

Targeting ncRNAs to overcome metabolic reprogramming-mediated drug resistance in cancer (Review)

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Abstract. The emergence of resistance to antitumor drugs in cancer cells presents a notable obstacle in cancer therapy. Metabolic reprogramming is characterized by enhanced glycolysis, disrupted lipid metabolism, glutamine dependence and mitochondrial dysfunction. In addition to promoting tumor growth and metastasis, metabolic reprogramming mediates drug resistance through diverse molecular mechanisms, offering novel opportunities for therapeutic intervention. Non-coding RNAs (ncRNAs), a diverse class of RNA molecules that lack protein-coding function, represent a notable fraction of the human genome. Due to their distinct expression profiles and multifaceted roles in various cancers, ncRNAs have relevance in cancer pathophysiology. ncRNAs orchestrate metabolic abnormalities associated with drug resistance in cancer cells. The present review provides a comprehensive analysis of the mechanisms by which metabolic reprogramming drives drug resistance, with an emphasis on the regulatory roles of ncRNAs in glycolysis, lipid metabolism, mitochondrial dysfunction and glutamine metabolism. Furthermore, the present review aimed to discuss the potential of ncRNAs as biomarkers for predicting chemotherapy responses, as well as emerging strategies to target ncRNAs that modulate metabolism, particularly in the context of combination therapy with anti-cancer drugs.

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1. Introduction

Cancer is the second leading cause of global mortality, with ~20 million cases and 9.7 million deaths reported in 2022 (1). While therapeutic strategies such as surgical resection, chemotherapy, radiotherapy, targeted therapy and immunotherapy have advanced, drug resistance and adverse reactions undermine clinical outcomes (2,3). Drug resistance not only drives tumor recurrence but also perpetuates cancer as a key public health challenge (4).

Current investigations into therapy resistance mechanisms extend beyond ATP-binding cassette (ABC) transporter-mediated drug efflux to encompass metabolic reprogramming, exemplified by the Warburg effect, alongside dynamic mitochondrial interactions (5,6). Cancer cells exhibit a range of metabolic adaptations, enabling them to secure energy despite limited nutrient and oxygen availability (7). In the 1920s, Otto Warburg demonstrated that cancer cells preferentially generate ATP through glycolysis, even in the presence of sufficient oxygen (8). Research on cancer cell metabolism primarily focuses on glycolysis, glutamine metabolism and mitochondrial protective mechanisms (9,10). Moreover, abnormal lipid metabolism is a hallmark of metabolic reprogramming (11). These adaptations create interconnected networks that sustain tumorigenesis and therapeutic evasion.

Targeting cancer metabolism gained momentum in the 20th century with nucleotide metabolism inhibitors such as methotrexate (12). However, clinical setbacks with glycolysis inhibitors such as 2-deoxyglucose (13) shifted focus toward oncogene-targeting therapies due to the limited efficacy and undesirable side effects. Metabolic intervention strategies

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have been facilitated by discoveries linking non-coding RNAs (ncRNAs) to cancer molecular biology. ncRNAs are a class of RNAs that lack protein-coding potential and were once considered non-essential components of the genome. Functionally diverse ncRNAs, including long ncRNAs (lncRNAs), circular RNAs (circRNAs) and microRNAs (miRNAs or miRs) (14), regulate tumor progression through nuclear chromatin remodeling, cytoplasmic mRNA interactions and competing endogenous RNA (ceRNA) network formation (15,16). In addition to their roles in cell proliferation, invasion, migration, and apoptosis, ncRNAs orchestrate metabolic reprogramming across glycolysis, mitochondrial function and glutamine and lipid metabolism (17), thereby driving drug resistance in multiple types of cancer, such as prostate and breast cancer (BC) (18,19). ncRNAs have thus become an increasingly recognized target for cancer treatment, as well as potential biomarkers (14,19). The present review aimed to outline the mechanisms through which metabolic changes influence drug resistance in tumor cells and how ncRNAs mediate drug resistance via metabolic regulation. Metabolism-regulating ncRNAs hold promise as both biomarkers and therapeutic targets for overcoming drug resistance in cancer.

2. ncRNAs regulate drug resistance by mediating metabolic reprogramming

Chromosomal variability and immune escape predispose tumors to both intrinsic and acquired resistance to treatment. Intrinsic drug resistance stems from cancer cell genetic and epigenetic traits, making certain types of tumor hard to treat with conventional therapy (20). For example, in colorectal cancer (CRC), the activation of the Wnt/ β -catenin signaling pathway enhances stem cell characteristics, thereby rendering the cells resistant to cisplatin (20). Acquired drug resistance develops gradually under therapeutic pressure, driven by dynamic changes in cancer cell behavior and signaling pathways (21). In parallel with tumor metabolism research, drug resistance is frequently driven by metabolic reprogramming (10,17) (Fig. 1). As a hallmark of cancer, metabolic reprogramming supplies the essential nutrients and energy required for tumor progression, while ncRNAs exert a notable impact. ncRNAs modulate tumor metabolism by activating metabolism-associated signaling pathways or targeting key metabolic enzymes (22,23). In metabolically dysregulated tumor cells, ncRNAs display aberrant expression, influenced by factors such as DNA methylation (24), transcription factors (25), and hypoxic or oncogenic stimuli (26,27). Additionally, ncRNAs can be transferred between cells via exosomes. For example, temozolomide (TMZ)-resistant glioma cells transfer circ-0072083 to TMZ-sensitive cells through exosomes (28). The deregulation of ncRNAs disrupts metabolic pathways in tumor cells, thereby driving metabolic reprogramming and altering tumor sensitivity to therapeutic intervention (Table I).

Key processes in glycolysis. Aerobic glycolysis serves as a prominent example of a reprogrammed metabolic pathway in cancer cells. Tumor cells uptake glucose in large quantities, which is converted to pyruvate by enzymes such as hexokinase

(HK), phosphofructokinase (PFK) and pyruvate kinase (PK). Pyruvate is subsequently converted to lactic acid by lactate dehydrogenase A (LDHA) or transported to the mitochondria, where it is catalyzed by pyruvate dehydrogenase (PDH) to form acetyl-CoA (9).

Mechanism of glycolysis-induced drug resistance. Glycolysis contributes to drug resistance through multiple mechanism. Glycolysis provides cancer cells with sufficient energy to maintain malignancy (6). 3-bromopyruvate is a glycolysis inhibitor that markedly decreases glycolytic activity by inhibiting the enzyme HK2. This inhibition impairs the energy supply derived from glycolysis, leading to a decrease in ATP and glutathione (GSH) levels in tumor cells, thereby enhancing their sensitivity to chloroethylnitrosoureas, a bifunctional anti-tumor alkylating agent (29). In drug-resistant cancer cells, the PI3K/AKT signaling pathway is activated, which regulates glycolysis (30), causing higher ATP levels than in drug-sensitive cells (31,32). This process provides the necessary energy for ABC transporters to facilitate drug efflux (33). Chondroitin sulfate disrupts mitochondrial electron transport and glycolysis to deplete ATP. This energy depletion impairs P-glycoprotein (P-gp) activity, thereby decreasing doxorubicin efflux (34).

Numerous glycolysis enzymes are associated with cell death. For example, HK2 translocates to mitochondria where it inhibits mitochondrial permeability transition pores to block cytochrome c/Bax release, enhancing tumor cell survival (35). Mitochondrial PKM2 binds BCL2 to suppress reactive oxygen species (ROS)-mediated apoptosis (36). Additionally, fructose-1,6-diphosphate aldolase delays drug-induced apoptosis by decreasing caspase-3 activity through catalytic product accumulation (37). Furthermore, PDH kinase 3 (PDK3) overexpression promotes lycorine hydrochloride resistance in glioblastoma cells via apoptosis inhibition (38). 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) activates cyclin-dependent kinases (CDKs), leading to the phosphorylation of p27, a potent inhibitor of G1/S transformation and activator of apoptosis (39). PFKFB3 also regulates angiogenesis through vascular endothelial growth factor (VEGF)-mediated endothelial morphogenesis and Notch signaling suppression (40). The morphology of tumor blood vessels is irregular. This leads to localized nutritional and oxygen deficiency, which in turn promote tumor metastasis (41). Combining anti-angiogenic therapies that target PFKFB3 reverses the abnormal changes in tumor blood vessels, improving the delivery of chemotherapy drugs (41).

The Warburg effect results in the accumulation of lactic acid, which dilates blood vessels and stimulates angiogenesis to enhance local energy supply through an increase in oxygen and nutrients (42). Excessive lactic acid also decreases the pH around tumor cells, creating a pH gradient both inside and outside the cells (43). Weakly basic drugs dissociate in the acidic extracellular environment, hindering their passage through the cell membrane or sequestering them in acidic lysosomal vesicles (43,44), rendering them ineffective. Conversely, weakly acidic drugs enter cells but are often inactivated before reaching their target due to the alkaline intracellular conditions (45). Furthermore, extracellular acidosis promotes drug efflux via P-gp (46), multidrug

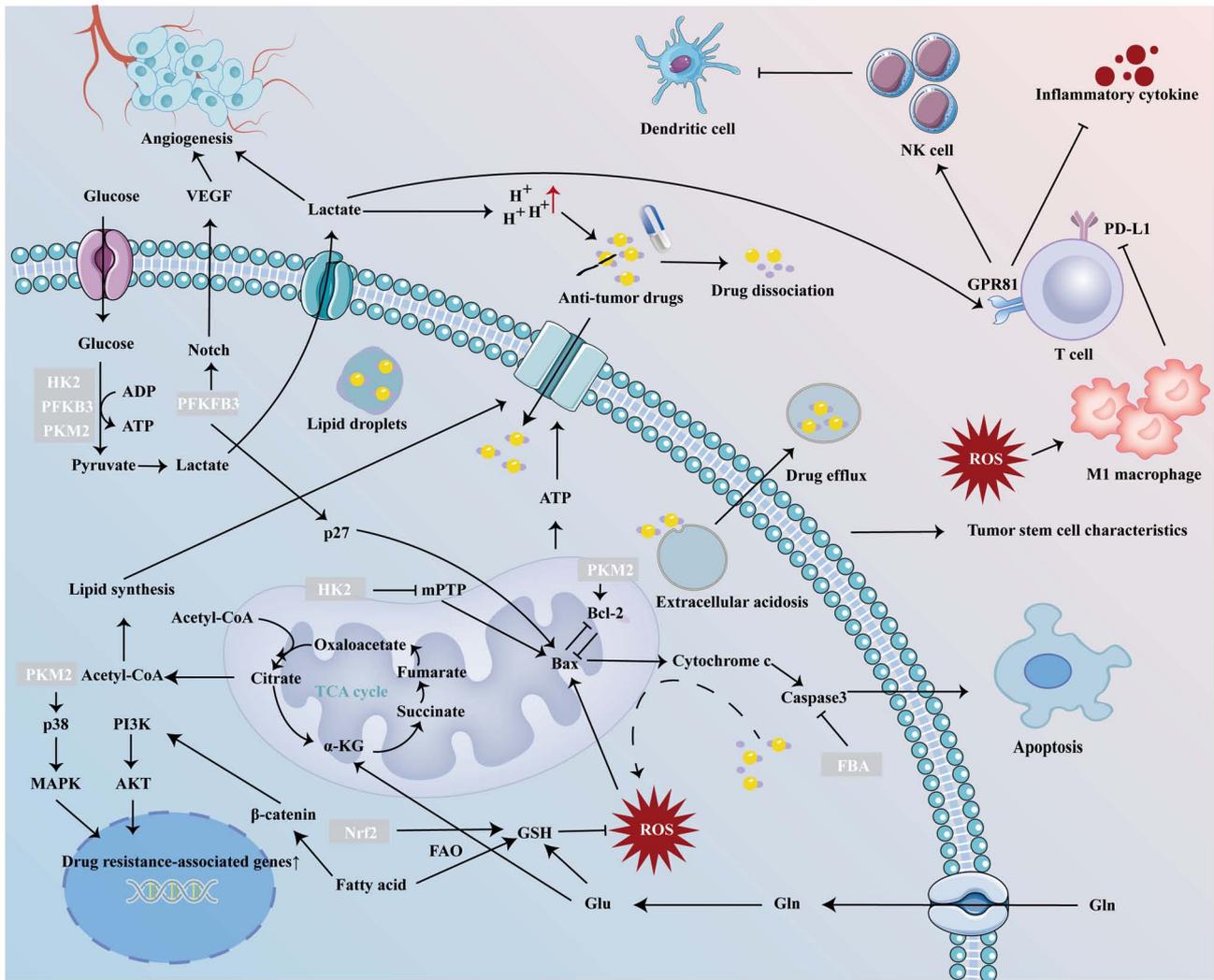


Figure 1. Metabolism promotes tumor drug resistance. Abnormal metabolism in tumor cells encompasses glycolysis, lipid metabolism, glutamine metabolism and mitochondrial dysfunction. Metabolic reprogramming equips tumor cells with adequate ATP, facilitates angiogenesis and activates signaling pathways associated with drug resistance. An imbalance in the redox system resulting from metabolic disorder renders cells resistant to oxidative stress induced by drugs. The increased lipid synthesis and lactic acid secretion in cancer cells promote the decomposition and efflux of therapeutic agents. Byproducts of abnormal metabolism enhance the stem cell characteristics of tumor cells, allowing them to evade attacks from immune cells within the tumor microenvironment. NK, natural killer; PD-L, programmed death ligand; GPR, G protein-coupled receptor; HK, Hexokinase; PFKB, Phosphofructo-2-kinase/fructose-2,6-biphosphatase; PKM, Pyruvate kinase M; TCA, tricarboxylic acid cycle; α -KG, α -ketoglutarate; FAO, fatty acid oxidation; GSH, glutathione; ROS, reactive oxygen species; FBA, fructose-1,6-diphosphite aldolase; mPTP, mitochondrial permeability transition pores.

resistance-related protein 1 (MRP1) (47) and intracellular acidic vesicles (48), further contributing to chemotherapy resistance. Elevated lactate levels serve as agonists for the G protein-coupled receptor GPR81, which is expressed on immune cells. Activation of GPR81 decreases the release of pro-inflammatory cytokines from T cells and may impair the function of natural killer cells, partially through recruitment of monocyte-derived dendritic cells (49). Monocarboxylate transporter-1-mediated lactate transport is essential for maintaining intracellular pH in cancer cells, a process that supports the stem cell properties of pancreatic adenocarcinoma and glioblastoma stem cells (50,51). Additionally, when several key enzymes, such as HK2, PFKFB3 and PKM2, are abnormally elevated, the Wnt/ β -catenin, Erk1/2 and YAP/Hippo signaling pathways become activated (52-54). These pathways are recognized as key regulators that promote resistance to anti-cancer drugs.

ncRNAs target the key factors of glycolysis

Hypoxia-inducible factor (HIF)-1 α . In solid tumors, cancer cells frequently exist in a hypoxic environment, where they tend to derive energy primarily through glycolysis. HIF-1 serves as a crucial regulator of cancer cell responses to hypoxia and facilitates metabolic switching, while HIF-1 α is an important subtype (55). The enhancement of glycolysis by HIF-1 is associated with its ability to induce the expression of various glycolytic enzymes at the transcriptional level (56). These enzymes differ from the subtypes of glycolytic enzymes present in non-malignant cells, including HK2, PKM and LDHA, playing a key role in the metabolic shift of cancer cells from oxidative phosphorylation to glycolysis (57). Besides, HIF-1 α also enhances the expression of Bcl-2/adenovirus E1B 19 kDa interacting protein 3, which triggers mitochondrial selective autophagy, thereby decreasing oxidative metabolism in cancer cells (58).

