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Review article

Non-coding RNAs derailed: The many influences on the fatty acid reprogramming of cancer

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ABSTRACT

Non-coding RNAs (NcRNAs), a family of functional RNA molecules that cannot translate into proteins but control specific gene expression programs, have been shown to be implicated in various biological processes, including fatty acid metabolism. Fast-growing tumor cells rewire their fatty acid metabolic circuitry in order to meet the needs of energy storage, membrane proliferation, and the generation of signaling molecules, which is achieved by regulating a variety of key enzymes along with related signaling pathways in fatty acid metabolism. This review presents an update of our knowledge about the regulatory network of ncRNAs—specifically, microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs)—in this metabolic shift and discusses the possibility of ncRNA-based therapeutics being applied to the restoration of cancer-related fatty acid metabolism.

1. Introduction

Fatty acid (FA) is a various class of molecules comprised of a long aliphatic hydrocarbon chain with different lengths and saturations and a carboxyl group at one end, the metabolism of which consist of a series of courses including FA intake, transportation, synthesis, store, release and decomposition, playing an significant role in many biological processes [1]. Serving as the hydrophobic tails, FAs contribute to the biosynthesis of phospholipids and glycolipids, the major components for biofilms assemblage. FAs are also responsible for the formation of certain second messengers, such as synthetic diacylglycerol (DG), involved in the response to extracellular signals. The epigenetic modification of some proteins also requires the participation of FAs. In addition, fatty acids can also be esterified with glycerol to compound triglycerides, storing energy when nutrient-rich and releasing it in alimentary deficiency [2].

In terms of such a pivotal role in biological process, aberrant fatty acid metabolism altered in tumors has gradually received substantial attention. A growing body of researches have shown a positive correlation between a shift in fatty acid metabolism (FAM) and tumor characteristics such as different chemo-chemotherapy sensitivity, unlimited cell proliferation, abnormal angiogenesis, multiple tumors and invasiveness, consistent with the hypothesis that FAM disorder might be the key factor triggering human tumorigenesis [3–6]. This malignant

Abbreviations: ncRNAs, non-coding RNAs; miRNAs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; FA, fatty acid; DG, diacylglycerol; FAM, fatty acid metabolism; ACLY, ATP citrate lyase; IRS1, insulin receptor substrate-1;ACC:acetyl-CoA carboxylase; PDK4, pyruvate dehydrogenase kinase 4; FAO, fatty acid oxidation; UTR, untranslated region; NSCLC, non-small cell lung cancer; ACS, acyl-CoA synthetase; ACSL, long-chain acyl-CoA synthetases; SREBP, sterol-regulatory element binding protein; CRC, colorectal cancer; SCD, stearoyl-CoA desaturase; HCC, hepatocellular carcinoma; CPT1, carnitine palmitoyl transferase1; TG, triglyceride; GPAT, glycerol-3-phosphate acyltransferase; AGPAT, acylglycerolphosphate acyltransferase; PAP, phosphatidic acid phosphohydrolase; DGAT, diacylglycerol acyltransferase; ATGL, adipose triglyceride lipase; HSL, hormone sensitive lipase; MAGL, monoacylglycerol lipase; FFA, free fatty acids; FABP, fatty acid–binding protein; FAT, fatty acid translocase; CD36, Cluster of differentiation 36

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transformation has been regarded as an emerging hallmark of cancer, and targeting the FAM-associated molecules represents a potential strategy for cancer therapy [7]. However, our knowledge about the modulation of fatty acid metabolic reprogramming in cancer cells remains deficient.

NcRNAs, a family of remarkably powerful, flexible, and pervasive functional RNA molecules, exert power though modulation of the expression of target genes in multiple levels rather than protein translation [8]. NcRNAs can mainly be classified into three categories, including short RNA, long non-coding RNA and circular RNA, based on their size and structure [9]. According to a comparatively broad size threshold, ncRNAs are usually called short if they are smaller than 200 nucleotides, and long if longer. And among them, microRNAs, the most studied group of short RNAs, have a size of about 20 nt. Besides these liner ncRNAs, circRNAs, firstly observed in 1970s, constitute an indispensable category of non-coding RNA molecules characterised with a closed ring structure by covalent bonds without 5′–3′ polarities or polyadenylated tails [10,11]. Used to be regarded as “evolutionary junk,” ncRNAs have been gradually revealed to cover a broad spectrum of functions on cellular and molecular levels [9]. MiRNAs, negative modulators of gene expression, execute their functions through directly targeting mRNA and inducing its degradation or suppression of its translation [12]. Though intricate interplay with nucleic acids and proteins, lncRNAs modulate gene expression via chromatin modification, transcriptional and posttranscriptional regulations [13,14]. And circRNAs exert influence on gene expression by sponging miRNA, modulating splicing and transcription, and modifying parental gene [15]. Through various complicated regulatory networks, ncRNAs are widely involved in multiple physiological and pathological processes, including cancer.

Previous studies have shown that multiple ncRNAs participated in the modulation of cancer cell proliferation, apoptosis, invasion and metastasis, thereby exerting influence on the occurrence and progression of various tumors, such as prostate, breast and cervical cancer [16–18]. One possible crucial mechanism underlying this effect may attribute to the fine tuning of ncRNAs on FA metabolism reprogramming occurring in cancer cells. Growing evidence suggests that ncRNAs perform the regulation on FAM rewiring in malignant cells either through the direct targeting on associated enzymes in FA synthesis, degradation, storage, and release, or the indirect modulation of cancer-related signaling pathways (Figs. 1, 2, 3). Herein, we discuss the current state of knowledge about the significant roles of ncRNAs in the modulation of fatty acid metabolism.

