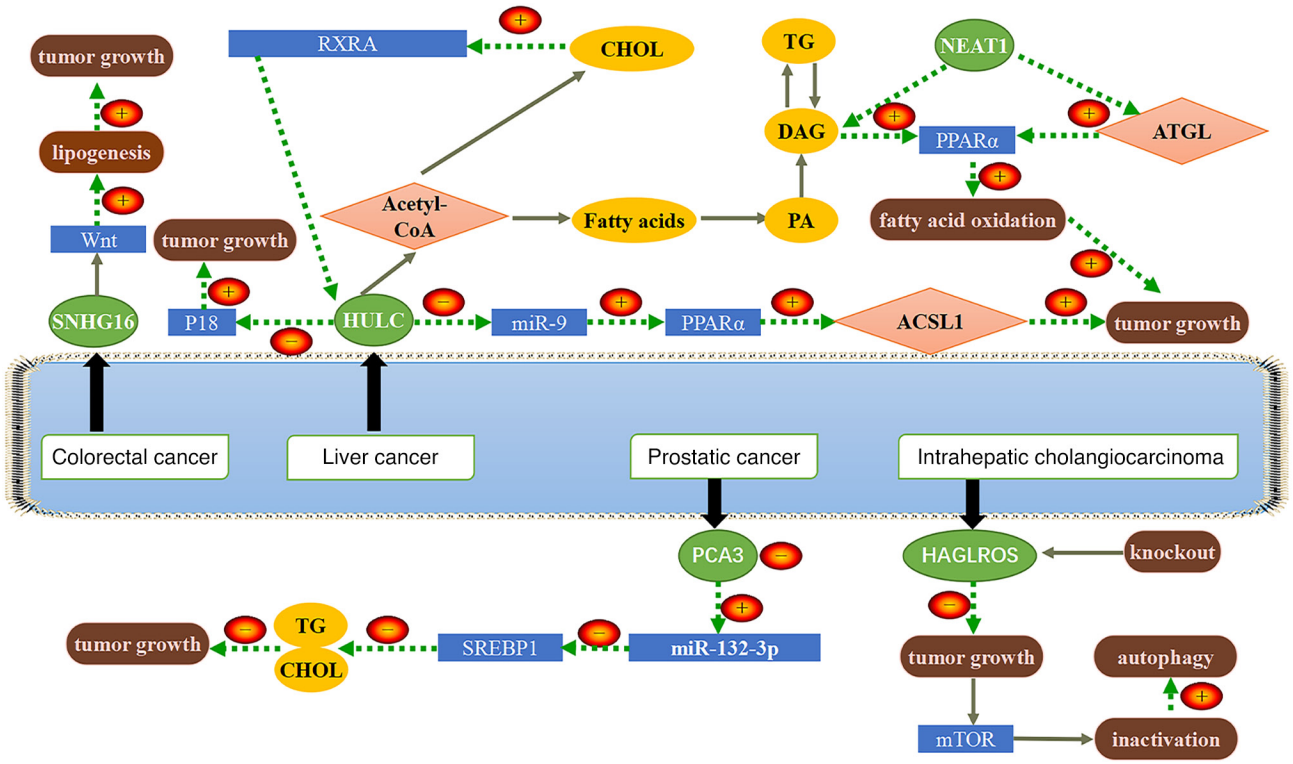

Figure 1. lncRNAs are involved in tumor cell lipid metabolism by targeting different signaling pathways. Colorectal cancer: SNHG16 targets the Wnt signaling pathway to promote lipid synthesis and tumor growth. Liver cancer: HULC downregulates the expression of tumor suppressor p18 and promotes tumor cell growth. The aberrant lipid metabolism regulated by HULC promotes cancer cell proliferation and rapid tumor growth, a process that requires the involvement of ACSL1 and cholesterol throughout. Cholesterol synthesized from acetyl CoA upregulates HULC expression through the activation of RXRA, and high HULC expression downregulates miR-9 expression, which in turn upregulates the expression of the transcription factor PPARα in hepatocellular carcinoma cells to activate ACSL1, thereby significantly upregulating ACSL1 and promoting tumor growth. Acetyl-CoA also synthesizes FAs and palmitic acid is an FA that produces diglycerides, which may be interconverted with triglycerides. NEAT1 activates the PPARα signaling pathway directly through ATGL or indirectly through free fatty acids and DAG, thereby increasing FA oxidation and thus, the tumor keeps growing. Prostatic cancer: Low expression of PCA3 upregulates miR-132-3P expression, while high expression of miR-132-3P inhibits SREBP-1 expression, thereby suppressing TG and cholesterol levels in prostate cancer cells and slowing down the tumor cell growth. Intrahepatic cholangiocarcinoma: Knockout of HAGLROS inhibits intrahepatic cholangiocarcinoma proliferation and growth, inactivates the mTOR axis and promotes autophagy. ACSL1, long-chain acyl CoA synthetase 1; ATGL, adipose tissue triglyceride lipase; CHOL, cholesterol; DAG, diacylglycerol; HAGLROS, HAGLR opposite strand long non-coding RNA; HULC, highly upregulated in liver cancer; miR, microRNA; mTOR, mammalian target of rapamycin; NEAT1, nuclear paraspeckle assembly transcript 1; PA, palmitic acid; PCA3, prostate cancer antigen 3; PPARα, peroxisomal proliferator-activated receptor α; RXRA, RXR-α; SNHG16, small nucleolar RNA host gene 16; SREBP-1, sterol regulatory element-binding protein 1; TG, triglyceride; FA, fatty acid.

experimental study demonstrated that SNHG16 and SREBP-2 promote the proliferation, migration, invasion and lipogenesis of pancreatic cancer cells, while miR-195 inhibits the above processes (65). SREBP-2 is a potential downstream target of miR-195 and SNHG16 regulates SREBP-2 expression by directly targeting miR-195, thereby inducing SREBP-2 to promote pancreatic cancer growth and lipogenesis in pancreatic cancer cells.