Table I. ncRNAs and their molecular targets in metabolic reprogramming-mediated drug resistance.

A, miR			
ncRNA	Molecular target	Mechanism	(Refs.)
miR-140, -143, -218 and -1291-5p	GLUT1	Inhibition of cancer glycolysis	(66,68,69)
miR-202 and -125b	HK2		(74,75)
miR-488	PFKFB3		(78)
miR-122	PKM2		(87-89)
miR-326	HNRNPA1, HNRNPA2 and PTBP1	Inhibition of PKM2 and glycolysis	(85)
miR-374b	HNRNPA1		(91)
miR-329-3p	LDHA	Inhibition of cancer glycolysis	(97)
miR-3679-5p	NEDD4L/C-Myc/LDHA	Promotion of cancer glycolysis	(102)
miR-21-5p	PDH1	Inhibition of cancer glycolysis	(105)
miR-4290 and -148a	PDK1		(107,108)
miR-134	PTBP1		(25)
miR-155 and -149-3p	PI3K/AKT	Promotion of cancer glycolysis	(116,117)
miR-143	HK2	Downregulated by EGFR to inhibit glycolysis	(121,123)
miR-186-3p	EREG/EGFR	Inhibition of cancer glycolysis	(124)
miR-27a	AMPK/mTOR	Promotion of cancer glycolysis	(132)
miR-95	SGPPI1/AKT	Promotion of sphingolipid synthesis	(151)
miR-128 and -223	HMGCS1, LDLR and ABCA1	Modulation of cholesterol biosynthesis	(153)
miR-33a	HDL	Prevention of HDL-mediated cholesterol extraction	(154)
miR-23a-3p	ACSL4	Inhibition of ferroptosis	(170)
miR-128-3p	GPX4	Promotion of ferroptosis	(188)
miR-522	ALOX15	Inhibition of ferroptosis	(190)
miR-432-5	CHAC1		(191)
miR-125b	PARP	Induction of apoptosis	(201)
miR-518d-5p	c-Jun/PUMA	Inhibition of apoptosis	(205)
miR-2329	Complexes I, III and IV	Elevation of mitochondrial ROS	(206)
miR-150, -328 and -616	CD46, CD55 and CD59	Regulation of mitochondrial activity	(208)
miR-98	LASS2	Promotion of mitochondrial fission	(209)
miR-5787	MT-CO3	Inhibition of oxidative stress	(210)
miR-34b/c	c-Myc/ γ -GCS	Enhancement of cellular tolerance to ROS	(211)
miR-27a	Nrf2	Decreased cellular resistance to ROS	(213)
miR-23b-3p, -200a-3p, -141-3p and -203	GLS	Inhibition of the conversion of Gln to Glu	(215-218)

B, lncRNA

ncRNA	Molecular target	Mechanism	(Refs.)
lnc-RP11-536K7.3	SOX2/USP7/HIF1 α	Promotion of cancer glycolysis	(61)
lnc-HISLA	HIF-1 and PHD2		(62)
lnc-HIF1 α -AS1	AKT/YB1/HIF1 α		(63)
lnc-SNHG1	miR-216b-5p/HK		(71)
lnc-DANCR	miR-125b-5p/HK2		(72)
lnc-MBNL1-AS1	miR-708-5p/HK2		(73)
lnc-UCA1	miR-125a/HK2		(76,77)
lnc-SNHG3	miR-139-5p/PKM2		(83)
lnc-PCIF1	miR-326/PKM		(84)
LINC01852l	SRSF5/PKM2		(86)
lnc-TBX15	miR-152/KIF2C/PKM2		(92)

Table I. Continued.

B, lncRNA			
ncRNA	Molecular target	Mechanism	(Refs.)
lnc-CTSLP8	PKM2		(93)
lnc-SNHG7	miR-34a/LDHA		(95)
lnc-XIST	miR-101-3p/LDHA		(96)
lnc-HAGLR	miR-338-3p/LDHA		(98)
lnc-NEAT	miR-34a/LDHA		(99)
lnc-GLTC	SIRT5/LDHA		(100)
lnc-SNHG16	miR-506-3p/PTBP1		(109)
lnc-DIO3OS	PTBP1		(110)
lnc-FGD5-AS1	miR-330-3p/HK		(121)
LINC00665	miR-665/MAPK1		(128)
lnc-HOTAIRM1	Wnt/ β -catenin/PFK		(134)
lnc-ROPM	PLA2G16	Enhanced production of FFAs and arachidonic acid	(141)
lnc-DLGAP1-AS2	FAM3D/PLD	Promotion of PA production	(150)
LINC01056	PPAR α	Inhibition of FAO	(163)
lnc-MACC1-AS1	miR-145-5P/OCT4 and CPT1	Promotion of FAO	(26)
lnc-HCP5	miR-3619-5p/PPARGC1A		(164)
lnc-PVT1	PLAG1/GPX4	Inhibition of ferroptosis	(187)
lnc-HCG18	miR-450b-5p/GPX4		(189)
lnc-SAMMSON	Complex I	Elevation of mitochondrial ROS	(207)
lnc-H19	Nrf2	Promotion of GSH production	(212)
lnc-SLC7A11-AS1	SCF ^{β-TRCP} /Nrf2	Decreased intracellular ROS levels	(213)
lnc-PVT1	miR-181a-5p/GLS	Promotion of the conversion of Gln to Glu	(219)
lnc-FEZF1-AS1	miR-32/GLS		(220)
lnc-PXN-AS1	miR-653/GS	Promotion of Gln synthesis	(222)

C, circRNA

ncRNA	Molecular target	Mechanism	(Refs.)
circHIF1A	miR-361-5p/HIF1 α	Promotion of cancer glycolysis	(59)
circNRIP1	miR-138-5p/HIF1 α		(60)
circZNF91	miR-23b-3p/SIRT1		(64)
circRNA-0002130	miR-498/GLUT1		(67)
circ-SAMD4A	miR-545-3p/PFKFB3		(79)
circARHGAP29	IGF2BP2/C-Myc/LDHA		(103)
circQSOX1	miR-326 and miR-330-5p/PGAM1		(112)
circSNX6	miR-1184/GPCPD1	Promotion of LPA levels	(148)
circRNA-101093	FABP3	Decreased AA content	(149)

lnc, long non-coding; miR, microRNA; ROS, reactive oxygen species; HDL, high-density lipoprotein; GLUT, Glucose transporter; HK, Hexokinase; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PKM, Pyruvate kinase M; HNRNPA1, Heterogeneous Nuclear Ribonucleoprotein A1; PTBP1, Polypyrimidine Tract-Binding Protein 1; LDHA, Lactate dehydrogenase A; NEDD4L, NEDD4-like E3 ubiquitin protein ligase; PDH, Pyruvate Dehydrogenase; PDK, Pyruvate Dehydrogenase Kinase; GSH, Glutathione; FAO, Fatty acid oxidation; EREG, Epregrulin; SGPP, Sphingolipid Phosphatase; HMGCS1, 3-Hydroxy-3-methylglutaryl-CoA Synthase 1; LDLR, Low-Density Lipoprotein Receptor; ABCA, ATP-Binding Cassette Transporter A; HDL, High-Density Lipoprotein; ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; GPX, Glutathione Peroxidase; ALOX, Lipoxygenase; CHAC, Cyclotransferase; PUMA, p53-upregulated modulator of apoptosis; LASS, Longevity Assurance Homologue; MT-CO3, Mitochondrial Cytochrome c Oxidase Subunit 3; GCS, glutamyl-cysteine synthetase; GLS, Glutaminase; USP, Ubiquitin-Specific Protease; HIF, Hypoxia-inducible factor; SRSF, Serine/Arginine-Rich Splicing Factor; KIFC2, Kinesin Family Member 2C; SIRT, Sirtuin; PFK, Phosphofructokinase; PLA2G16, Phospholipase A2 Group 16; FAM3D, FAM3 metabolic regulatory signaling molecule D; PLD, Phospholipase D; OCT, Octamer-binding Transcription Factor; CPT, Carnitine Palmitoyltransferase; FFA, Free fatty acids; PA, Phosphatidic Acid; PPARGC1A, PPARG coactivator 1 α ; PLAG, Pleiomorphic Adenoma Gene; SCF ^{β -TRCP}, SKP1-Cul1-Rbx1; GS, Glutamine Synthetase; IGF2BP2, Insulin-like Growth Factor 2 mRNA-Binding Protein 2; PGAM, Phosphoglycerate mutase; GPCPD1, Glycerol phosphocholine phosphodiesterase 1; LPA, Lysophosphatidic Acid; AA, Arachidonic Acid; FABP, Fatty Acid-Binding Protein; Glu, glutamate.

A number of ncRNAs regulate HIF-1 α to promote glycolysis. For example, circHIF1A upregulates HIF1 α by competitively binding miR-361-5p, leading to the overexpression of enzymes such as glucose transporter 1 (GLUT1) and LDHA. In a xenograft model, silencing circHIF1A enhances sensitivity to cetuximab treatment (59). Similarly, circNRIP1 acts as a miR-138-5p sponge, promoting HIF-1 α -dependent glycolysis and contributing to 5-fluorouracil (FU) resistance in gastric cancer (GC) (60). Li *et al.* (61) demonstrated that lncRNA RP11-536K7.3 recruits sex-determining region Y-box2 (SOX2) to activate Ubiquitin-specific protease 7 (USP7) transcription, which stabilizes HIF-1 α by deubiquitination, thus enhancing glycolysis and conferring resistance to oxaliplatin in CRC. In BC, tumor-associated macrophages (TAMs) transfer HIF1-stabilizing lncRNA HISLA to cancer cells via extracellular vesicles. HISLA facilitates glycolysis and enhances resistance to chemotherapy-induced apoptosis by preventing the interaction between prolyl-4-hydroxylase domain protein 2 and HIF-1. Additionally, elevated HIF-1 induces lactic acid release from BC cells, which upregulates HISLA expression in TAMs, creating a positive feedback loop (62). Such positive feedback mechanisms of HIF-1 α on ncRNAs are common. For example, lncRNA HIF1 α -AS1 activates AKT, promoting the phosphorylation of Y-box binding protein 1 (YB1), which recruits phosphorylated-YB1 to HIF-1 α mRNA, enhancing its translation. HIF1 α directly binds the HIF1 α -AS1 promoter, driving its transcription (63). HIF1 α also regulates the transcription of circZNF91, notably increasing its presence in exosomes derived from hypoxic pancreatic cancer (PC) cells. circZNF91 is subsequently transferred to normoxic PC cells, where it competitively binds miR-23b-3p, thereby alleviating miR-23b-3p's inhibition of sirtuin1 (SIRT1). Elevated SIRT1 then promotes glycolysis and confers resistance to gemcitabine (GEM) in PC cells (64).

GLUT1. GLUT is a high-affinity membrane protein responsible for glucose uptake into the cytoplasm. In cancer cells, GLUT1 is often overexpressed, facilitating enhanced glucose uptake to meet the energy demands required for aerobic glycolysis (62). A recent study (65) indicated that elevated GLUT1 expression in endometrial cancer (EC) is associated with increased cell proliferation and invasion and glycolysis. Moreover, GLUT1 overexpression promotes the expression of MMP1, MMP14 and Cyclin D1 in EC cells (66). Dual-luciferase assays confirmed GLUT1 as a direct target of miR-140 and miR-143, which suppress EC cell proliferation and glycolysis by inhibiting GLUT1 expression, thereby enhancing sensitivity to Paclitaxel (PTX) (66). Additionally, circRNA-0002130, secreted in serum exosomes of patients with non-small cell lung cancer (NSCLC), promotes glycolysis and exacerbates resistance to osimertinib. Mechanistically, circRNA-0002130 serves as a sponge for miR-498, which targets GLUT1, thereby indirectly upregulating GLUT1 expression in NSCLC cells (67). Furthermore, miR-1291-5p and miR-218 serve as direct regulators of GLUT1, counteracting cisplatin resistance in pancreatic and bladder cancer cells (68,69).

HK2. HKs, located in the cytoplasm, are the primary rate-limiting enzymes in glycolysis. HKs catalyzes the phosphorylation of glucose to form glucose-6-phosphate,

representing the initial step in the glycolytic pathway (70). HK2, in particular, is overexpressed in numerous types of cancer and is associated with resistance to chemotherapy (34). A study demonstrated that HK2 can enhance cisplatin-induced phosphorylation of ERK1/2, thereby promoting cellular autophagy induced by cisplatin (52). miRNAs can directly target the 3' untranslated region (UTR) of HK2 to suppress its expression, including miR-708-5p, miR-202, miR-125b-5p and miR-216b-5p (71-74). These miRNAs inhibit glycolysis by downregulating HK2 expression. However, in cancer cells, these miRNAs may be suppressed by upstream lncRNAs, contributing to drug resistance (71-74), along with increased glucose uptake and lactate secretion (74,75). For example, lncRNA-UCA1, functioning as an oncogene in both solid and hematological tumors, is associated with decreased drug sensitivity. Overexpression of UCA1 promotes glycolysis by upregulating HK2, and UCA1 can indirectly regulate HK2 by sponging miR-125a, thereby promoting drug resistance (76). Inhibiting UCA1 enhances the sensitivity of cancer cells to chemotherapy drugs such as PTX and doxorubicin (76,77).

PFK. PFK, located in the cytoplasm, is divided into two subtypes: PFK1, which catalyzes the conversion of fructose 6-phosphate to fructose-1,6-bisphosphate, marking the second rate-limiting step in glycolysis, and PFKFB, which converts fructose-6-phosphate to fructose-2,6-bisphosphate (F2,6P2) (70). PFKFB3, the most active isoform of PFKFB, is upregulated in numerous types of cancer in response to activation of hypoxic signals, RAS signaling, estrogen receptor and P53 mutations, driving glycolytic metabolism in tumors (40). PFKFB3 generates F2,6P2, which activates CDKs. This triggers CDK-mediated phosphorylation of p27, leading to its ubiquitination and proteasomal degradation via CDK1, thereby reducing p27 levels (40). PFKFB3 also enhances cancer cell stemness and promotes resistance to numerous chemotherapeutic agents by upregulating the YAP/Hippo signaling pathway in small cell lung carcinoma (53). In CRC, miR-488 has been shown to target and inhibit PFKFB3 expression (78). High levels of PFKFB3 promote the proliferation, invasion and migration of CRC cells, while also contributing to resistance to chemotherapy agents such as 5-FU and oxaliplatin (78). Similarly, the circ-SAMD4A is highly expressed in CRC. SAMD4A can indirectly upregulate PFKFB3 by sponging miR-545-3p, thereby inhibiting apoptosis and decreasing sensitivity to 5-FU in CRC cells through the miR-545-3p/PFKFB3 axis (79).