2. NcRNAs and key enzymes in FA synthesis

Increasing de novo synthesis of fatty acids is an important metabolic change in tumor cells. And a variety of enzymes are involved in this process and responsible for the regulation of fatty acid homeostasis.

2.1. ATP citrate lyase (ACLY)

ACLY, a cytosolic enzyme bridging glucose metabolism and FAM, is responsible for the conversion of citrate to acetyl-CoA, an essential substrate for endogenous lipogenic pathways and required for isoprenoid-based protein modifications [19,20]. Located in both nucleus and cytoplasm, ACLY protein is a homotetramer comprised by four identical subunits [21]. Normally, ACLY is abundant in white adipose tissue and the liver while scarce in the others [22]. However, under certain pathological conditions, for instance, cancer, the expression of ACLY may present excessive and active. Previous studies have documented that this over-expression of ACLY were observed in various cancers, and suppression of ACLY, both in vitro and in vivo, led to proliferation arrest of cancer cells, suggesting the significant role of ACLY in neoplastic diseases [23–25].

By directly targeting insulin receptor substrate-1(IRS1), miR-126b inhibited the activation of Akt, a down-stream effector of IRS1, and then achieved the suppression of ACLY, resulting in the restoration of the TCA cycle for ATP synthesis rather than the conversion from citrate co acetyl-CoA which facilitated the synthesis of other macromolecules for cellular biosynthesis. Therefore, through the indirect inhibition on ACLY, miR-126b reprogrammed the mitochondrial citrate metabolism and restrained the de novo synthesis of FA, leading to the suppression of mesothelioma initiation and promotion [26].

It was reported that miR-22, through binding to 3′-untranslated region of ACLY, induced the de novo lipogenesis inhibition which contributed to the attenuation of cell proliferation, invasion and metastasis in osteosarcoma, prostate, cervical and lung cancers, both in vitro and in vivo [27]. Consistent with this result, miR-22 was reported to refrain fatty acid synthesis in cancer cells by inhibiting ACLY, which was implicated in the later tumor staging and poor prognosis in breast cancer, implying the possibility of regarding miR-22 as the biomarker of outcomes of this malignancy [28]. Moreover, miR-182 promoted lung tumorigenesis by inhibiting pyruvate dehydrogenase kinase 4 (PDK4), an enzyme correlated with acetyl-CoA. Interestingly, this phenomenon could be reversed through suppression of ACLY, suggesting that miR-182-PDK4 axis might execute their function via mechanisms associated with ACLY and de novo lipogenesis in lung cancer [29]. Moreover, miR-133b suppresses gastric cancer cell proliferation, the mechanism of which might be the repression of the expression and activity of ACLY in a PPARγ-dependent manner [30]. Thus, taken together, the aforementioned evidences indicate that manipulation of ACLY may be a novel strategy for cancer treatment.

2.2. Acetyl-CoA carboxylase (ACC)

ACC, including the cytosolic isoform ACC1 and the mitochondrion-located ACC2, carboxylates the conversion of acetyl-CoA to malonyl-CoA, constituting the committed step in FAM. Prior research substantiates the belief that ACC1 is the predominant enzyme facilitating fatty acid synthesis while ACC2 anchoring on the mitochondrion membrane suppresses the activity of CPT1, resulting in the fatty acid oxidation (FAO) inhibition [31]. Fine tuning in ACC1 and ACC2 determines the equilibrium between FAS and FAO. In accordance with the astonishingly elevated level of FAM, ACC1 has been suggested to be constantly overexpressed in a wide panel of tumors, supporting tumor proliferation and survival-the opposite of ACC2, which was reported to be abnormally expressed in various cancers ([32–35]. Of course, aberrant ACC in cancer cells is also dominated by ncRNAs. By directly targeting the 1231–1237 nt of 3′untranslated region (UTR) of ACC1, miR-195 inhibited cell proliferation, migration, invasion, and the expression of EMT-related genes in breast cancer, rendering it an attractive target for antineoplastic intervention [36].

2.3. Fatty acid synthase (FASN)

FASN, a 250–270 kD multifunctional, homodimeric protein locating in cytoplasm and intracellular membranes, catalyzes successive condensation reactions to synthesize fatty acid, mainly the 16-carbon palmitate, from substrates of acetyl-CoA and malonyl-CoA [37,38]. As the key metabolic multi-enzyme in fatty acid synthesis, the dysregulation of FASN is closely associated with various diseases such as obesity, type 2 diabetes, and malignancies [39]. Correlating with incremental tumor burden, later staging and poor prognosis of cancers, FASN has been identified as oncoprotein for over 20 years and found to be hyperactive and overexpressed in various types of tumors, constituting critical components of tumor cell survival, proliferation and invasion, since firstly observed in breast cancer in 1994 [40–42].