PPARα. lncRNA NEAT1 maintains the high expression of ATGL and its catalytic products free FA (FFA) and diacylglycerol (DAG) and PPARα at the transcriptional level but knockdown of NEAT1 downregulates ATGL expression by upregulating miR-124-3p levels, which in turn reduces the expression of FFA, DAG and PPARα and inhibits HCC growth (60).

*LncRNAs affect tumor progression by regulating signaling pathways related to lipid metabolism. lncRNA*s are involved in tumor lipid metabolism through the regulation of signaling pathways (Fig. 1). Highly upregulated in liver cancer (HULC) lncRNA is specifically highly expressed in HCC and is highly upregulated in liver cancer (66). HULC downregulates the expression of tumor suppressors (p18), which promote the proliferation of liver cancer cells and dysregulation of lipid metabolism (67). HULC-regulated abnormal lipid metabolism promotes the proliferation of cancer cells and causes the rapid growth of tumors, and this process requires full-scale participation of long-chain acyl CoA synthetase 1 (ACSL1) and its products, TG and cholesterol. Cholesterol is able to upregulate the expression of HULC in liver cancer cells by activating the retinoid receptor RXR-α (RXRA), which in turn significantly increases the levels of ACSL1 by upregulating the transcription factor PPARα in liver cancer cells to activate ACSL1. MiR-9 targets the 3'UTR to inhibit the expression of PPARα and HULC induces CpG island methylation of the miR-9 promoter, thereby downregulating the expression of miR-9. Therefore, HULC regulates abnormal lipid metabolism in liver cancer cells through miR-9/PPARα/ACSL1/cholesterol/RXRA signaling (68). Immune cells have an important role in HCC. The function of immune cells in the TME is closely related to abnormal lipid metabolism. The mTOR

Table I. Roles of lncRNAs associated with tumor lipid metabolism and underlying mechanisms.

A, Involvement in signal transduction pathways

lncRNA	Tumor type	Molecular mechanisms	Effect on lipid metabolism	(Refs.)
CCAT1	Adenocarcinoma of lung	CCAT1 upregulation activates the PI3K/AKT/ mTOR signaling pathway	Increased lipogenesis	(76)
MALAT1	HCC	MALAT1 upregulation promotes the AMPK signaling pathway	Increased lipogenesis	(77)
ROPM	Breast cancer	High expression of ROPM activates the PI3K/AKT, Wnt/β-catenin and Hippo/YAP signaling pathways	Increased lipogenesis	(78)
SLC25A21-AS1	ESCC	High expression of SLC25A21-AS1 regulates the NPM1/c-Myc axis and SLC25A21 expression promotes proliferation and migration of ESCC cells	SLC25A21-AS1 expression is downregulated by PA and inhibits ESCC	(79)