PKM2. PKM2 catalyzes the final rate-limiting step of glycolysis in cancer cells, producing pyruvate and ATP (80). The upregulation of PKM2 isoforms in cancer is associated with drug resistance (81). In the cytoplasm, PKM2 facilitates the process of glycolysis. Following post-translational modification, PKM2 is translocated to the nucleus, where it serves as a transcriptional co-activator for STAT3, β -catenin and NF- κ B. This activates drug resistance-related genes, which enhance cancer drug resistance (54). TGF- β and STAT3 synergistically promote the expression of PKM2, which upregulates PD-L1 expression in cancer cells, further enhancing cancer immune escape (82). Recent studies (83-86) have revealed that ncRNAs mediate PKM2-associated drug resistance through various

mechanisms. For example, miR-122 directly binds the 3'UTR of PKM2, inhibiting its expression and reversing resistance to oxaliplatin, docetaxel and doxorubicin by attenuating glycolysis (87-89). The glycolysis-related lncRNA SNHG3 promotes resistance to enzalutamide in prostate cancer via the miR-139-5p/PKM2 axis (83). In tumor cells, the ratio of PKM1 to PKM2 serves a critical role in regulating both glycolysis and drug resistance. PKM1 and PKM2 are isoforms generated by alternative splicing of PKM pre-mRNA, which is regulated by the PKM gene. In cisplatin-resistant NSCLC cells, the highly expressed lncRNA PCIF1 competes with miR-326, which can directly interact with PKM to downregulate its expression. This decreases the production of PKM2 by influencing PKM splicing. Knockdown of lncRNA PCIF1 restores miR-326 expression, leading to decreased glycolysis and PKM2 levels, which enhances cellular sensitivity to cisplatin (84). Additionally, RNA-binding proteins, such as Heterogeneous Nuclear Ribonucleoprotein A1 (HNRNPA1), Polypyrimidine tract binding protein 1 (PTBP1) and Sam68, serve critical roles in the specific splicing of PKM (90). miR-326 also regulates PKM2 production by inhibiting HNRNPA1, HNRNPA2 and PTBP1 (85). In hepatocellular carcinoma (HCC), miR-374b directly binds to HNRNPA1, reducing selective splicing of PKM into PKM2 and increasing cellular sensitivity to sorafenib (91). In CRC, the lncRNA LINC018521 interacts with the RNA-binding protein SR-like splicing factors5 (SRSF5), which promotes PKM splicing to generate PKM2. Overexpression of LINC018521 leads to upregulated PKM2 levels and increased glycolysis, thereby contributing to resistance to 5-FU (86). Furthermore, in doxorubicin-resistant BC, lncRNA TBX15 is downregulated. TBX15 serves as a sponge for miR-152, which targets Kinesin family member 2C (KIF2C) to inhibit PKM2-mediated glycolysis. KIF2C binds PKM2 and promotes the ubiquitination of PKM2 domain 2, enhancing PKM2 stability. The TBX15/miR-152 axis reverses doxorubicin resistance in BC by targeting KIF2C and blocking cellular glycolysis and autophagy (92). In ovarian cancer (OC), the lncRNA CTSLP8 directly binds to PKM2, forming a dimer. This PKM2-CTSLP8 dimer transcriptionally regulates c-Myc, promoting glycolysis and cisplatin resistance in OC cells (93).

LDHA. LDH, located in the cytoplasm, catalyzes the conversion of pyruvate to lactic acid, the final product of glycolysis. LDHA, a prominent isoform of LDH that is upregulated in cancer, stimulates cellular lactate production, which contributes to the acidic tumor microenvironment and enhances cancer cell resistance to chemotherapy drugs (94). In various cancers, miRNAs such as miR-34a, miR-101-3p and miR-329-3p target and inhibit LDHA, suppressing lactate production and enhancing cancer cell sensitivity to cisplatin. miR-34a and miR-101-3p are sponged by upstream lncRNAs such as SNHG7 and XIST, respectively, leading to their downregulation. Overexpression of these miRNAs can reverse glycolytic metabolism and lactate-mediated cisplatin resistance (95-97). In GC cells, the lncRNA HAGLR sponges miR-338-3p to promote 5-FU resistance by targeting LDHA (98). Similarly, in cervical cancer (CC), knocking down lncRNA-NEAT1 restores miR-34a expression, reversing LDHA-induced 5-FU resistance (99). Besides these

ncRNAs that directly bind to and inhibit LDHA expression, Shi *et al* (100) recently discovered that lncRNA GLTC is overexpressed in thyroid cancer and negatively associated with clinical prognosis. GLTC enhances LDHA succinylation at the K155 site by disrupting the interaction between SIRT5 and LDHA. This modification increases lactate content and the NAD⁺/NADH ratio in papillary thyroid carcinoma cells, promoting resistance to ¹³¹I therapy (100). c-Myc, a transcription factor highly expressed in cancers, is closely linked to the tumor microenvironment, metabolic reprogramming and the activation of various oncogenic signaling pathways (101). c-Myc promotes glycolysis in cancer cells by upregulating key enzymes of glycolytic metabolism. Several ncRNAs have been shown to promote glycolysis and drug resistance by stabilizing c-Myc mRNA. For example, circARHGAP12, through m6A modification, binds c-Myc, promoting doxorubicin resistance. Inhibition of circARHGAP29 decreases its interaction with Insulin-like Growth Factor 2 mRNA-Binding Protein 1 (IGF2BP2), enhancing c-Myc stability and increasing tumor cell sensitivity to docetaxel. Similarly, miR-3679-5p stabilizes c-Myc by inhibiting NEDD4-like E3 ubiquitin protein ligase (NEDD4L). Mechanistically, c-Myc enhances the transcription of LDHA, promoting glycolysis, ATP production and lactate generation in tumor cells, thereby mediating cellular drug resistance (24,102,103).

Other glycolysis-associated enzymes. PDH is an enzyme in the pyruvate dehydrogenase complex (PDC), which catalyzes the irreversible decarboxylation of pyruvate to acetyl-CoA in mitochondria. However, cancer cells exhibit a preference for aerobic glycolysis rather than the mitochondrial oxidation of pyruvate (104). miR-21-5p contributes to cisplatin resistance in OC cells by targeting PDH E1 subunit α 1 (PDHA1) (105). Additionally, PDK1 regulates the activity of the PDC by inhibiting PDH (104). The upregulation of PDK1 inhibits the tricarboxylic acid cycle (TCA), leading to enhanced ATP synthesis and decreased production of ROS under cellular hypoxic conditions (106). Previous studies have identified upstream regulators of PDK1, including miR-148a and miR-4290, which suppress cellular glycolysis and promote sensitivity to cisplatin and doxorubicin by inhibiting PDK1 expression (107,108). Overexpression of PDK1 can reverse the effects of these miRNAs, promoting cell proliferation and drug resistance (107,108). PTBP1 is a nuclear regulator of alternative splicing. miR-134 and miR-506-3p directly bind to PTBP1, reducing its expression and inhibiting glucose uptake and lactate production in cells. The inhibition of miR-134 and miR-506-3p induces resistance to doxorubicin and 5-FU, respectively (25,109). PTBP1 can bind to the 3' UTR of LDHA, enhancing its stability. In aromatase inhibitor (AI)-resistant BC cells, the lncRNA DIO3OS interacts with PTBP1 in the nucleus, promoting BC cell proliferation and glycolysis (110). Phosphoglycerate mutase 1 (PGAM1) is a key enzyme in glycolysis, catalyzing the conversion of 2-phosphoglycerate to 3-phosphoglycerate (111). The m6A-modified circQSOX1 indirectly upregulates PGAM1 expression by sponging miR-326 and miR-330-5p, thereby activating glycolysis in CRC cells. This decreases the response of CRC to anti-CTLA-4 therapy and promotes immune evasion in CRC (112).

ncRNAs are involved in activation of signaling pathways driving-glycolysis. Previous studies have highlighted the activation of signaling pathways such as PI3K/AKT, MAPK and EGFR as key drivers of glycolysis in cancer cells through the upregulation of glycolysis-associated genes (113,114). For example, the PI3K/AKT signaling pathway can directly promote the phosphorylation of glycolytic enzymes HK2 and PFKFB. Additionally, PI3K/AKT regulates the expression of the transcription factor MYC, which further enhances the expression of HK2, PFK-1, PDK1, PKM2 and LDHA (115). In FMS-like tyrosine kinase 3 (FLT3)-resistant acute myeloid leukemia (AML) cells, elevated expression of miR-155 activates the PI3K/AKT pathway by directly binding to the 3'UTR of PIK3R1, a PI3K inhibitor. This process enhances glycolysis, which is a key feature of resistance to FLT3 tyrosine kinase inhibitors (116). By contrast, the inhibitory effect of miR-149-3p on AKT1 decreases the expression of HK2, LDHA and GLUT1 in AML cells, thereby enhancing the sensitivity of AML to chemotherapy drugs (117).

EGFR stimulation can enhance the activation of HK2 and PKM2, thereby increasing lactate excretion to support the acidic tumor microenvironment (118). This phenomenon may be associated with the upregulation of HIF-1 α and LDHA expression (119). Targeting EGFR has been shown to improve glycolysis-mediated chemotherapy (120-122). Gao *et al* (120) found that EGFR positively regulates lncRNA FGD5-AS1 expression in CRC. FGD5-AS1 indirectly upregulates HK2 by sponging miR-330-3p, a negative regulator of HK2. The EGFR-targeted inhibitor erlotinib suppresses HK2 expression and glycolysis in CRC, enhancing sensitivity to 5-FU (119). miR-143 can target and inhibit HK2, restoring sensitivity to cisplatin and 5-FU by decreasing HK2-dependent glycolysis. Notably, EGFR negatively regulates miR-143, and its down-regulation in drug-resistant cancer cells results in excess HK2 (121,122). Eregulin (EREG) is an EGFR ligand, which upregulates HK2, GLUT3 and PDK1 by activating EGFR (123). miR-186-3p suppresses the expression of EREG. However, tamoxifen decreases miR-186-3p levels in ER-positive BC cells. The miR-186-3p/EREG axis activates EGFR signaling, promoting glycolysis and mediating tamoxifen resistance in BC cells (124).

The interaction between ncRNAs and the MAPK signal transduction pathways plays a key role in tumor cell proliferation, survival and metabolic reprogramming (125). ERK1/2 serves as the downstream and final effector of the MAPK pathway (125) and promotes glycolysis by facilitating the nuclear translocation of PKM2 or upregulating HIF-1 α (126,127). In apatinib-resistant GC cells, both LINC00665 and ERK2 are upregulated. LINC00665 enhances ERK2 expression by sequestering miR-665, which stimulates the expression of GLUT1, LDHB and HK2, thereby promoting glycolysis and inducing apatinib resistance (128).

AMPK has been regarded as a signaling pathway that promotes glycolysis (129). However, some evidence suggests that inhibiting glycolysis through AMPK activation can reverse drug resistance (130,131). Mechanistically, this involves the suppression of AMPK, which activates the mTOR/HIF- α axis (130,131). In CRC, miR-27a inhibits AMPK signaling while enhancing mTOR signaling, a mechanism that allows CRC cells to obtain energy through aerobic glycolysis. This

adaptation fosters CRC cell proliferation and contributes to resistance against chemotherapeutic agents such as 5-FU and oxaliplatin (132). The Wnt/ β -catenin pathway is associated with the activation of HIF-1 α and has also been found to upregulate the expression of PFKFB3 (133). The lncRNA HOTAIRM1 is upregulated in AML and has been linked to resistance to cytarabine (134). Knockdown of HOTAIRM1 can inhibit the Wnt/ β -catenin signaling pathway, decrease the expression of its downstream target PFK and suppress glycolysis, which enhances the sensitivity of AML cells to cytarabine (134).

In summary, ncRNAs target key glycolytic enzymes and associated signaling pathways (Fig. 2; Table II). These crucial glycolytic enzymes not only facilitate glycolysis in cancer cells but also activate downstream signaling pathways associated with drug resistance (Fig. 3). While some studies suggest ncRNAs contribute to chemotherapy resistance through glycolysis enhancement (135,136), the precise mechanisms by which downstream targets promote glycolysis remain unclear, with only phenotypical changes in glycolysis observed.

Lipid metabolism and ferroptosis

Lipid metabolism and drug resistance. By contrast with normal cells, tumor cells require dysregulated lipid metabolism to support proliferation, metastasis, membrane synthesis and signaling (137). Fatty acids (FAs) accumulate in tumor cells through both direct external uptake and *de novo* synthesis (138). These up-regulated FAs participate in lipid synthesis, leading to the production of phospholipids, cholesterol and other lipid metabolites, thereby fueling processes such as FA oxidation (FAO) (138). This provides essential ATP, lipid products and signaling molecules for tumor cell proliferation, metastasis and drug resistance.

Mechanisms of lipid metabolism mediating drug resistance. In drug-resistant cancer cells, the uptake and synthesis of FAs are notably enhanced. This leads to the accumulation of cholesterol and lipid droplets within the cells, which decreases ROS levels and promote stemness, thereby contributing to drug resistance (138). Furthermore, FAs and synthesized lipid products regulate the activation of the PI3K/AKT, Wnt/ β -catenin and Hippo/YAP signaling pathways, thereby promoting survival and drug resistance in cancer cells (Fig. 4A) (139-141).