NcRNAs have also participated in the regulation of FASN in many types of cancer. It was reported that miR-15a and miR-16-1, through binding to FASN 3′UTR, induced decreased protein expression of FASN, which correlated with poor prognosis of breast cancer [43]. And miR-

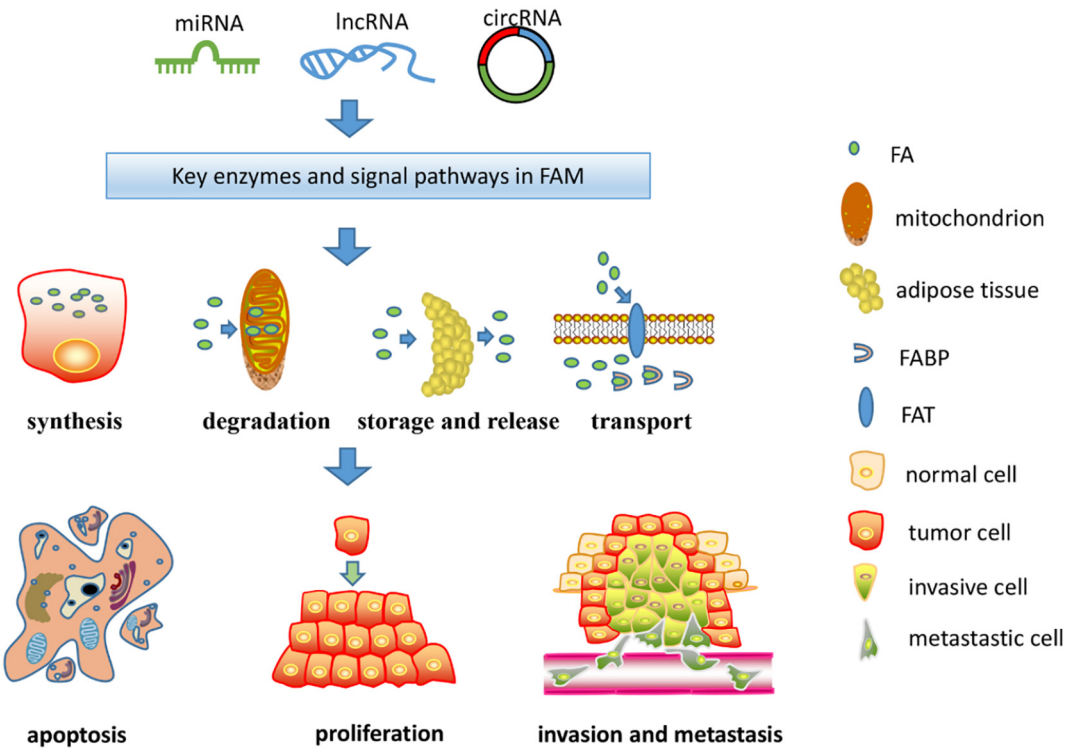

Fig. 1. Potential mechanisms by which ncRNAs exert influence on FAM reprogramming in cancer. By directly targeting FAM-associated enzymes or indirectly modulating cancer-related signaling pathways, ncRNAs regulate the FAs synthesis, degradation, storage and release as wells as the uptake and intracellular transport of FAs, thus inducing a series of alterations of biological behaviours of cancer, including apoptosis, proliferation, invasion and metastasis.

193b, elevated by metformin stimulation, might directly target FASN 3′UTR, inducing decreased FASN protein expression and increased apoptosis of triple-negative breast cancer (TNBC) cells, which consequently facilitated the metformin-depended killing of TNBC [44]. Similarly, previous studies have documented that miR-142-3p could suppress the osteosarcoma cell proliferation though targeting FASN and blocking the protein expression [45]. And miR-1207-5p was reported to suppress HCC cell survival and proliferation by targeting the FASN-associated Akt/mTOR signaling pathway [46]. In vitro studies have shown that miR-195-mediated suppression of FASN protein expression also resulted in the survival, proliferation, invasion and metastasis inhibition in osteosarcoma and breast cancer, implicating the therapeutic value of exogenous miR-195 in treating tumors [36,47]. Moreover, miR-320 was also reported to directly target FASN to exert inhibitory effect in progression of non-small cell lung cancer (NSCLC) and osteosarcoma [48,49]. The lncRNA HAGLR, which was implicated in the later tumor staging and poor prognosis of NSCLC, might promote the proliferation and invasion of NSCLC by inducing the expression of FASN and increasing the cellular FFA content of cancer cells [50]. In osteosarcoma, lncRNA PVT1 could elevate the FASN expression to expedite proliferation, migration and invasion and decrease apoptosis, thereby leading to cancer progression, the specific mechanism of which was largely mediated by lncPVT1 acting as a molecular sponge for miR-195 that targeted FASN [51]. Similarly, significantly upregulated circFARSA in NSCLC could also facilitate cancer cell migration and invasion by acting as a sponge of miR-330-5p and miR-326 and exerting the suppressive impacts on carcinogenic FASN [52].

2.4. Acyl-CoA synthetase (ACS)

Fatty acids, no matter derived from exogenous dietary intake or endogenous de novo synthesis, must be activated by ACS, which generate bioactive FA-CoA, for further turnovers including undergoing a cascade of β-oxidation processes and following tricarboxylic acid cycle to produce ATP or participating in the synthesis of TAG, phospholipids and cholesterol esters [53,54]. Among them, Long-chain ASCs (ACSLs) are the most pivotal enzymes responsible for the activation of most abundant fatty acids, 12–20 carbons [55]. There are 5 ACSL isoforms in mammals, named ACSL1, ACSL3, ACSL4, ACSL5 and ACSL6, individually functioning in fatty acid metabolism depending on different subcellular location, structure and tissue specificity [53]. The dysregulated expression of ACSL has been reported to contribute to various pathological process, such as obesity, atherosclerosis, neurological disorders and diabetes, as well as cancers [56–58]. By enhancing the survivability and invasiveness of malignant cells, and resisting to FA-induced lipotoxicity and ferroptosis, ACSL, especially ACSL1 and ACSL4, exhibit distinct oncogenic activities in multiple types of tumors, covering melanoma, breast, prostate and colon cancer [59–61] (see Table 1).