B, Regulation of miRNAs

lncRNA	Tumor type	Molecular mechanisms	Effect on lipid metabolism	(Refs.)
LINC00174	Thymic epithelial tumor	High expression of LINC00174 targets miR-145-5p downregulation and promotes the gene expressions of SYBU, FEM1B and SCD5	Increased lipogenesis	(80)
LINC00467	Breast cancer	High expression of LINC00467 targets miRNA of TGFB2	Increased lipogenesis	(81)
LINC 00958	HCC	High expression of LINC00958 acts on miR-3619-5p to down-regulate its expression, thereby upregulating HDGF expression	Increased lipogenesis	(82)
MACC1-AS1	GC	MACC1-AS1 up-regulates antagonism of miR-145-5p	Promotes FA oxidation	(83)
MYOSLID	SCCHN and osteosarcoma	High expression of MYOSLID targets miR-1286 downregulation, promotes RAB13 expression or promotes invasion and metastasis by partially regulating epithelial-mesenchymal transition	Increased lipogenesis	(84)
NEAT1	HCC	High expression of NEAT1 downregulates miR-124-3p and upregulates expressions of ATGL, DAG and FFA	Increased lipogenesis	(85)

C, Mediating factors

lncRNA	Tumor type	Molecular mechanisms	Effect on lipid metabolism	(Refs.)
HAGLR	NSCLC	Increased HAGLR expression activates FASN, MMP-9 and p21	Increased lipogenesis	(86)
SPRY4IT-1	Melanoma	Targets lipoprotein 2	Knocking out SPRY4IT-1 increases acylcarnitines, fatty acyl chains and TG	(87)

AMPK, AMP-activated protein kinase; ATGL, adipose tissue triglyceride lipase; CCAT1, colon cancer-associated transcript 1; DAG, diacylglycerol; ESCC, esophageal squamous cell carcinoma; FASN, FA synthase; FFA, free FA; FEM1B, fem-1 homolog B; GC, gastric cancer; HCC, hepatocellular carcinoma; HAGLR, HOXD antisense growth-associated long non-coding RNA; HDGF, hepatoma-derived growth factor; lncRNA, long non-coding RNA; MACC1-AS1, MACC1 antisense RNA 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; miRNA/miR, microRNA; mTOR, mammalian target of rapamycin; MYOSLID, myocardin-induced smooth muscle lncRNA, inducer of differentiation; NEAT1, nuclear paraspeckle assembly transcript 1; NPM1, nucleophosmin 1; NSCLC, non-small cell lung carcinoma; PA, palmitic acid; PI3K, phosphatidylinositol 3-kinase; ROPM, regulator of phospholipid metabolism; SCCHN, squamous cell carcinoma of the head and neck; SCD5, stearoyl-CoA desaturase 5; SLC25A21-AS1, SLC25A21 antisense RNA 1; SPRY4IT-1, SPRY4 intronic transcript 1; SYBU, syntabulin; TG, triglyceride; TGFB2, transforming growth factor β2; YAP, Yes-associated protein.

pathway may be targeted to regulate cellular lipid metabolism to modulate immune cells, which is a novel strategy for the treatment of HCC (69).

It has been indicated that SNHG16 may have an oncogenic role in CRC, targeting the Wnt signaling pathway to promote lipogenesis (70). Therefore, SNHG16 is a promising tumor biomarker and therapeutic target. Experimental results have demonstrated that miR-132-3p can directly interact with SREBP-1; high expression of the lncRNA prostate cancer antigen 3 promoted the growth of prostate cancer and inhibited TG and cholesterol levels in prostate cancer cells through the miR-132-3p/SREBP-1 axis (71). HAGLR opposite strand long non-coding RNA (lncRNA HAGLROS) is highly expressed in intrahepatic cholangiocarcinoma (ICC) and has an oncogenic role. Knockdown of HAGLROS inhibited ICC proliferation, inactivated the mTOR axis and promoted autophagy. Lipid metabolic reprogramming of ICC was indicated to be promoted by inactivation of the mTOR pathway. Patients with ICC having high expression of HAGLROS had poor prognosis and HAGLROS may be used as a biomarker to predict the treatment efficacy of ICC (72). NEAT1 is able to increase FA oxidation through the direct activation of ATGL or indirect activation of the PPARα signaling pathway by FFA and DAG, whereas miR-124-3p, a gene downstream of NEAT1, inhibits ATGL, thereby attenuating FA oxidation, so the tumor grows (60). The above findings indicated that lncRNAs and lipid metabolism are associated with multiple signal transduction pathways and the downstream specific signal transduction mechanisms require further investigation.