As numerous chemotherapeutic agents require cellular entry to target DNA and induce cell death, lipid metabolism also mitigate toxic effects by altering drug uptake in cancer cells (142). Drugs typically enter cells through non-specific lipophilic interactions with the cell membrane. Abnormal lipid metabolism alters the membrane composition, decreasing its permeability to anti-cancer drugs (143). Although the exact changes in membrane composition are not fully understood, the low permeability of certain drugs is associated with poor membrane fluidity (144). Additionally, lipid metabolism affects the expression of transporters on the cell membrane. Free FAs activate the G protein-coupled receptor GPR120, which in turn upregulates ABC transporter expression via the AKT/NF- κ B signaling pathway, leading to decreased epirubicin accumulation in BC cells (145). By contrast, long-chain PUFAs decrease multidrug resistance 1 gene (MDR1) expression on the cell membrane, thereby decreasing PTX efflux and enhancing the chemotherapy sensitivity of tumor cells (146). Furthermore,

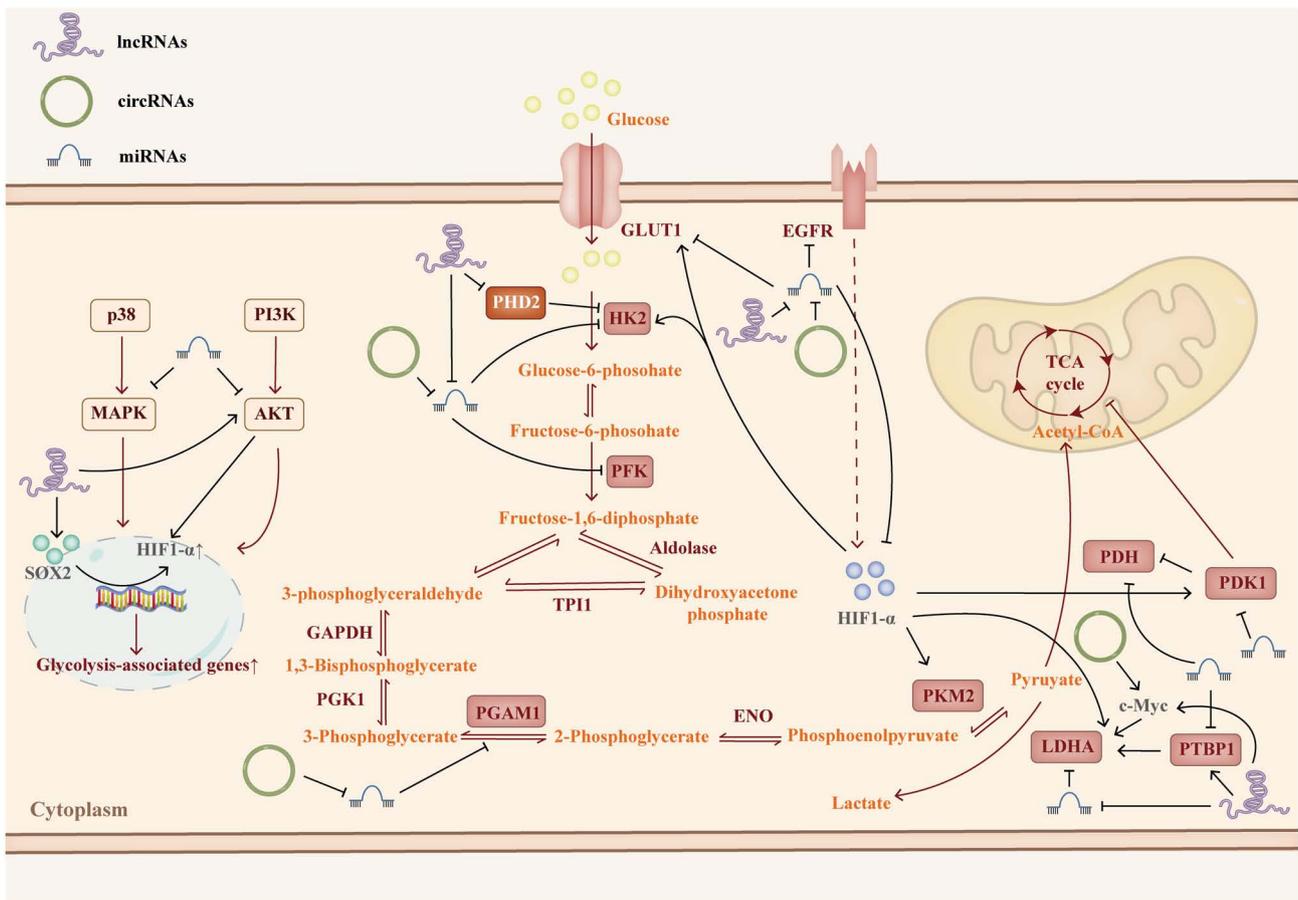


Figure 2. ncRNAs regulate key processes in glycolysis. ncRNAs target key enzymes within the glycolysis pathway and associated signaling pathways to modulate drug resistance mediated by glycolysis. Inc, long non-coding; circ, circular; miRNA, microRNA; HIF, hypoxia-inducible factor; GLUT, Glucose transporter; PHD, Prolyl-4-hydroxylase domain protein; HK, Hexokinase; PFK, Phosphofruktokinase; PGK, Phosphoglycerate kinase; TPI, Triose phosphate isomerase; PGAM, Phosphoglycerate mutase; ENO, Enolase; TCA, Tricarboxylic acid cycle; PDH, Pyruvate dehydrogenase; PDK, Pyruvate dehydrogenase kinase; LDHA, Lactate dehydrogenase A; PTBP1, Polypyrimidine tract-binding protein 1.

lipid metabolism promotes adipocyte-like transformation in cancer cells, leading to the production of lipid droplets, which act as storage sites for fat-soluble drugs. This results in diminished concentrations of chemotherapeutic agents reaching intracellular targets (147).

ncRNAs promote drug resistance by regulating synthesis of phospholipid and cholestasis. Previous studies (141,148-151) have emphasized the effect of ncRNAs on intracellular signaling pathways by modulating active lipid molecules, such as arachidonic acid (AA), phosphatidic acid (PA) and lysophosphatidic acid (LPA), which are produced during phospholipid metabolism. For example, circSNX6 serves as an upstream molecular sponge for miR-1184, mitigating its inhibitory effect on the target gene glycerol phosphocholine phosphodiesterase 1. This interaction leads to increased intracellular LPA levels, thereby promoting resistance to sunitinib in renal cell carcinoma cells (148). The lncRNA ROPM is highly expressed in BC stem cells (BCSCs) and stabilizes Phospholipase A2 group 16 (PLA2G16) mRNA by directly binding to it. Elevated PLA2G16 levels enhance the production of free FAs and AA, thereby driving BCSC stemness and doxorubicin resistance (141). Zhang *et al* (149) demonstrated that exosomal circRNA-101093 interacts with FA-binding protein 3 (FABP3),

augmenting its role in transporting AA and decreasing intracellular AA content. This increase in circRNA-101093 levels enhances FABP3 expression and limits AA incorporation into the plasma membrane, thereby desensitizing cells to ferroptosis (149). FAM3D metabolic regulatory signaling molecule D (FAM3D) effectively inhibits phospholipase D (PLD) activity via interactions with Gai-coupled G protein-coupled receptors, specifically formyl peptide receptor 1 and 2. The lncRNA DLGAP1-AS2 decreases FAM3D mRNA transcription and extracellular secretion by modulating chromatin accessibility at the histone marker H3K27ac, leading to PLD activation. This promotes PA production and confers cisplatin resistance (150). Moreover, miR-95 targets sphingolipid phosphatase 1, inhibiting the sphingosine-1-phosphate signaling pathway involved in AKT phosphorylation and decreasing the protective effects of AKT signaling on tumor cells (151).

Cholesterol serves a pivotal role in cell membrane protein function, receptor transport, proliferation, membrane biogenesis and signal transduction. Increased cholesterol synthesis is associated with poorer survival rates and cancer progression (152). High cholesterol levels are observed in BC cells, where miR-128 and miR-223 regulate cholesterol metabolism by targeting genes such as 3-Hydroxy-3-methylglutaryl-CoA Synthase 1 (HMGCS1), Low-density lipoprotein receptor

Table II. ncRNAs regulating glycolysis-mediated drug resistance in cancer.

ncRNA	Molecular target	Function	Cancer	Drug	(Refs.)
circHIF1A	miR-361-5p/HIF1 α	Promotes glycolysis and drug resistance	CRC	Cetuximab	(59)
circNRIP1	miR-138-5p/HIF1 α		GC	5-FU	(60)
lnc-RP11-536K7.3	SOX2/USP7/HIF1 α		CRC	Oxaliplatin	(61)
lnc-HISLA	HIF-1 and PHD2		BC	PTX	(62)
lnc-HIF1 α -AS1	AKT/YB1/HIF1 α		Pancreatic	GEM	(63)
circZNF91	miR-23b-3p/SIRT1		PC	GEM	(64)
miR-140 and miR-143	GLUT1	Suppresses EC cell proliferation and glycolysis and promotes drug sensitivity	EC	PTX	(66)
circRNA-0002130	miR-498/GLUT1	Promotes glycolysis and drug resistance	NSCLC	Osimertinib	(67)
miR-218	GLUT1	Suppresses glycolysis and drug resistance	Bladder	Cisplatin	(68)
miR-1291-5p			Pancreatic		(69)
lnc-SNHG1	miR-216b-5p/HK2	Promotes glycolysis and drug resistance	GC	Paclitaxel	(70)
lnc-DANCR	miR-125b-5p/HK2		Colon	Cisplatin	(72)
lnc-MBNL1-AS1	miR-708-5p/HK2		HCC	Tripteryine	(73)
miR-202	HK2	Inhibits glycolysis and resensitizes cancer cells to drug	CML	Imatinib	(74)
miR-125b	HK2	Inhibits glycolysis and drug resistance	HCC	5-FU	(75)
lnc-UCA1	miR-125a/HK2	Promotes glycolysis and drug resistance	AML and CRC	PTX and doxorubicin	(76,77)
miR-488	PFKFB3	Inhibits glycolysis and drug resistance	CRC	5-FU and oxaliplatin	(78)
circ-SAMD4A	miR-545-3p/PFKFB3	Promotes glycolysis and drug resistance	CRC	5-FU	(79)
miR-122	PKM2	Inhibits glycolysis and drug resistance	Prostate, HCC and CRC	Oxaliplatin, docetaxel and doxorubicin	(87-89)
lnc-SNHG3	miR-139-5p/PKM2	Promotes glycolysis and drug resistance	Prostate	Enzalutamide	(83)
lnc-PCIF1	miR-326/PKM		NSCLC	Cisplatin	(84)
miR-326	HNRNPA1, HNRNPA2 and PTBP1	Inhibits glycolysis and drug resistance	CRC	5-FU	(85)
miR-374b	HNRNPA1	Decreases PKM2 levels and increases sorafenib sensitivity	HCC	Sorafenib	(90)
LINC018521	SRSF5/PKM2	Promotes glycolysis and drug resistance	CRC	5-FU	(86)
lnc-TBX15	miR-152/KIF2C/PKM2		BC	Doxorubicin	(92)
lnc-CTSLP8	PKM2		OC	Cisplatin	(93)
lnc-SNHG7	miR-34a/LDHA		GC		(95)
lnc-XIST	miR-101-3p/LDHA		NSCLC		(96)

Table II. Continued.

ncRNA	Molecular target	Function	Cancer	Drug	(Refs.)
miR-329-3p	LDHA	Inhibits glycolysis and drug resistance	Osteosarcoma		(97)
lnc-HAGLR	miR-338-3p/LDHA	Promotes glycolysis and drug resistance	GC	5-FU	(98)
lnc-NEAT	miR-34a/LDHA		CC	5-FU	(99)
lnc-GLTC	SIRT5/LDHA		PTC	¹³¹ I	(100)
miR-3679-5p	NEDD4L/c-Myc/LDHA		NSCLC	Cisplatin	(102)
circARHGAP29	IGF2BP2/c-Myc/LDHA		Prostate	DTX	(103)
miR-21-5p	PDH1	Inhibits glycolysis and drug resistance	OC	Cisplatin	(105)
miR-4290	PDK1	Increases drug sensitivity	GC	Cisplatin	(107)
miR-148a			BC	Adriamycin	(108)
miR-134	PTBP1	Inhibits glycolysis and drug resistance	Osteosarcoma	Doxorubicin	(25)
lnc-SNHG16	miR-506-3p/PTBP1	Promotes glycolysis and drug resistance	GC	5-FU	(119)
lnc-DIO3OS	PTBP1		BC	AI	(110)
circQSOX1	miR-326 and miR-330-5p/PGAM1		CRC	Anti-CTLA-4	(112)
miR-155	PI3K/AKT		AML	FLT3	(116)
miR-149-3p	PI3K/AKT		AML	Doxorubicin and cisplatin	(117)
lnc-FGD5-AS1	miR-330-3p/HK2	Upregulated by EGFR to promote glycolysis and drug resistance	CRC	5-FU	(120)
miR-143	HK2	Downregulated by EGFR to inhibit glycolysis	Osteosarcoma and CRC	Cisplatin and 5-FU	(121, 122)
miR-186-3p	EREG/EGFR	Inhibits glycolysis and drug resistance	BC	Tamoxifen	(124)
LINC00665	miR-665/MAPK1	Promotes glycolysis and drug resistance	GC	Apatinib	(128)
miR-27a	AMPK/mTOR		CRC	5-FU and oxaliplatin	(132)
lnc-HOTAIRM1	Wnt/ β -catenin/PFK		AML	Cytarabine	(134)

lnc, long non-coding; circ, circular; miR, microRNA; HIF, hypoxia-inducible factor; USP, Ubiquitin-Specific Protease; PHD, Prolyl-4-hydroxylase domain protein; YB1, Y-box binding protein 1; SIRT, Sirtuin; GLUT, Glucose transporter; CRC, Colorectal Cancer; FU, Fluorouracil; GC, Gastric Cancer; BC, Breast Cancer; EC, Endometrial Cancer; PTX, Paclitaxel; GEM, Gemcitabine; NSCLC, Non-Small Cell Lung Cancer; HCC, Hepatocellular Carcinoma; CML, Chronic Myelogenous Leukemia; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PKM, Pyruvate kinase M; HNRNPA1, Heterogeneous Nuclear Ribonucleoprotein A1; PTBP1, Polypyrimidine Tract-Binding Protein 1; AML, Acute Myeloid Leukemia; SRSF5, Serine/Arginine-Rich Splicing Factor 5; KIF2C, Kinesin Family Member 2C; OC, Ovarian Cancer; PTC, Papillary Thyroid Carcinoma; DTX, Docetaxel; NEDD4L, NEDD4-like E3 ubiquitin protein ligase; LDHA, Lactate dehydrogenase A; IGF2BP2, Insulin-like Growth Factor 2 mRNA-Binding Protein 2; PGAM, Phosphoglycerate mutase; AI, Aromatase Inhibitor; FLT3, FMS-like Tyrosine Kinase 3; EREG, Epregrulin.