NcRNAs have shown the ability of regulating expression and activity of ACSL to get involved in carcinogenesis and cancer development. It was reported that miR-205, which could be suppressed by cancerogenic Hepatitis B virus in HCC (hepatocellular carcinoma), might exert its antineoplastic effect by directly targeting the 3′UTR of ACSL4 to dampen its expression, contributing new insights into the disadjust lipid metabolism occurring in HCC [62]. Another research reported that miR-205-mediated suppression of ACSL1 also resulted in the decrease of lipogenesis in HCC cells, further highlighting the significant roles of ncRNAs in the reprogramming of FA metabolism [63]. Furthermore, remarkably upregulated lncHULC was demonstrated to drive malignant development of HCC acting mechanically by relieving the repression of miR-9 on PPARA through the induction of miR-9 promoter methylation, thereby increasing the expression of downstream ACSL1 and levels of triglycerides and cholesterol, accelerating the growth of liver cancer [64]. More than that, miR19-1, the lower expression of which strongly associated with later stages and poorer outcome in colorectal cancer (CRC) patients, could endow CRC cells with invasive and metastatic properties. One possible mechanism underlying this relevance may

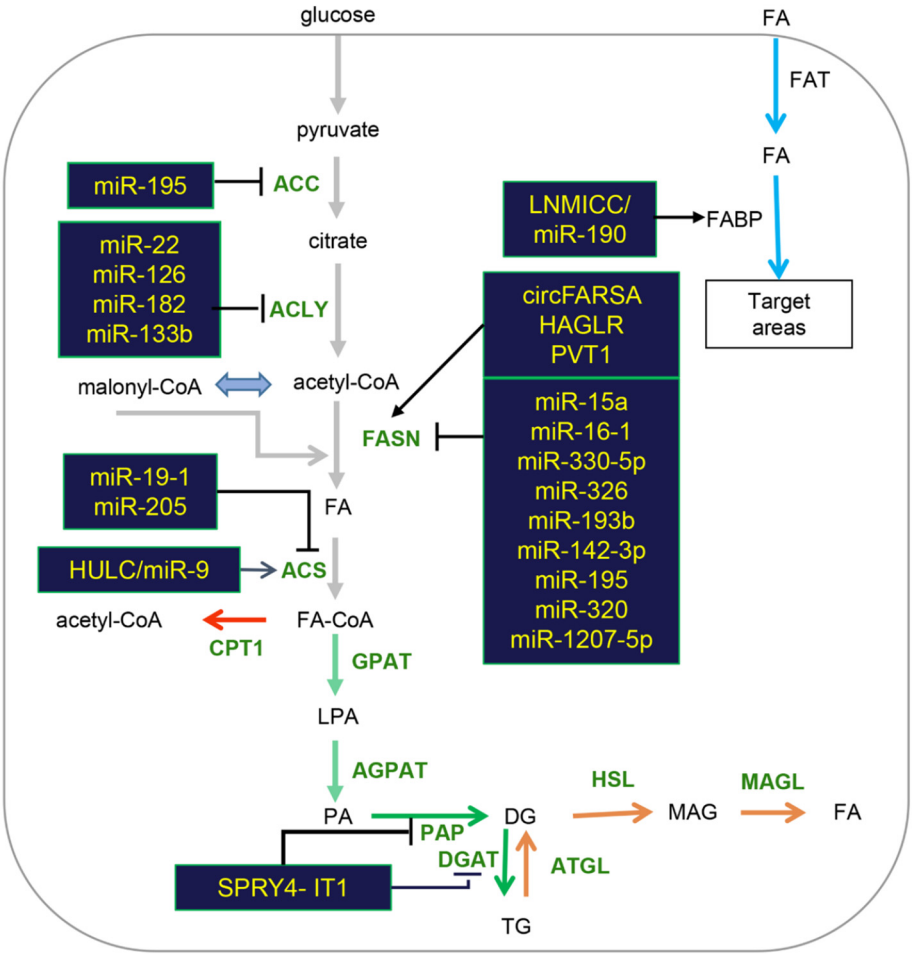

Fig. 2. FAM reprogramming in cancer cells by ncRNAs. MiRNAs, lncRNAs and circRNAs regulates the synthesis, degradation, storage as well as release and transport of fatty acids mechanically by targeting the key enzymes in each link of fatty acid metabolism processes. And in this figure, arrowheads with diverse colors represent different processes in FAM. The arrowheads associated with the FA synthesis, degradation, storage, release and transport are shown in gray, red, green, orange and blue, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