Other mechanisms by which lncRNAs and lipid metabolism regulate tumors. Long intergenic non-protein coding RNA 00514 (LINC00514) is a novel lncRNA. Overexpression of LINC00514 promotes the proliferation and lipogenesis of EC cells. Conversely, knocking down LINC00514 inhibits EC cell proliferation and reduces lipogenesis. These results suggest that LINC00514 may participate in EC lipogenesis and regulate alterations in EC lipid metabolism, and thus, targeting LINC00514 may provide a new strategy for the treatment of patients with EC (73). The lncRNA RP11-386G11.10 is a ceRNA for miR-345-3p and high expression of RP11-386G11.10 results in elevated expression of both heterogeneous nuclear ribonucleoprotein U (HNRNPU), a multifunctional protein that regulates precursor messenger ribonucleic acid, and its downstream lipogenic enzymes, further causing lipid accumulation in HCC cells. HNRNPU also promotes the expression of the transcription factor of RP11-386G11.10, as well as zinc finger and BTB domain containing 7A (ZBTB7A), in HCC cells. The ZBTB7A/RP11-386G11.10/HNRNPU positive feedback loop promotes HCC cell growth and metastasis by regulating lipid anabolism (74). Certain lncRNAs promote cancer development by regulating sphingolipid metabolism-related enzymes, such as ceramide synthase (CERS) and targeting these lncRNAs may provide new avenues for treating cancer. For instance, CERS6-AS1, an antisense lncRNA for CERS6, is significantly upregulated in breast cancer cells and binds to insulin-like growth factor 2 mRNA-binding protein 3 to maintain CERS6 mRNA stability and promote cancer progression (75). In Table I (76-87), certain lncRNAs that regulate tumor lipid metabolism are presented, aiming to more comprehensively elaborate on the current research progress in this field. For instance, lncROPM is highly expressed in breast cancer cells, and high expression of ROPM activates the phosphatidylinositol 3-kinase/AKT, Wnt/β-catenin and Hippo/YAP signaling pathways, thereby promoting adipogenesis and the development of breast cancer (78). Zuo *et al* (82) found that the expression of LINC00958, an lncRNA associated with adipogenesis, was upregulated in HCC cells. Dual luciferase reporter, RNA immunoprecipitation, biotin-labelled miRNA pull-down and fluorescence *in situ* hybridisation showed that LINC00958 sponged miR-3619-5p to promote HCC progression. Bioinformatics and RNA sequencing results identified hepatocellular carcinoma-derived growth factor as a downstream signalling molecule of the LINC00958/miR-3619-5p axis. *In vitro* cellular experiments demonstrated that the knocked down expression of miR-3619-5p resulted in increased expression levels of hepatocellular carcinoma-derived growth factor. In summary, overexpression of LINC00958 inhibited miR-3619-5p expression, which upregulated hepatocellular carcinoma-derived growth factor expression and promoted HCC adipogenesis and progression. Lu *et al* (86) found that increased HAGLR expression may activate the expression of FASN, MMP-9 and p21 in non-small cell lung cancer (NSCLC) cells, which in turn promotes NSCLC progression.

7. Conclusions

In summary, lncRNAs are involved in the proliferation, migration and invasion of cancer cells. Simultaneously, our understanding of the changes in lipid metabolism during the occurrence and development of tumors has markedly improved and lipid metabolism is one of the most significant metabolic alterations in tumors. Existing studies have indicated that lipid metabolic reprogramming and lncRNAs have a key role in the occurrence and development of tumors; however, the underlying mechanism has remained to be fully elucidated and requires further research. Targeting lncRNAs and reprogramming lipid metabolism may provide potential therapeutic targets and prognostic monitoring indicators for cancer treatment. Therefore, in-depth research on the role of lncRNAs and lipid metabolism in tumor development is expected to facilitate the development of clinical applications of lncRNAs, thereby providing a reference for early diagnosis and prognostic evaluation of patients with cancer and the development of novel anti-tumor drugs.

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Authors' contributions

ZZ, XH, XC and XW retrieved the relevant literature and drafted the manuscript. ZZ and XW participated in the design of the review and drafted the manuscript. ZZ critically revised the manuscript for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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