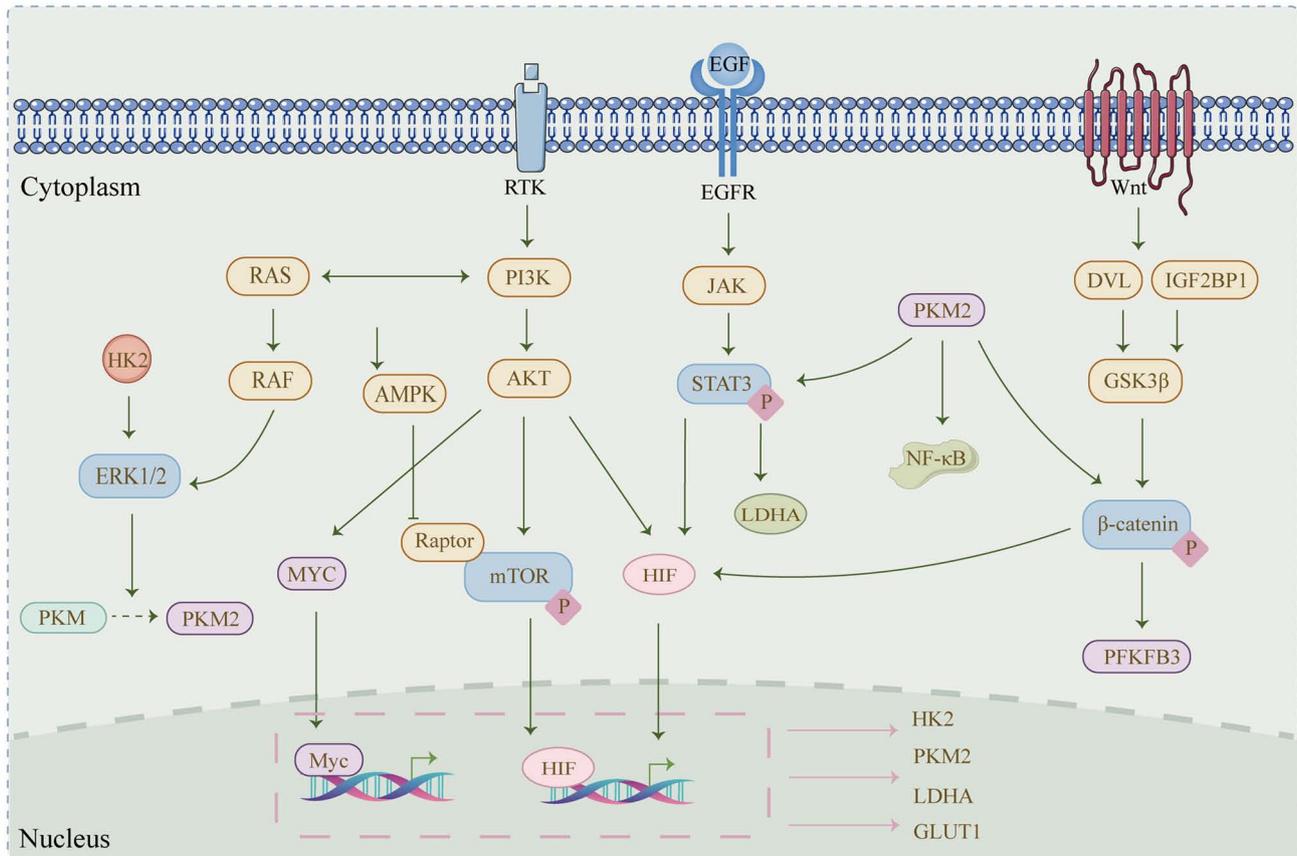


Figure 3. Signaling pathways in drug-resistant cancer cells are influenced by glycolysis. The activation of PI3K/AKT, EGFR, MAPK, AMPK and Wnt/ β -catenin promotes glycolytic activity. Certain glycolytic enzymes serve as regulators of the signaling pathways associated with drug resistance. RTK, Receptor tyrosine kinase; HK, Hexokinase; PKM, Pyruvate kinase M; HIF, Hypoxia-inducible factor; LDHA, Lactate dehydrogenase A; GSK3 β , Glycogen Synthase Kinase 3 β ; DVL, Dishevelled; IGF2BP1, Insulin-like Growth Factor 2 mRNA-Binding Protein 1; PFKFB3, phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; GLUT, Glucose transporter.

(LDLR) and ATP-Binding Cassette Transporter A1 (ABCA1), modulating cholesterol biosynthesis, uptake and efflux. Cholesterol accumulation enhances lipid raft formation and membrane rigidity, decreasing membrane permeability and contributing to drug resistance. These miRNAs indirectly influence cell sensitivity to tamoxifen via the regulation of cholesterol (153). Additionally, miR-33a mitigates drug resistance in BC by inhibiting high-density lipoprotein (HDL) expression and preventing HDL-mediated cholesterol extraction (154).

FAO induces drug resistance. FAs that accumulate in cancer cells are converted into fatty acyl-CoA through the action of acyl-CoA synthetase (ACS). Acyl-CoA is transported to the mitochondrial matrix, where it undergoes β -oxidation to generate acetyl-CoA and ATP (43). Long-term exposure of cancer cells to elevated ROS levels induced by chemotherapy may enhance resistance to further treatment. This phenomenon is due to the activation of several factors, including Nrf2, c-Jun and HIF-1 α , which enhance the antioxidant capacity of cancer cells (155). To neutralize ROS, tumor cells produce large amounts of antioxidants such as GSH, which is reduced from its oxidized form via NADPH (156). Elevated ROS levels can promote FAO, enabling cancer cells to generate sufficient NADPH and reduced GSH (157). Increased FAO has been observed in drug-resistant GC and AML (158,159).

This increase not only meets the energy demands of tumor cells but also supports their survival in oxidative stress environments (160). Inhibition of FAO reduces NADPH and GSH production in tumor cells while simultaneously increasing ROS production (161). In addition, cancer cells counteract ferroptosis by enhancing FAO and phospholipid synthesis, which elevates the levels of saturated FAs and restores GSH levels, thereby improving resistance to ROS (162).

ncRNAs mediate cancer drug resistance by regulating the FAO pathway. In sorafenib-resistant HCC cells, the lncRNA LINC01056 is notably downregulated and inversely associated with sorafenib resistance. Mechanistically, LINC01056 binds specifically to peroxisome proliferator-activated receptor α (PPAR α), inhibiting its nuclear translocation and transcriptional activity, thus decreasing the expression of FAO-related genes. Overexpression of LINC01056 suppresses PPAR α , attenuating FAO in HCC cells and restoring their sensitivity to sorafenib *in vitro* (163). Previous studies (26,164) have highlighted the key role of mesenchymal stem cells (MSCs) in mediating drug resistance in GC cells. MSCs stimulate the expression of lncRNA MACC1-AS1 in GC through TGF- β secretion. As a sponge for miR-145-5p, MACC1-AS1 enhances the expression of FAO-associated metabolic enzymes such as octamer-binding transcription factor 4 and carnitine palmitoyl-transferase 1 (CPT1), thereby promoting FAO in GC cells and

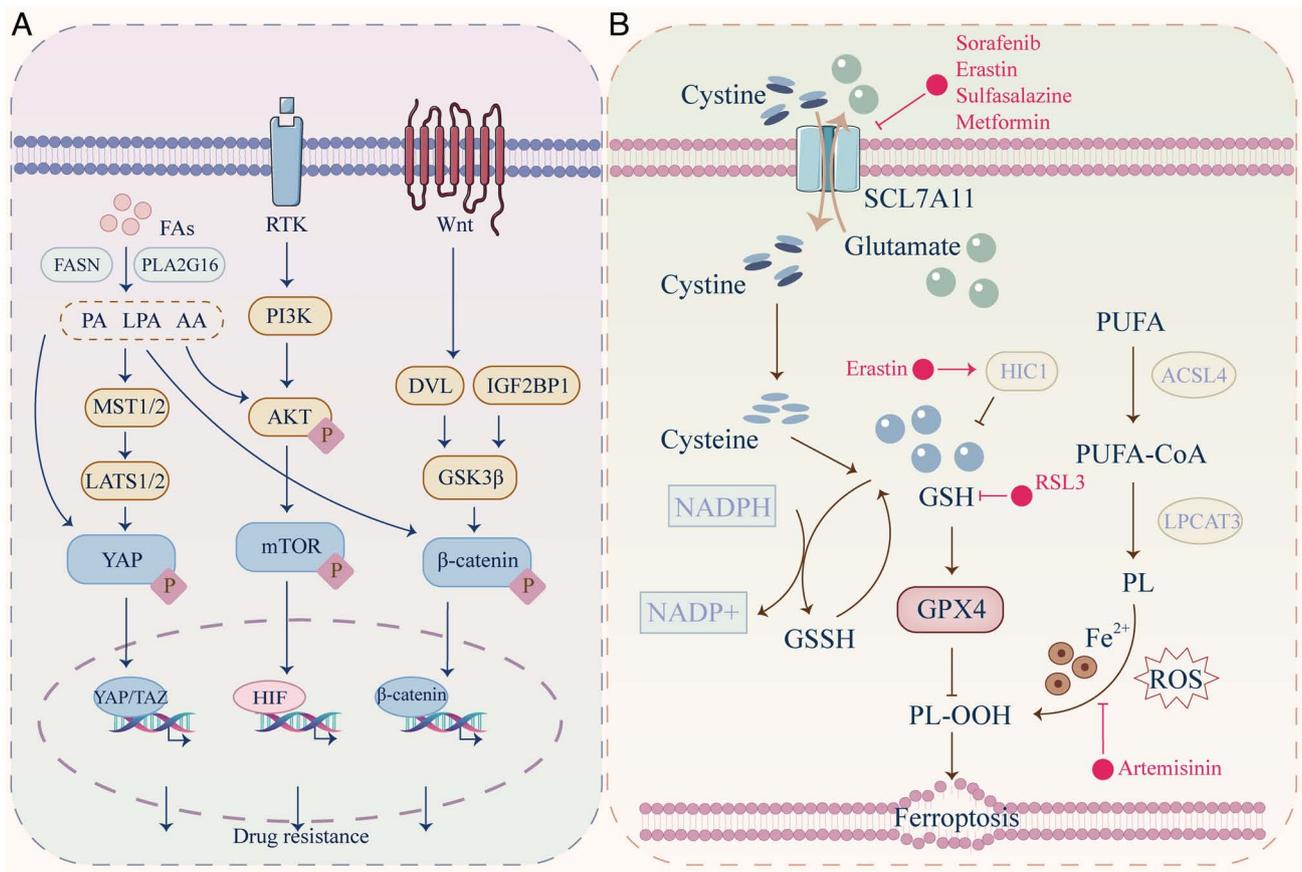


Figure 4. Mechanisms of lipid metabolism and ferroptosis in regulating tumor drug resistance. (A) Lipid molecules activate the PI3K/AKT, Wnt/β-catenin and Hippo/YAP signaling pathways. (B) Ferroptosis regulates the sensitivity of cancer cells to drugs. PUFA, polyunsaturated fatty acid; RTK, Receptor Tyrosine Kinase; FASN, Fatty acid synthase; PLA2G16, Phospholipase A2 group 16; PA, Phosphatidic acid; LPA, lysophosphatidic acid; AA, Arachidonic acid; MST, Mammalian Sterile 20-like Kinase; LATS, Large Tumor Suppressor Kinase; DVL, Dishevelled; IGF2BP1, Insulin-like Growth Factor 2 mRNA-Binding Protein 1; GSK3β, Glycogen Synthase Kinase 3β; TAZ, Transcriptional co-activator with PDZ-binding motif; HIF, Hypoxia-inducible factor; SCL7A11, Solute Carrier Family 7 Member 11; HIC1, Hypermethylated in Cancer 1 gene; GSH, Glutathione; GSSH, Oxidized Glutathione; GPX, Glutathione Peroxidase; PL-OOH, Phospholipid hydroperoxide; ROS, reactive oxygen species.

contributing to resistance to the 5-FU+leucovorin + oxaliplatin (FOLFOX) regimen (26). Furthermore, exosomes derived from MSCs elevate the expression of lncRNA HCP5 in GC cells, which specifically inhibits miR-3619-5p. By preventing miR-3619-5p from binding PPARγ coactivator 1α, HCP5 enhances the transcriptional complex of PPARγ coactivator 1-α/CEBPB, leading to the induction of CPT1 transcription. This process promotes stemness and chemoresistance in GC cancer cells by driving FAO (164).

Lipid peroxidation-mediated ferroptosis and drug resistance. Ferroptosis is a form of programmed cell death characterized by the accumulation of lipid peroxidation products that serves a key role in cancer occurrence, treatment resistance and tumor suppression (165). Polyunsaturated FAs (PUFAs) are catalyzed by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferases to produce phospholipids (PLs). Catalyzed by lipoxygenase and P450 oxidoreductase, PL interacts with ROS and iron ions to form PL hydroperoxides (PLOOH). The significant production of PLOOH results in the instability and increased permeability of cell membranes, leading to cell death (166). The occurrence of ferroptosis is influenced by two pathways. The crucial pathway is the inactivation of GSH peroxidase 4 (GPX4). GPX4 serves

a pivotal role in the reduction of PLOOH through the utilization of GSH. The other pathway involves inhibition of the cystine/glutamate antiporter system (xCT), mediated by solute carrier family 7A member 11 (SLC7A11). SLC7A11 facilitates the uptake of cysteine, which is key for the synthesis of GSH, a prerequisite for the functional activity of GPX4 (167).

Ferroptosis resistance influences cancer response to therapy. Ferroptosis is induced by anti-tumor drugs that suppress GPX4 or promote lipid peroxidation, as summarized by Li *et al* (168). For example, the combined treatment of albumin-bound paclitaxel and TMZ enhances ferroptosis in glioblastoma by inhibiting GPX4 expression (169). Sorafenib induces lipid peroxidation in HCC by inhibiting solute carrier family 3A member 2 (SLC3A2) and SLC7A11, thereby suppressing GSH production and GPX4 expression, which upregulates ferroptosis in HCC cells (170). However, in drug-resistant tumor cells, numerous types of lipid metabolic enzyme and endogenous antioxidant mitigate the occurrence of ferroptosis by decreasing lipid peroxidation (171). The SLC7A11-GPX4 system is dysregulated in numerous types of drug-resistant cancer, contributing to resistance against oxaliplatin (172). HER2-positive BC cells activate the β-catenin signaling pathway via fibroblast growth factor receptor 4, leading to

an increased synthesis of GSH via the transcription factor 4/SLC7A11 axis (173). Nrf2 is also implicated in cancer drug resistance and ferroptosis. Excessive ROS inactivate Keap1 via oxidation of its cysteine residues, releasing the transcription factor Nrf2 into the nucleus, where it activates the transcription of antioxidant genes, such as GPX4 (174). Furthermore, the activation of Nrf2 induces Metallothionein-1G, which reduces GSH depletion and lipid peroxidation, thereby inhibiting sorafenib-induced ferroptosis (175).

Inducing ferroptosis reverses drug resistance. Efficacy of anti-tumor drugs is increased by inducing ferroptosis (Fig. 4B) (176). Erastin, the earliest compound discovered to induce ferroptosis, directly inhibits SLC7A11/xCT, which regulates ferroptosis (177). In CRC, erastin reduces GSH by targeting SLC7A11, thereby enhancing ROS production and chemotherapy sensitivity in CRC cells (178). Additionally, erastin indirectly inhibits GPX4 by upregulating the expression of the hypermethylated in cancer 1 gene, which impairs the resistance of cancer cells to ferroptosis (179). Sulfasalazine and metformin promote ferroptosis by inhibiting SLC7A11, thus suppressing tumor growth and drug resistance (180,181). RAS-selective lethal 3 (RSL3) (182) and A 1,2-dioxolane (183) are ferroptosis inducers that target GPX4. Their mechanism of action involves decreasing the accumulation of ROS in cells by inhibiting the expression of GPX4. A recent study demonstrated that RSL3 does not directly inhibit GPX4; rather, it promotes ferroptosis by inhibiting thioredoxin reductase 1 (TXNRD1) (184). Artemisinin is a drug that induces ferroptosis through various mechanisms. By inhibiting the activity of superoxide dismutase and catalase, artemisinin reduces the clearance of ROS, which leads to the accumulation of lipid peroxide (185). Additionally, it can induce lysosomal degradation of ferritin, increase the levels of cellular free iron, and make cells more susceptible to ferroptosis (186).