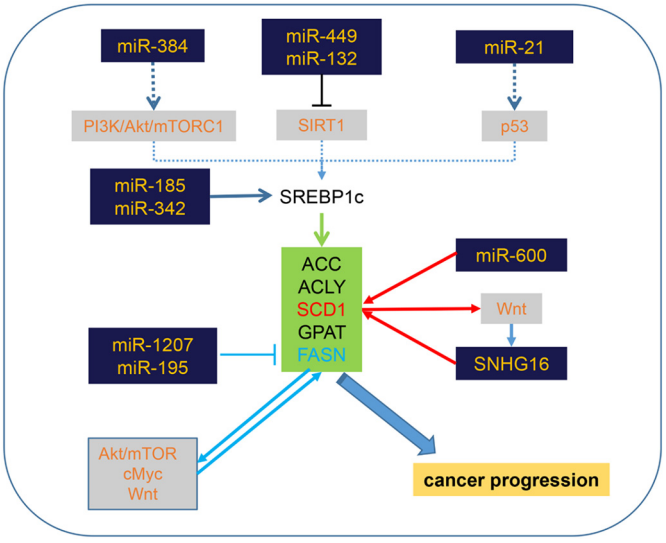

Fig. 3. FAM-associated signal pathways regulated by ncRNAs. NcRNAs modulate FAM-related signal pathways to achieve the regulation of FAM in cancer, inducing cancer progression. SNHG16 and miR-600 modulate SCD1, and SREBP1c regulates the expression of ACC, ACLY, SCD1, GPAT and FASN. Moreover, FASN, which could be regulated by miR-1207 and miR-195, is involved in the Akt/mTOR, cMyc and Wnt pathway.

attribute to the diminishment of miR-19-1 on ACSL1, ACSL4 and stearoyl-CoA desaturase (SCD), the regulators in lipid metabolism, hinting the potential of miR-19-1 as a noninvasive biomarker of CRC prognosis and a novel target in cancer therapy [65].

In view of the critical roles of ACSL in FA metabolism reprogramming, lucubrating the regulatory network of ncRNAs on ACSL may be instructive for targeting drug discovery and precise therapeutic strategies in cancer treatment.

2.5. Sterol-regulatory element binding protein 1 (SREBP1)

First identified by Brown and Goldstein in 1997, sterol regulatory element-binding protein 1 (SREBP1), including SREBP-1a and SREBP-1c, are key transcription factors associated with the metabolism of fatty acids [66]. SREBP1a can modulate both lipogenic and cholesterogenic gene expression while SREBP1c mainly activate ACC, ACLY, FASN and SCD1 to facilitate the synthesis of FA [67]. Besides these canonical functions in transcriptional regulation of genes correlate with FA metabolism, SREBP1 also integrates multiple signal pathways to regulate lipogenesis, participating in myriad physiological and pathophysiological processes, including cancer [68]. Precious studies have reported that SREBP1 was dysregulated in various types of tumors and closely related to survival and proliferation of cancer cells [69]. And SREBP1 also functioned as the downstream effector of mutant TP53 and oncogenic PI3K–Akt–mTORC1 pathways to get involved in carcinogenesis and cancer development [70,71].

Table 1
Non-coding RNAs known to regulate cancer fatty acid metabolism.

	Target	NcRNAs	Cancer types	References
FAM associated enzymes	ACLY	miR-126b	Mesothelioma	[26]
		miR-22	Osteosarcoma, prostate, cervical and lung cancers	[27]
			Breast cancer	[28]
		miR-182	Lung cancer	[29]
		miR-133b	Gastric cancer	[30]
	ACC	miR-195	Breast cancer	[36]
	FASN	miR-15a and miR-16-1	Breast cancer	[43]
		miR-193b	TNBC	[44]
		miR-142-3p	Osteosarcoma	[45]
		miR-1207-5p	HCC	[46]
		miR-195	Osteosarcoma	[47]
			Breast cancer	[36]
		miR-320	Osteosarcoma	C et al., 2014
			NSCLC	[49]
		lncRNA HAGLR	NSCLC	[50]
		lncRNA -PVT1-miR-195	Osteosarcoma	[51]
		circFARSA-miR-330-5p/miR-326	NSCLC	[52]
	ACS	miR-205-ACSL4	HCC	[62]
		miR-205-ACSL1	HCC	[63]
		lncHULC/miR9/ACSL1	HCC	[64]
		miR-19-1	CRC	[65]
	SREBP1	miR-21	HCC	[72]
		miR-132	Glioma	[73]
		miR-449	HCC	[74]
		miR-185 miR-342	Prostate cancer	[75]
		miR-384	HCC	[76]
	SCD	miR-600	Breast cancer	[80]
		lncSNHG16	CRC	[81]
	DGAT	lnc SPRY4-IT1	Melanoma	[95]
	PAP	lnc SPRY4-IT1	Melanoma	[95]
	FABP	Lnc LNMICC/miR-190	Cervical cancer	[104]
		miR-190		

Multiple ncRNAs are implicated in the modulation of SREBP1-induced FA remodeling in cancer. Significant up-regulated miR-21 in HCC directly target HBP1, the activator of p53, inducing the suppression of p53 and downstream SREBP1c, thereby accelerating lipid production and hepatic tumorigenesis [72]. And, it was reported that miR-132 could repress the expression of FASN via blockade of SIRT and downstream SREBP1 to induce the apoptosis, as well as inhibit the tumorigenicity and invasion of glioma cells, and similarly, miR-449 was shown to suppress lipid accumulation and hepatocarcinogenesis mechanically by decreasing the expression of SIRT1 and SREBP1c, both of which highlighted the significance of lipid metabolism in malignancies [73,74]. Moreover, miR-185 and 342, by inhibiting the expression of SREBPs and downstream lipogenic genes, including FASN, facilitated the biosynthesis of FA, causing apoptosis of prostate cancer cells, which suggested the critical roles of miRNAs in cancer development and progression [75]. Furthermore, it was reported that downregulated miR-384 was implicated in poor prognosis in HBV-related HCC patients. The underlying mechanism of this effect might be the upregulation of SREBP1c and FASN expression, which was induced by pleiotrophin, targeted by miR-384 [76].