Targeting ncRNAs to treat ferroptosis pathway-mediated drug resistance. The lncRNA PVT1 enhances pleiomorphic adenoma gene 1 (PLAG1) expression at the transcriptional level by targeting miR-195-5p. PLAG1 interacts with GPX4, facilitating its role in stabilizing lipid peroxidation and protecting HCC cells from sorafenib-induced ferroptosis (187). Both miR-128-3p and miR-450b-5p promote ferroptosis and lipid peroxidation by inhibiting the enzymatic activity of GSH and GPX4 (188,189). Additionally, sorafenib upregulates miR-23a-3p expression in HCC via ETS proto-oncogene 1 induction, which targets ACSL4. Sorafenib-mediated overexpression of miR-23a-3p decreases lipid peroxidation and ferroptosis in HCC cells by inhibiting ACSL4, thereby contributing to HCC cell resistance to sorafenib (170). Cancer-associated fibroblasts secrete miR-522 and miR-432-5p to inhibit lipoxygenase 15 (ALOX15) and cyclotransferase 1 (CHAC1). ALOX15 degrades ROS generated by lipid peroxidation, whereas CHAC1 enhances the production of GSH, thus inducing drug resistance (190,191).

In summary, ncRNAs modulate the sensitivity of tumor cells to drugs by influencing lipid metabolism (Fig. 5; Table III). These mechanisms involve lipid synthesis, FAO and the regulation of ferroptosis. While most of the aforementioned studies have focused on how ncRNAs affect lipid

oxidation balance within cancer cells, future investigations should explore how ncRNA-mediated lipid metabolism alters cell membrane components and intracellular lipid droplets to promote drug resistance.

Mitochondrial function and oxidative stress. Mitochondria are key in metabolic reprogramming, supporting the catabolism of amino acids, nucleotides and lipids, as well as the production of NADH and NADPH (192). In tumor cells, mitochondrial DNA (mtDNA) mutations or alterations in content lead to mitochondrial dysfunction. For example, the deletion of mtDNA in PC cells results in mitochondrial dysfunction, driving a shift to the Warburg effect and promoting stem cell-like characteristics. This reprogramming helps the cells resist docetaxel treatment (193). In HCC, mtDNA loss contributes to chemotherapy resistance by activating the NRF-2 signaling pathway and upregulating multidrug resistance genes such as MDR1 and MRP1/2 (194). Further evidence from colon cancer cells with mtDNA deletions supports the involvement of MDR1 in resistance mechanisms (195). On the contrary, chemotherapy-induced mitochondrial dysfunction in cancer cells is often accompanied by mutations in mtDNA, which increase ROS production (196).

Resistance to apoptosis and oxidative stress. Resistance to apoptosis is a key mechanism underlying drug resistance in cancer. Under physiological and pathological conditions, cells maintain a balance in redox homeostasis. However, certain chemotherapeutic agents, such as 5-FU, epirubicin and gemcitabine, induce oxidative stress by inhibiting the antioxidant system or mitochondrial function, leading to excessive production of ROS (197). Elevated ROS levels disrupt mitochondrial membrane potential, resulting in the release of cytochrome c and activation of caspases-3, -6 and -7, thereby triggering apoptosis in cancer cells (198). Additionally, tumors often release excess ROS into the microenvironment, which can induce macrophages to adopt a pro-cancer phenotype (199). This phenotype reduces T cell infiltration into tumors and decreases the expression of programmed death-ligand 1 (PD-L1), thereby hindering the effectiveness of anti-PD-L1 immunotherapy (200). The dysregulation of apoptosis is a key factor in cancer resistance to chemotherapy.

Role of ncRNAs in mitochondrial dysfunction and drug resistance. Dysregulated ncRNAs within mitochondria modulate the activation of mitochondrial-mediated signaling pathways, promoting tumor growth and drug resistance. miR-125b is associated with increased release of mitochondrial cytochrome c, the induction of apoptotic protease activating factor 1 and the activation of caspase-3 and poly (ADP-ribose) polymerase (201). Furthermore, the overexpression of miR-125b can inhibit the expression of BCL-2 while simultaneously increasing the expression of Bax (201).

Chemotherapy agents, including cisplatin, doxorubicin and PTX, are known pro-oxidants that induce cell death through mitochondrial dysfunction and increased ROS production (202). This has intensified interest in the role of ncRNAs in modulating ROS generation within mitochondria (203,204). Sorafenib, for example, induces

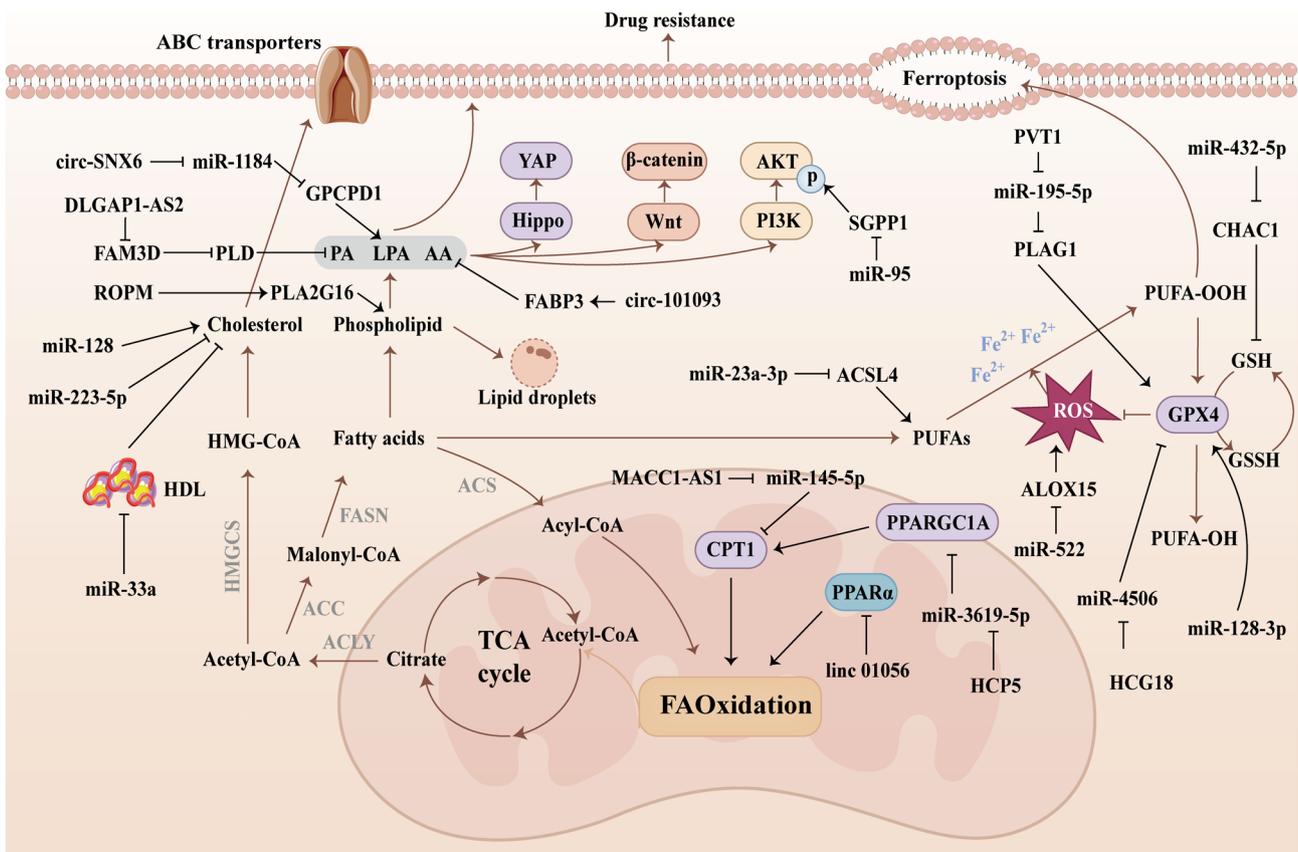


Figure 5. ncRNAs serve a key role in regulating lipid metabolism, which is linked to tumor drug resistance. ncRNAs influence the synthesis of lipids, including sphingomyelin and cholesterol, and modulate key targets within the FA oxidation and lipid peroxidation pathways. nc, non-coding; FA, fatty acid; ABC, ATP-binding cassette; linc, Long intergenic non-protein-coding RNA; circ, circular RNA; miR, microRNA; DLGAP1-AS2, Dlg associated protein 1 antisense RNA 2; FAM3D, FAM3 metabolic regulatory signaling molecule D; PLD, Phospholipase D; GPCPD1, Glycerol phosphocholine phosphodiesterase 1; PA, Phosphatidic acid; LPA, Lysophosphatidic acid; AA, Arachidonic acid; PLA2G16, Phospholipase A2 Group 16; HMG, 3-Hydroxy-3-methylglutaryl-CoA; HDL, High-density lipoprotein; HMGCS, 3-Hydroxy-3-methylglutaryl-CoA synthase; FASN, Fatty acid synthase; ACC, Acetyl-CoA carboxylase; ACLY, ATP-Citrate Lyase; ACS, Acyl-CoA Synthetase; TCA, Tricarboxylic acid cycle; CPT1, Carnitine palmitoyltransferase 1; FABP3, Fatty acid-Binding Protein 3; SGPP, Sphingolipid phosphatase; PPARGC1A, PPARG coactivator 1α; ACSL4, Acyl-CoA synthetase long-chain family member 4; PUFA, Polyunsaturated fatty acid; ALOX, Lipoxygenase; ROS, Reactive oxygen species; GPX, Glutathione Peroxidase; GSSH, Oxidized Glutathione; GSH, Glutathione; PVT, Plasmacytoma variant translocation 1; PLAG1, Pleiomorphic adenoma gene 1.

mitochondrial dysfunction and ROS production via the C-Jun/p53-upregulated modulator of apoptosis signaling pathway, while miR-518d-5p impedes this process by targeting and inhibiting C-Jun, resulting in sorafenib resistance (205). Mitochondrial miRNA (mitomiRNA)-2329 is significantly upregulated in cisplatin-resistant cells. It inhibits the activity of mitochondrial complexes I, III and IV, leading to elevated mitochondrial ROS and decreased ATP production. Additionally, mitomiR-2329 partially regulates mtDNA transcription in an Argonaute2 (AGO2)-dependent manner, promoting glycolysis and lactate production (206). Similarly, the lncRNA SAMMSON increases ROS production in BC cells by inhibiting mitochondrial complex I (207). These findings underscore the key role of ncRNAs targeting mitochondrial complexes in regulating mitochondrial function. Furthermore, Hillman *et al* (208) demonstrated that miR-150, miR-328 and miR-616 target membrane complement regulatory factors CD46, CD55 and CD59, thereby rendering mitochondria resistant to complement lysis and enhancing cellular tolerance to complement-dependent cytotoxicity. miR-98 regulates mitochondrial fusion and fission by directly targeting Longevity Assurance Homologue 2,

promoting mitochondrial fission and increasing mitochondrial membrane potential, which contributes to resistance to cisplatin and doxorubicin (209). Notably, mitomiR-5787 inhibits oxidative stress and glycolysis in mitochondria by binding mitochondrial cytochrome c oxidase subunit 3 (MT-CO3), restoring cisplatin sensitivity (205). Conversely, the binding of mitomiR-5787 to MT-CO3 does not suppress MT-CO3 expression but enhances its translation. This may be due to the absence of the RNA-induced silencing complex (RISC)-associated factor GW182, which is responsible for mRNA cleavage, within mitochondria (210).

ncRNAs in ROS and GSH regulation. ncRNAs serve a key role in mitigating intracellular ROS and oxidative stress by promoting the production of GSH. For example, in prostate cancer, miR-34b/c facilitates the generation of GSH and Bcl-2 via the c-Myc/ γ -glutamyl-cysteine synthetase axis, which decreases the cytotoxic effects of oxidative stress and enhances cellular tolerance to ROS (211). lncRNA H19 is overexpressed in cisplatin-resistant high-grade serous ovarian cancer (HGSC), and its overexpression enhances cisplatin resistance. H19 upregulates Nrf2 expression, promoting the

Table III. ncRNAs that regulate lipid metabolism.

ncRNA	Molecular target	Function	Cancer	Therapy	(Refs.)
circSNX6	miR-1184/GPCPD1	Promotes LPA levels and drug resistance	RCC	Sunitinib	(148)
lncROPM	PLA2G16	Enhances the production of FFAs and AA	BC	Doxorubicin	(141)
circRNA101093	FABP3	Facilitates transport of AA and reduces intracellular AA content	NSCLC	/	(149)
lncDLGAP1-AS2	FAM3D/PLD	Promotes PA production and drug resistance	Squamous cell carcinoma	Cisplatin	(150)
miR-95	SGPP1/AKT	Promotes drug resistance	BC	Radio-resistance	(151)
miR-128 and -223	HMGCS1, LDLR and ABCA1	Modulates cholesterol biosynthesis, uptake and efflux		Tamoxifen	(152)
miR-33a	HDL	Prevents HDL-mediated cholesterol extraction		Radio-resistance	(154)
Linc01056	PPAR α	Inhibits FAO	HCC	sorafenib	(163)
lncMACC1-AS1	miR-145-5P/ OCT4 and CPT1	Promotes FAO	GC	FOLFOX	(26)
lncHCP5	miR-3619-5p/ PPARGC1A				(164)
miR-23a-3p	ACSL4	Promotes drug resistance	HCC	Sorafenib	(170)
lncPVT1	PLAG1/GPX4				(187)
miR-128-3p	GPX4	Inhibits drug resistance	BC	Anoikis	(188)
lncHCG18	miR-450b-5p/GPX4	Promotes drug resistance	HCC	Sorafenib	(189)
miR-522	ALOX15	Inhibits ROS production and drug sensitivity	GC	Cisplatin	(190)
miR-432-5p	CHAC1		Prostate	DTX	(191)

/, not applicable; lnc, long non-coding; circ, circular; miR, microRNA; GPCPD1, Glycerol phosphocholine phosphodiesterase 1; LPA, Lysophosphatidic Acid; RCC, Renal Cell Carcinoma; PLA2G16, Phospholipase A2 group 16; FFA, Free fatty acids; AA, Arachidonic Acid; BC, Breast Cancer; FABP3, Fatty Acid-Binding Protein 3; NSCLC, Non-Small Cell Lung Cancer; FAM3D, FAM3 metabolic regulatory signaling molecule D; PLD, Phospholipase; PA, Phosphatidic Acid; SGPP1, Sphingolipid Phosphatase; HMGCS1, 3-Hydroxy-3-methylglutaryl-CoA Synthase 1; LDLR, Low-density lipoprotein receptor; ABCA, ATP-Binding Cassette Transporter A; HDL, High-Density Lipoprotein; OCT, Octamer-binding Transcription Factor; CPT, Carnitine Palmitoyltransferase; PPARGC1A, PPAR γ coactivator 1 α ; PLAG1, Pleiomorphic Adenoma Gene 1; GPX, Glutathione Peroxidase; ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; HCC, Hepatocellular Carcinoma; GC, Gastric Cancer; ALOX, Lipoxigenase; CHAC, Cyclotransferase; DTX, Docetaxel.

transcription of GSH-associated proteins such as Glutathione reductase (GSR), Glutamate-cysteine ligase catalytic subunit (GCLC) and Glutamate-cysteine ligase modifier subunit (GCLM), which increases intracellular GSH accumulation (212). Conversely, miR-27a targets GSH-associated genes such as cystathionine gamma-lyase, xCT and Nrf2, reducing cellular resistance to ROS and increasing sensitivity to chemotherapy (213). Moreover, Nrf2 is regulated by its upstream regulatory factor SKP1-Cul1-Rbx1 (SCF $^{\beta}$ -TRCP). SLC7A11-AS1 blocks SCF $^{\beta}$ -TRCP-mediated Nrf2 ubiquitination, resulting in low intracellular ROS levels (214).

In conclusion, ncRNAs regulate mitochondrial complexes, apoptosis-related proteins and other factors, playing a key role in mediating mitochondrial dysfunction in cancer cells. Targeting ncRNAs can modify the ROS/GSH balance within

mitochondria, diminishing the tolerance of cancer cells to drug-induced ROS (Fig. 6, Table IV).

Glutamine metabolism. Glutamine (Gln), a non-essential amino acid, serves a key role in cancer initiation and progression. Cancer cells depend on glutamine for its involvement in the TCA, as well as for the biosynthesis of nucleotides, GSH and other non-essential amino acids, thus providing essential nutrients for cancer drug resistance (10). Numerous studies (215-220) have demonstrated that ncRNAs regulate GSH metabolism in cancer cells primarily by targeting glutaminase (GLS), a mitochondrial enzyme responsible for catalyzing the deamidation of glutamine (Fig. 7; Table V). GLS is a key player in cancer drug resistance, tumor growth and metastasis (221). In cancers such as HCC and NSCLC,

Table IV. Mitochondrial dysfunction mediated by ncRNAs and tumor drug resistance.

ncRNA	Molecular target	Function	Cancer	Therapy	(Refs.)
miR-125b	PARP	Promotes drug-induced apoptosis	Glioblastoma	TMZ	(201)
miR-518d-5p	c-Jun/PUMA	Inhibits drug induced ROS	Liver	Sorafenib	(205)
miR-2329	Complexes I, III and IV	Elevates mitochondrial ROS and decreases ATP production	Tongue squamous cell carcinoma	Cisplatin	(206)
lncSAMMSON	Complex I	Elevates mitochondrial ROS	BC	Doxorubicin	(207)
miR-150, miR-328 and miR-616	CD46, CD55 and CD59	Affects complement regulator expression and mitochondrial activity	CML	Complement lysis	(208)
miR-98	LASS2	Promotes mitochondrial fission and increases mitochondrial membrane potential	Bladder	Cisplatin and doxorubicin	(209)
miR-5787	MT-CO3	Inhibits oxidative stress and glycolysis	Tongue squamous cell carcinoma	Cisplatin	(210)
miR-34b/c	c-Myc/ γ -GCS	Enhances cellular tolerance to ROS	Prostate	Cisplatin and doxorubicin	(211)
lncH19	Nrf2	Promotes GSH production	HGSC	Cisplatin	(212)
miR-27a	Nrf2	Decreases cellular resistance to ROS and increases sensitivity to chemotherapy	BC	Doxorubicin	(213)
lncSLC7A11-AS1	SCF ^{β-TRCP} / Nrf2	Decreases intracellular ROS levels	Pancreatic	GEM	(214)

lnc, long non-coding; miR, microRNA; TMZ, Temozolomide; PUMA, p53-upregulated modulator of apoptosis; ROS, Reactive oxygen species; BC, Breast Cancer; CML, Chronic Myelogenous Leukemia; LASS2, Longevity Assurance Homologue 2; MT-CO3, Mitochondrial Cytochrome c Oxidase Subunit 3; GCS, glutamyl-cysteine synthetase; GSH, Glutathione; HGSC, High-Grade Serous Ovarian Cancer; GEM, Gemcitabine; SCF ^{β -TRCP}, SKP1-Cul1-Rbx1.

5-FU resistance by suppressing glycolysis (122). Inhibiting glycolysis-related ncRNAs, such as circ-SAMD4A or miR-143, may disrupt energy supply and stemness, thereby overcoming chemoresistance.

HCC. HCC cells exploit abnormal lipid metabolism and resistance to ferroptosis, a key mechanism of sorafenib-induced cell death (170,187). In HCC, miR-23a-3p is upregulated by sorafenib and suppresses ACSL4, a key enzyme in lipid peroxidation, thereby inhibiting ferroptosis (170). lncRNA PVT1 promotes PLAG1 expression by sponging miR-195-5p, enhancing GPX4 activity (187), while miR-128-3p directly inhibits GPX4, promoting ferroptosis and overcoming sorafenib resistance (188). Additionally, LINC01056 inhibits PPAR α , suppressing FAO and restoring sorafenib sensitivity (163). Other ncRNAs, such as miR-374b, target HNRNPA1 to reduce PKM2 expression and sensitize HCC cells to sorafenib (91).

Restoring lipid peroxidation, for example by inhibiting miR-23a-3p or PVT1, may enhance sorafenib efficacy in patients with HCC.

BC. BC, particularly ER⁺ subtypes, relies on glycolysis and cholesterol metabolism to sustain tumor growth and evade endocrine therapies such as tamoxifen (59,154). In BC, lncRNA HISLA stabilizes HIF-1 α , promoting glycolysis and resistance to chemotherapy-induced apoptosis (59). Additionally, miR-186-3p suppresses EREG to inhibit glycolysis and reverse tamoxifen resistance (123). Moreover, lncRNA DIO3OS interacts with PTBP1 to stabilize LDHA mRNA, enhancing glycolysis and aromatase inhibitor resistance (110). Another key regulator, miR-128, targets ABCA1, a cholesterol efflux transporter, leading to cholesterol accumulation and tamoxifen resistance, while miR-33a inhibits HDL-mediated cholesterol efflux, contributing to drug

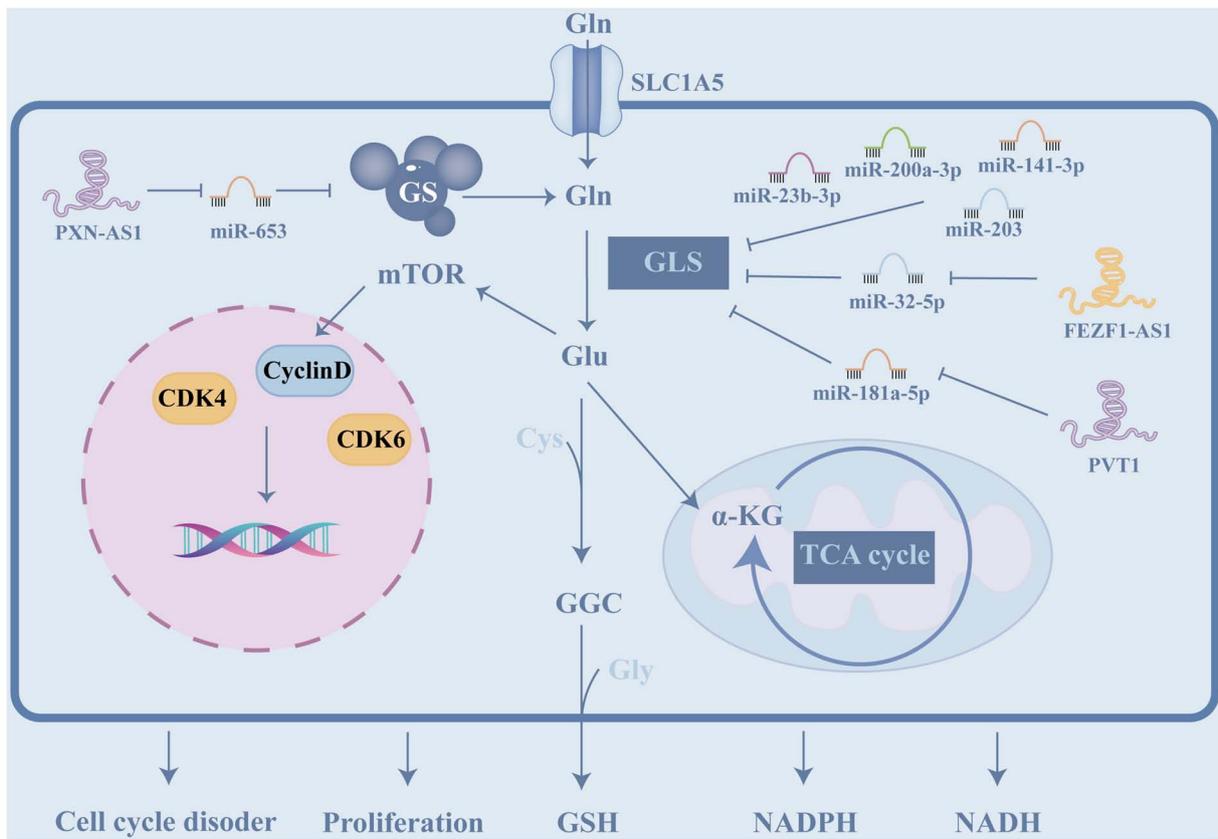


Figure 7. ncRNAs govern Gln metabolism in drug-resistant cancer cells. ncRNAs mediate Gln by targeting GLS and GS, which are key enzymes involved in Gln synthesis and metabolism. nc, non-coding; GLS, Glutaminase; GS, Glutamine synthetase; SLC1A5, Solute Carrier Family 1 Member 5; miR, microRNA; GGC, Glutamylcystine; KG, ketoglutarate; TCA, Tricarboxylic acid cycle; PVT1, Plasmacytoma variant translocation 1; Glu, glutamate.

resistance (153,154). Targeting HISLA or restoring miR-128 expression may disrupt metabolic adaptations and restore sensitivity to endocrine therapy.

OC. OC cells exhibit enhanced glycolysis and antioxidant capacity, which contribute to cisplatin resistance (93,210). In OC, lncRNA CTSLP8 binds to PKM2, forming a dimer that transcriptionally activates c-Myc, driving glycolysis and cisplatin resistance (93). Another key player, lncRNA H19, upregulates Nrf2, enhancing GSH synthesis and oxidative stress resistance (210). Additionally, miR-21-5p targets PDHA1, suppressing mitochondrial metabolism and promoting cisplatin resistance (105). Targeting CTSLP8 or H19 may disrupt glycolysis and redox balance, sensitizing OC cells to platinum-based therapy.

4. Clinical application

ncRNAs serve as biomarkers that indicate abnormal tumor metabolism and responses to anti-tumor drugs. Early detection, diagnosis and treatment are critical for improving cancer prognosis. However, many patients with cancer experience disease progression due to drug resistance, which delays treatment opportunities. ncRNAs, particularly circulating miRNAs, are found in bodily fluids such as blood, urine and saliva and exhibit high stability when stored under appropriate conditions (223). These ncRNAs are specifically expressed in cancer cells and enter bodily fluids after binding

proteins or being encapsulated by exosomes, making them potential biomarkers for cancer (Fig. 8) (224). Numerous studies have demonstrated that ncRNAs can predict patient responses to treatment (67,93,225). For example, the upregulation of circ-0002130 in serum exosomes from patients with osimertinib-resistant NSCLC can predict sensitivity to osimertinib (67). In OC, patients with high CTSLP8 expression have notably reduced overall survival (93). Liu *et al* (225) used changes in the levels of eight lncRNAs to predict the response of patients with HGSC to platinum-based chemotherapy.

Additionally, ncRNAs reflect the association between drug resistance and metabolic changes in cancer cells (226). AIs, the first-line endocrine therapy for postmenopausal patients with ER⁺ BC, have resistance closely linked to glycolysis (225). High baseline expression of miR-155 is associated with increased glycolysis and poor response to AI treatment (227). Changes in the expression of lncRNAs associated with cholesterol and sphingolipids predict the prognosis of HCC and pancreatic cancer and assess their sensitivity to immunotherapy (228,229). A study used 11 lncRNAs associated with FA metabolism to construct a risk prediction model for skin melanoma, aimed at predicting melanoma sensitivity to immunotherapy (230). Ongoing research efforts are being made to establish ncRNAs as biomarkers of tumor drug resistance (231-233). For example, a clinical trial involving 144 patients with BC found that lncRNA MEG3 is associated with the response and toxicity of PTX and cisplatin chemotherapy (231).

Table V. Role of ncRNAs in Gln-mediated drug resistance.

ncRNA	Molecular target	Function	Cancer	Drug	(Refs.)
miR-23b-3p	GLS	Inhibits the conversion of Gln to Glu and drug resistance	HCC	Sorafenib	(215)
miR-200a-3p			NSCLC	Cisplatin	(216)
miR-141-3p			Osteosarcoma		(217)
miR-203			Melanoma	TMZ	(218)
lncPVT1	miR-181a-5p/GLS	Promotes the conversion of Gln to Glu and drug resistance	Esophageal	Cisplatin	(219)
lncFEZF1-AS1	miR-32/GLS		NSCLC		(220)
lncPXN-AS1	miR-653/GS	Promotes Gln synthesis	CML	Imatinib	(222)

lnc, long non-coding; miR, microRNA; GLS, Glutaminase; GS, Glutamine Synthetase; HCC, Hepatocellular Carcinoma; NSCLC, Non-Small Cell Lung Cancer; CML, Chronic Myelogenous Leukemi; TMZ, Temozolomide.