These results are indicative of an important fact that SREBP1 mediates the modulation of ncRNA on FA metabolism acting as important nodes of convergence and divergence in this regulatory network, which provides a foundation for the development of novel therapy by targeting ncRNAs and lipogenesis in cancer.

2.6. Stearoyl-CoA desaturase (SCD)

SCD, a key enzyme in the biosynthesis of monounsaturated fatty acids from saturated fatty acids, converts palmitoyl- and stearoyl-CoA into palmitoleoyl- and oleoyl-CoA, respectively, by promoting the introduction of cis-double bonds into short-chain FAs in the C9 position [77]. These productions, monounsaturated FAs, have altered physical properties and constitute the building blocks of multiple molecules including membrane phospholipids, triglycerides, cholesterol esters, wax esters and alkyl-1,2-diacylglycerol [78]. The dysregulated expression and activity have been observed in many types of cancers, and its significance for cancer biology has been increasingly recognized [79]. NcRNAs were also reported to participate in the regulation of SCD in neoplastic disease. MiR-600 acted as a bimodal switch that modulated the choice between self-renewal and differentiation of breast cancer stem cells, which were implicated in therapeutic resistance and tumor progression, by directly targeting SCD1, an enzyme required for the production of bioactive, lipid-modified WNT proteins. Furthermore, low level of miR-600 was associated with both active WNT signaling and poor outcomes in 120 breast tumors [80]. Moreover, Lise L. et al. also demonstrated that lnc SNHG16 modulated the expression SCD1, possibly through competing endogenous RNA (ceRNA) related mechanisms, leading to lipid metabolism reprogramming and cancer progression in CRC [81]. These findings reveal a ncRNAs-centered signaling network that regulates SCD1 and lipid metabolism in cancer development.

3. NcRNAs and key enzymes in FA degradation

Carnitine palmitoyltransferase 1A (CPT1A), located in the outer membrane of mitochondria, is a rate-limiting enzyme in the oxidation of fatty acids mechanically by catalyzing the synthesis of fatty acylcarnitine from long-chain fatty acyl-CoA and carnitine to promote the transport of fatty acids into mitochondria. CPT1A has been reported to be abnormally highly expressed in various tumors and plays a significant role in the tumor cell proliferation and metastasis. It was reported that PD1 could induce T cell metabolism reprogramming by inhibiting glycolysis and promoting lipolysis and FAO, which was achieved by increasing the expression of CPT1A [82].

And overexpression of CPT1A was shown to accelerate the

proliferation of ovarian cancer cells by increasing the oxidation of fatty acids and intracellular ATP levels. Correspondingly, etomoxir, a specific inhibitor of CTP1A, could significantly inhibit the proliferation of tumor cells [83]. Similarly, inhibition of CPT1A activity or expression in lymphoma could significantly suppress tumor cell proliferation, migration and metastasis [84]. In addition, vascular damage caused by changes in vascular endothelial cell permeability is also an important marker of malignant tumors. CPT1A also plays an important role in maintaining intracellular oxidative phosphorylation and Ca + homeostasis as well as maintaining normal permeability of vascular endothelial cells [85]. Meanwhile, increasing studies have found that overexpression of CPT1A is closely associated with clinical pathological parameters of tumors and may become a novel molecular marker for tumor diagnosis. In glioblastoma the high expression of CPT1A was significantly positively correlated with the highly differentiated state of the patient's tumor cells [86]. And in esophageal squamous cell carcinoma the overexpression of CPT1A also indicated the poor prognosis and lymph node metastasis status [87]. All these evidences are indicative of the critical role of CPT1 in carcinogenesis and cancer development. Therefore, CPT1 may serve as a promising target in cancer therapy. However, the relationship between ncRNAs and CPT1 remains unexplored yet, which might be a potential area for further study.

4. NcRNAs and key enzymes in FA storage

Exogenously or endogenously accumulated fatty acids in tumor cells can serve as substrates for the synthesis of membrane phospholipids and signal lipids or as substrates for β-oxidation to support the survival, proliferation and metastasis of cancer. It is conceivable that increasing the storage of FAs in TG is bound to result in a decrease in FAs available, leading to the suppression of tumor cells [2,88].

The main pathway for TG synthesis is the Kennedy pathway and a variety of enzymes participate in this process [89]. With the assistance of FA-CoA, glycerol-3-phosphate acyltransferase (GPAT) catalyzes the production of lysophosphatidic acid (LPA), which is subsequently converted to phosphatidic acid (PA) by acylglycerolphosphate acyltransferase (AGPAT). Then PA is catalyzed by lipin to synthesize DG and diacylglycerol acyltransferase (DGAT) is responsible for esterification of DG to constitute TG [90]. Therefore, the reprogramming of fatty acid metabolism can be achieved by regulating these enzymes related to fatty acid storage.

4.1. DGAT and lipin

DGAT, a transmembrane protein anchored to the endoplasmic reticulum, is responsible for esterification of DG and a fatty acyl moiety to constitute TG and accordingly inhibits the synthesis of DG to membrane phospholipids. As the pivotal rate-limiting enzyme in the Kennedy pathway, DGAT plays an important role in the synthesis and accumulation of TG. wo DGATs, including DGAT1 and DGAT2, have been identified to exert irreplaceable influence in TG synthesis and they are similar but not identical in evolution, localization, membrane topologies and biological functions (Bhumika et al.). Current research on DGAT focuses on obesity, insulin resistance and diabetes. Moreover, DGAT has also been reported to be abnormally expressed in a variety of tumors, such as prostate cancer, affecting the occurrence and progression of tumors [91].