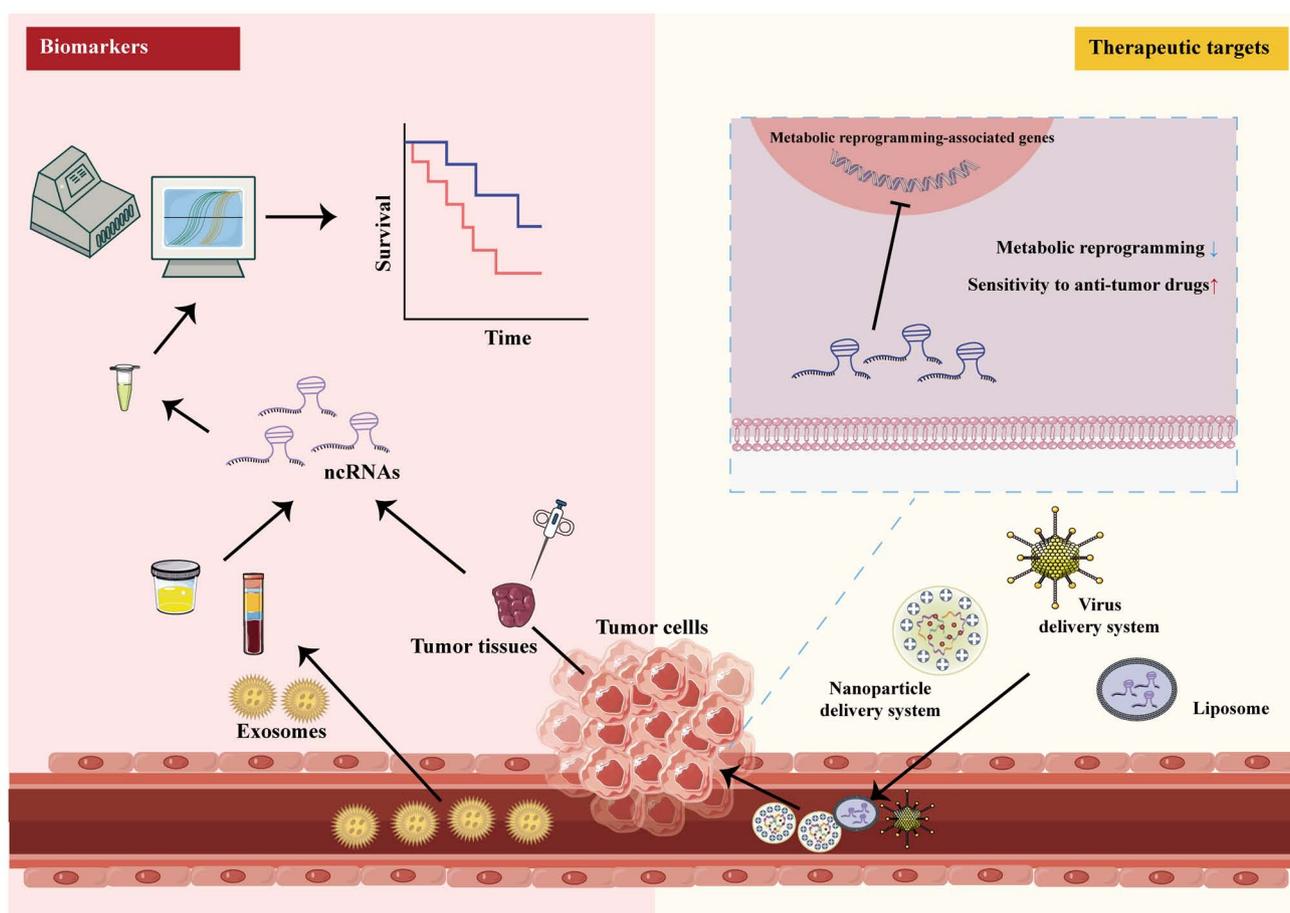


Figure 8. ncRNAs serve as biomarkers and therapeutic targets. Abnormally expressed ncRNAs in tumor cells are released into bodily fluids via exosomes and can be subsequently collected. Quantitative analyses of ncRNAs extracted from body fluids or directly from cancerous tissue provide insight into the altered metabolism of patients with cancer and their sensitivity to pharmacological treatments. Furthermore, the targeted delivery of drugs aimed at ncRNAs to tumor cells using nano-delivery systems, liposomes and viral vectors mitigates the development of drug resistance in cancer through regulatory mechanisms. nc, non-coding.

Targeting ncRNAs alleviates tumor drug resistance by regulating metabolism. The regulation of metabolism in combination with anti-tumor therapy is a promising strategy to overcome tumor drug resistance (234). Numerous studies have demonstrated that blocking key metabolic pathways

in cancer cells contributes to the eradication of recurrent or drug-resistant cancer cells (234,235). However, non-cancerous and immune cells exhibit metabolic fragility; targeting the intrinsic metabolism of cancer cells can also affect these essential cells, leading to severe adverse reactions (12). The

advantage of targeting ncRNAs to regulate metabolism is the specific abnormal expression of these ncRNAs in cancer cells. This specificity allows more targeted ncRNA-based therapy. miRNAs promoting glycolysis are notably elevated in drug-resistant cancer cells. When anti-miR drugs are delivered to these cells, specific miRNAs are notably inhibited (236). Although these miRNAs are inhibited in normal cells as well, the impact on normal cells, where these miRNAs are expressed at low levels, is smaller compared with that on cancer cells. Furthermore, certain ncRNAs bind to multiple sites simultaneously. For example, miR-498 binds GLUT1, HK2 and LDHA to inhibit cellular glycolysis (64). In mitochondria, miR-634 binds to multiple sites, including optic atrophy 1, lysosomal-associated membrane 2 gene and Nrf2, thereby regulating mitochondrial homeostasis, autophagy and the production of apoptosis-related proteins (237).

Medina *et al* (238) achieved complete tumor regression within days by pharmacologically inactivating miR-21, highlighting the key role of targeting ncRNAs in cancer therapy. A recent review has summarized the effectiveness of targeting ncRNAs in treating cancer and improving tumor resistance to treatment (239). Recently, emerging strategies have been developed to ensure the precise delivery of targeted ncRNAs to cancer cells (240,241).

Emerging strategies to modulate cancer metabolism by targeting ncRNAs. The inherent instability of ncRNAs in the body makes them highly susceptible to degradation by RNases, which presents a notable challenge for therapeutic application. To overcome this, the development of effective delivery systems that ensure targeting specificity, decrease immunogenicity and maintain the stability of ncRNAs is crucial (242). Various approaches have been explored to address these challenges. Lin *et al* (243) developed a pH- and GSH-sensitive nanocarrier for the co-delivery of docetaxel and the miR-34 activator rubbone (RUB). This carrier demonstrates good stability *in vitro*, targets cancer cells efficiently and rapidly releases docetaxel and RUB into the cytoplasm, enhancing the sensitivity of tumor cells to docetaxel (243). Another study (244) designed GSH-sensitive nanoparticles. These nanoparticles lead to micellar degradation and facilitating drug release by reducing GSH to sulfhydryl groups. This strategy is used for the targeted delivery of GEM and miR-519c to pancreatic cancer tissue with elevated GSH levels, improving GEM resistance. Additionally, miR-519c decreases glycolysis and angiogenesis by inhibiting HIF-1 α (244). In melanoma, Guo *et al* (245) employed liposomes containing miR-21-3p to regulate lipid metabolism. The nanoparticles deliver miR-21-3p into melanoma cells, promoting lipid peroxidation and lipid ROS production by inhibiting TXNRD1, which enhances the response of melanoma cells to immunotherapy (245). Similarly, lipid-coated calcium carbonate nanoparticles are used to deliver 5-FU and miR-375-3p to tumor cells in a weakly acidic environment (246). miR-375-3p interferes with thymidylate metabolism by targeting thymidylate synthase, enhancing the chemotherapy effect of 5-FU (246). Targeting mitochondrial dysfunction in cancer, nanoparticles modified with mitochondria-targeting peptides and tumor-targeting ligands efficiently deliver miR-125 to mitochondria within cancer cells. This approach regulates mitochondrial dynamics-associated

proteins and suppresses intracellular ATP production (247). Bioengineered miRNAs targeting metabolic pathways have shown promise in cancer therapy (248,249). For example, the bioengineered tRNA/miR-328-3p enables controlled release of miR-328-3p in human osteosarcoma cells, inhibiting glycolysis and cell proliferation by targeting GLUT1 (249).

Exosomes serve a key role in intercellular communication and can be easily engineered with tumor-targeting properties through molecular biology techniques, making them a promising vehicle for ncRNA delivery (250). For example, exosomes targeting HER2 have been used to deliver oncomiR-21 inhibitors to CRC cells, successfully reversing 5-FU resistance in these cells (251). However, current research is mainly focused on encapsulating both antitumor drugs and ncRNAs within nanoparticles for synergistic antitumor effects (252), while the use of exosomes for concurrent delivery of drugs and ncRNAs remains underexplored. Stability issues surrounding dual delivery via exosomes need to be addressed in future studies. In addition to nanoparticle-based approaches, inhibition of miRNAs using antisense DNA oligomers that incorporate locked nucleic acids (LNAs) offers a promising strategy for gene therapy. A clinical trial investigated a 13-mer LNA inhibitor targeting miR-221 (LNA-i-miR-221) and found that, among 17 patients treated with this therapy, 16 demonstrated good tolerance, with eight achieving stable disease and one experiencing partial response (253). Furthermore, gene delivery systems based on viral vectors and clustered regularly interspaced short palindromic repeat-associated protein9 (Cas9) genome editing system have been explored for editing ncRNAs to hinder tumor progression (254).

In summary, ncRNAs exhibit specificity in targeting key pathways in tumor cell metabolism, serving a pivotal role in tumor growth and drug resistance. As such, ncRNAs represent valuable targets for metabolic regulation in treating drug-resistant cancer. Interfering with ncRNAs in tumor cells via targeted delivery systems, such as nanoparticles, can effectively modulate tumor metabolism and enhance the efficacy of anti-cancer therapy (Fig. 8).

5. Discussion and perspectives

The aforementioned studies underscored the importance of ncRNA-mediated metabolic regulation in combating drug resistance, yet limitations persist. Studies (97,189,205,213) often focus on individual ncRNAs in specific cancer models, neglecting the tissue-specific and context-dependent roles of ncRNAs and rarely account for spatiotemporal variations, which are key for predicting therapeutic outcomes. For example, miR-181a exhibits oncogenic properties in GC (255) but acts as a tumor suppressor in NSCLC (256). These fragmented views impede the identification of the complex ncRNA regulatory network in cancer. Metabolic reprogramming involves interconnected pathways, such as glycolysis, lipid and glutamine metabolism. yet most studies (66,215) investigate ncRNAs targeting a single pathway, which may trigger compensatory mechanisms. For example, inhibition of glycolysis can enhance glutamine dependency (257).

The regulatory mechanisms by which ncRNA influences metabolic reprogramming pathways require further investigation. The JAK/STAT pathway facilitates rapid

signal transduction from the cell membrane to the nucleus and induces the production of oncogenic factors, serving as a key pathway regulating cancer cell proliferation, metabolism and immune responses (258). The JAK/STAT3 pathway promotes glycolysis and FAO, thereby contributing to drug resistance (259,260). Several ncRNAs are effective regulators of the JAK/STAT3 pathway (261,262). However, further research is needed to elucidate the mechanisms by which these ncRNAs regulate JAK/STAT3 in the context of metabolism and cancer drug resistance. In addition, the circadian clock and cancer cell stemness are key phenotypes that profoundly influence metabolic reprogramming (263,264). ncRNAs serve a regulatory role in the circadian gene and stemness driving pathways (265-267). For example, in gastrointestinal tumors, miR-494-3p and miR-135b directly target the 3'UTR of brain and muscle arnt-like protein 1 (BMAL1) to inhibit its expression. BMAL1 interacts with Enhancer of zeste homolog 2 to suppress glycerol-3-phosphate acyltransferase mitochondrial, resulting in a reduction of LPA levels. By targeting BMAL1, miR-494-3p promotes LPA metabolism and proliferation of HCC cells (259). Meanwhile, miR-135b disrupts the tumor-suppressive circadian rhythm in pancreatic cancer via the BMAL1/Yin Yang-1 axis, thereby promoting pancreatic cancer progression and GEM resistance (268). ncRNAs mediate the occurrence and progression of EC by disrupting circadian rhythm in EC cells through the regulation of Zinc Finger and BTB Domain Containing 7A, p21) and Neuronal PAS domain protein 2 expression (266). Regarding tumor stemness, multiple ncRNAs enhance the expression of transcription factors such as NF- κ B and STAT3 in tumor cells to evade the toxic effects of chemotherapy and radiotherapy (267). Mechanistically, these ncRNAs activate key signaling pathways that promote the properties of cancer stem cells. These pathways include Wnt/ β -catenin, PI3K/AKT/mTOR, Notch and TGF- β (269). This process not only promotes cancer stemness but also facilitates the formation of feedback loops, which in turn leads to cancer metastasis and drug resistance (270). Exploring these ncRNAs, particularly their modulation of circadian rhythm and stemness-mediated metabolic alterations and drug resistance, offers a promising and valuable option for future research.

Targeting ncRNAs to regulate metabolism presents a promising strategy for personalized cancer therapy. However, several challenges must be overcome before this approach can be widely applied in clinical practice. A notable obstacle is the toxicity of ncRNA-targeting drugs. For example, the phase 1 trial of the liposomal miR-34a mimic MRX34 in patients with advanced solid tumors showed some clinical activity but was terminated due to four cases of immune-mediated serious adverse events (271). As methods for modulating ncRNA expression in cells, common vectors such as liposomes and chitosan and polymeric nanoparticles are relatively safe and effective for large gene transfer, but they suffer from limitations such as low transfection efficiency and poor transgene expression (272). Based on a mesenchymal stem cell (MSC)-based gene delivery system, tumor suppressor genes are introduced to enhance the specific expression of MSCs and improve their homing effect. This positions MSC-based therapy for cancer

as a potential and effective strategy (273). By contrast, viral vectors, including lentiviruses and adenoviruses, offer high infection efficiency and sustained transgene expression but are hampered by high immunogenicity and limited payload capacity (274). Future research may unlock the potential of ncRNA-based therapy to combat drug-resistant cancer. Collaborative efforts among molecular biologists, bioengineers and clinicians will be essential to translate these insights into clinically viable solutions.

6. Conclusion

The adaptability of tumor cells has led to a rising prevalence of drug resistance, notably decreasing the overall survival of patients with cancers (275). When resistance to first-line chemotherapy drugs arises, adjustments to the chemotherapy regimen or the addition of other agents are often required, which can result in suboptimal therapeutic outcomes or more severe adverse reactions. Previous studies (10,17) have demonstrated the pivotal role of metabolic reprogramming in tumor drug resistance. The present review systematically summarizes the mechanisms by which metabolic reprogramming contributes to drug resistance in tumors, with a focus on how ncRNAs mediate this process through the regulation of glycolysis, lipid and glutamine metabolism and mitochondrial dysfunction, as well as the potential of ncRNAs as biomarkers and therapeutic targets. The specific expression patterns of ncRNAs in tumor cells serve as indicators of both the metabolic state and drug sensitivity of these cells. Targeting ncRNAs that regulate metabolism may offer innovative strategies to combat tumor drug resistance in the future.

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Authors' contributions

JL wrote the manuscript and constructed figures and tables. YL wrote the manuscript. LF constructed figures. HC, ZW and FD revised the manuscript. YZ and YH revised the manuscript. YX and JM conceived the study. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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