Lipins, including lipin 1, lipin 2, and lipin 3, are multilayered regulators of lipid metabolism by directly catalyzing PA to form DG, or indirectly regulating the expression of lipid metabolism-related genes as a transcriptional co-stimulatory factor [92]. Prior researches have revealed the correlation between lipins and multiple diseases including AIDS, insulin resistance, obesity and diabetes. Moreover, lipins have also shown the regulatory roles in lung, colon and liver carcinogenesis [93,94].

Interestingly, inhibition of SPRY4-IT1 in melanoma by siRNA leads to suppression of growth and invasion and the induction of apoptosis in melanoma cells. Mechanically, the overexpression of lipin2 and DGAT aroused by decreased SPRY4-IT1 resulted the accumulation of TG, inducing lipotoxicity and apoptosis in cancer cells [95]. Conceivably, reducing the fatty acids necessary for cancer anabolism by up-regulating the expression of genes related to fatty acid storage may be a major blow to fatty acid metabolism which is vital in carcinogenesis and tumor development.

5. NcRNAs and key enzymes in FA release from storage

FA stored in the form of TG can be hydrolyzed by specific lipases and used as a substrate for further metabolism of cancer cells, promoting tumor proliferation and metastasis. Therefore, preventing the release of FA is also a possible cancer suppression strategy. In this process TG can be cleaved by adipose triglyceride lipase (ATGL) to generate DG, which is then converted to monoacylglycerol (MAG) by hormone sensitive lipase (HSL). And monoacylglycerol lipase (MAGL) contributes to the production of FA from MAG. Therefore, reprogramming of fatty acid metabolism can be achieved by regulating these enzymes related to fatty acid release.

5.1. ATGL

ATGL is a key lipohydrolase responsible for the hydrolysis of triglycerides to form diglycerides. Studies have shown that it is closely related to the occurrence of obesity, insulin resistance and type 2 diabetes. Although the exact mechanism of action of ATGL in cancer has not been studied clearly, ATGL has been found to be abnormally expressed in various cancers, such as lung and pancreatic cancer, and induce abnormal lipid metabolism in tumor cells. It was reported that miR-124a could inhibit the hydrolysis of TG by targeting ATGL to regulate lipid homeostasis and free fatty acids (FFA) concentration [96]. However, this regulatory mechanism has not been confirmed in cancer.

6. NcRNAs and key enzymes in FA transport

6.1. Fatty acid–binding protein (FABP)

Fatty acid–binding protein (FABP), a family of ~15-kDa abundant intracellular proteins, bind to hydrophobic ligands such as long-chain fatty acids with high affinity [97]. Once FFA enter the cell by free diffusion or passive transport, the FABPs immediately bind with high affinity to FFA and transfer it to the target area, including the endoplasmic reticulum, mitochondria, and cell nucleus, for further oxidation or esterification with the assistance of various proteins [98]. Since first identified in 1972, nine mammalian FABPs with highly conserved tertiary structures and unique tissue-specific distributions and functions have gradually been discovered, widely involved in cellular FA uptake, lipid composition and FA-dependent gene regulation [99,100]. The most glaring are FABP4 (adipocyte subtype) and FABP5 (epidermal subtype) due to their significant roles in metabolic disorders, atherosclerosis and cancer [101]. The disordered expression of FABPs has been observed in various cancers [102]. And some cancers scavenge lipids from their microenvironment, indicating the possibility of blocking FA uptake to treat cancer [103]. It was reported that lncLNMICC promoted nodal metastasis of primary cervical cancer through the regulation of fatty acid metabolism, mechanically by recruiting the nuclear factor NPM1 to the promoter of the FABP5, and interestingly this pro-tumor effect of LNMICC could be interdicted by miR-190, which established the roles of ncRNAs in the cancer-associated FAM reprogramming [104].

6.2. Fatty acid translocase (FAT/CD36)

Fatty acid translocase (FAT), also called as Cluster of differentiation 36(CD36), is a fatty acid receptor responsible for the recognition and transmembrane transport of extracellular FAs. CD36 can help tumor cells take up FA molecules from the surrounding environment to provide substrates for energy production and macromolecular synthesis, involved in various biological processes [105]. Early studies about FAT focused on the roles in angiogenesis and atherosclerosis through the regulation of foam cells formation, apoptosis and transportation of fatty acids [106]. With the recognition of the significance of fatty acid metabolism in cancer, the roles of CD36 in tumorigenesis and development have attracted more and more attention.

CD36 was reported to be dysregulated in various cancers and closely related to the tumor cell metabolism, survival, proliferation and especially, metastasis [107,108]. Pascual G et al. reported the unique ability of fatty acid receptor CD36 initiating metastasis, mechanically by relying on dietary lipids with a CD36 dependent manner to promote metastasis in human oral carcinomas [109]. And the similar pro-metastasis effect of CD36 also occurs in ovarian and cervical cancer [110,111]. Previous studies have reported that miR-133a and miR-758-5p could reduce the lipid accumulation in macrophages by modulating the expression of CD36 in atherosclerotic vascular disease, however, the regulation of CD36 by ncRNAs in carcinogenesis and cancer development is still poorly studied, which might be a promising research direction [112,113].

7. NcRNAs-based therapy in cancer treatment

Studies about the regulation of ncRNAs in tumor metabolism are in full swing and gradually applied to the clinic. The ncRNAs associated with cancer fatty acid metabolism mentioned in this paper are promising as novel biomarkers to aid cancer diagnosis and assess prognosis risk, due to the accessibility of ncRNAs with non-invasive methodology and their close association with cancers. Recent research reported the close correlation between low miR-205 expression and recurrence risk in NSCLC and described it as an efficient marker for prognostic evaluation [114]. And tumor-derived exosomal miR-320b, a squamous cell carcinoma-specific miRNA, was regarded as a powerful marker for early diagnosis of NSCLC due to its non-invasive convenience and high sensitivity to distinguish between squamous cell carcinoma and adenocarcinoma [115]. Besides, the level of miR-195 in plasma of patients with adrenocortical carcinoma was positively correlated with recurrence rate and overall survival, and the high specificity of the prediction of recurrence risk of adrenocortical carcinoma made it a significant non-invasive biomarker [116]. Furthermore, in addition to the diagnostic and prognostic value of ncRNAs involved in cancer fatty acid metabolism, their potential value in cancer treatment is also getting more attention. And a variety of pre-clinical animal experiments about ncRNAs in cancer treatment are being performed. Some scholars have found that compared with cisplatin alone, a combination of cisplatin and nanoliposomes loaded with miR-15a and miR-16 could significantly reduce the tumor burden in a preclinical orthotopic mouse model of drug-resistant ovarian cancer, which suggested a possible and promising application of ncRNAs in clinical cancer treatment [117].

In view of the vital roles of ncRNAs in transcriptome dynamics and proteome outcomes and the enormous potential in clinical application, various ncRNA tools has been explored to regulate the distorted ncRNAs network in cancer, by resetting tumor suppressive ncRNAs expression/function or inhibiting a druggable ncRNA target with RNA aptamers or antisense RNAs to elicit the pharmacological effects.

In the past two decades, several ncRNA-based drugs, such as fomivirsen, alicaforsen and pegaptanib, have gradually been approved for clinical use in the treatment of multiple diseases, demonstrating the possibility of RNA agents as a novel therapy [118]. And with the advancement of in vivo delivery technology, ncRNA-based therapy will become more common and efficient. However, these chemically engineered oligonucleotides or RNA “mimics” generally do not carry the important post-transcriptional modifications in natural RNA, which makes their biological activity and safety uncertain. So the development of bioengineered ncRNA agents, which have a cheaper and more efficient production method, more similarity to the nature and function of natural RNA as well as more precise safety and more effective treatment, are gradually arousing people's interest [119].

Furthermore, based on the critical role of ncRNAs in carcinogenesis, the clustered regularly interspaced short palindromic repeats-associated nuclease 9 (CRISPR/Cas9), a novel gene-editing technology, has also been applied into the ncRNAs-related precision oncology, mechanically by targeting non-coding area in genome [120]. Prior studies have reported the successful edition of ncRNAs and efficacious inhibition of malignant characteristics by CRISPR/Cas9 system in various cancers, such as HCC, colon and ovarian cancer, both in vivo and in vitro, implicating a feasible approach on cancer therapy [121–123].

Although there are some deficiencies in ncRNA-based therapy, this novel therapeutic strategy still holds great promise to the precision medicine in future. And functional ncRNAs associated with FAM remain as unexplored targets for pharmacotherapy, which thus offers new opportunities for drug development.

8. Conclusion and future perspectives

In the occurrence and progression of cancer, tumor cells reprogram fatty acid metabolism to adapt to the high demand for biomacromolecules during fast proliferation. NcRNAs participate in this process by regulating key enzymes or related signaling pathways in fatty acid metabolism, leading to cancer progression.

Many studies mentioned in this review have reported the significant effect of ncRNAs-mediated lipid metabolism on cancer cell survival, proliferation and metastasis, and these ncRNAs might be biomarkers for early diagnosis and prognosis of cancer. Moreover, the expression level of ncRNAs can be detected by non-invasive diagnostic methods, the simplicity and operability in which make it an attractive biomarker candidate. Circulating ncRNAs may gradually become mature biomarkers for metabolic diseases and ultimately been applied to cancer metabolism testing, risk assessment and disease grading. Meanwhile, from a therapeutics standpoint, ncRNAs have a variety of physiological targets, including not only key enzymes in fatty acid metabolism but also components of fatty acid metabolism-related signaling pathways, making targeting lipid metabolism associated ncRNAs a potential efficient cancer therapy. Nevertheless, due to the complexity of ncRNAs-mRNA interactions as well as the technological limitations of targeted drug synthesis and in vivo delivery, a thorough understanding of the roles of ncRNAs in systemic metabolism and tumor metabolic reprogramming and its clinical application are still challenging. Future research may adequately use human disease ncRNAs profiling data combined with more diverse sensitive and accurate detection techniques as well as bioinformatics/biostatistical analysis of complex data sets to further elucidate the ncRNAs-mediated lipid metabolism regulation network in cancers. And with the development in computer technology, advances in oligonucleotides miRNA mimics anti-miRNA oligonucleotides lncRNA or circular RNA synthesis techniques and improvements in in vivo delivery methods, ncRNAs can be used to make cancer more promising to be treated.

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