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LncRNA mediated metabolic reprogramming: the chief culprits of solid tumor malignant progression: an update review

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Abstract

Metabolism reprogramming (MR) is one of the top ten hallmarks of malignant tumors. The aberrant activation of MR has been recognized as a critical contributory factor to the malignant progression of solid tumors. Moreover, various long non-coding RNAs (lncRNAs) are implicated in the aberrant activation of MR in solid tumor cells. Therefore, in this review, we mainly focus on summarizing the functional relevance and molecular mechanistic underpinnings of lncRNAs in modulating MR of solid tumors by targeting glucose metabolism, lipid metabolism, affecting mitochondrial function, and regulating interactions between tumor and non-tumor cells in tumor microenvironment. Besides, we also underscore the potential for constructing lncRNAs-centered tumor metabolic regulation networks and developing novel anti-tumor strategies by targeting lncRNAs and abnormal MR. Ultimately, this review seeks to offer new targets and avenues for the clinical treatment of solid tumors in the future.

Keywords Long non-coding RNA, Metabolic reprogramming, Solid tumors, Therapeutic targets

Introduction

Approximately only 1-2% of the human DNA is transcribed into protein-coding messenger RNAs (mRNAs), while the majority is transcribed into non-coding RNAs (ncRNAs) [1]. Long non-coding RNAs (lncRNAs) represent a subtype of ncRNAs that exceed 200 nucleotides in length and are widely present in eukaryotes [2]. They are involved in almost all cellular activities, including cell differentiation, cell cycle regulation, cellular metabolism, cell proliferative potential, apoptotic capacity, invasive ability, and metastatic events [3–6]. Similar to mRNAs, lncRNAs feature the 5′ cap structure and the 3′ poly-A tail, allowing the formation of various lncRNA transcripts through alternative splicing. Unlike mRNAs, lncRNAs exhibit robust cellular localization specificity. Although they are ubiquitously distributed across the nucleus, cytoplasm, and organelles, they are most highly enriched in the nucleus, where lncRNAs are mainly transcribed

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and mature [7–9]. Therefore, they primarily influence oncogene expression through transcriptional regulation or post-transcriptional epigenetic modifications [10, 11]. This characteristic endows lncRNAs with the capability to modulate malignant tumor progression. Indeed, a mounting body of research highlights the close association between lncRNAs and the malignant progression of almost all human solid tumors [12].

Alterations in metabolic processes represent an essential marker in carcinogenesis and tumor growth, where energy metabolism reprogramming is one of the most crucial biological phenomena involved [13, 14]. Metabolic reprogramming (MR) refers to the metabolic alterations that cells undergo to meet energy demands in response to various stimuli and involve glucose, lipid, and amino acid metabolism pathways [15]. MR not only assists cells in resisting external stress but also endows them with new functionalities. For instance, altered energy metabolism through MR allows tumor cells to rapidly adapt to hypoxic, acidic, and nutrient-deficient microenvironments, thereby facilitating rapid tumor cell proliferation [16]. MR is not only an emerging hallmark of cancer but also a crucial regulator for cancer cells to adapt to their microenvironments. During tumor development, notable changes occur in metabolic enzymes, upstream regulatory molecules, and downstream metabolic products [17]. Currently, MR has been recognized as a critical hallmark among the ten defining features of cancer [18]. Multiple seminal studies have established their close association with malignant biological behaviors of tumors, such as abnormal proliferation, invasion, metastasis, immune evasion, and therapy resistance [13, 15, 18, 19]. Tumor recurrence and metastasis following surgical intervention remain the leading causes of mortality in patients with solid tumors [20]. Moreover, tumor cells manifest distinct MR abnormalities characterized by mitochondrial dysfunction and dysregulated lipid metabolism during malignant development and metastatic spread [21–23]. Abnormal MR alters the oncogenic signaling pathways in tumor cells and affects the surrounding normal cell populations through related metabolic products, including lipids [24]. Hence, this complex interaction highlights the need to delineate the metabolic networks in tumor cells and examine MR in the tumor microenvironment (TME). It is also imperative to delve into the tumor-specific MR regulatory mechanisms in the malignant progression of solid tumors.

The mediation and maintenance of tumor malignant transformation through MR are complex processes that involve the accumulation of numerous molecular changes, including ncRNA-mediated regulation, post-translational modifications, and other changes in epigenetic mechanisms [25–27]. LncRNAs are one of the major ncRNAs with function in tumors, which can be specifically expressed in tumor cells and serve as potential candidates for tumor biomarkers and precision medicine targets. LncRNAs can regulate gene expression in the form of different mechanisms that can be associated with metabolic reprogramming, such as acting as scaffolds to regulate protein-protein interactions, regulating the binding of transcription factors to promoters, and being involved in epigenetic regulation of chromatin [28]. Besides, lncRNAs may also serve as pivotal regulators to affect the malignant progression of solid tumors by modulating the MR landscape via central metabolic processes, such as glucose [31] and lipid metabolism [32], mitochondrial function [33], and the dynamic interplay within TME and between tumor cells [34]. Therefore, in this review, we thoroughly summarize the specific regulatory roles of lncRNAs in the MR of solid tumor cells during malignant progression. It proposes regulatory networks of tumor MR centered on lncRNAs to clarify the mechanistic underpinnings of lncRNA-mediated MR in fostering malignant phenotypes of solid tumors. Ultimately, this review unveils novel diagnostic and therapeutic targets for tumor diagnosis and management.

LncRNAs modulate MR of solid tumor cells by targeting glucose metabolism

Alterations in energy metabolism, particularly the aberrant activation of the aerobic glycolysis (AG) pathway in tumor cells, are critical indicators of tumor malignancy [35–38]. For example, glucose concentrations within tumor tissues are substantially lower than in adjacent non-neoplastic tissues [31], and this concentration disparity further activates AG in tumor cells. Activated AG increases lactate production in tumor cells when secreted into the TME, which causes a pronounced drop in the extracellular pH value adjacent to tumor cells [39]. Evidence suggests that the AG-mediated pH reduction in the TME prominently expedites the spread and metastasis of solid tumors, which is tightly associated with adverse prognoses in individuals with solid tumors [40]. In this context, lncRNAs orchestrate glucose metabolism by regulating the activity, stability, post-translational modification of metabolic enzymes and the expression of transporters or interacting with relevant signaling cascades, thereby controlling tumor MR and affecting the malignant progression of solid tumors.

MYC proto-oncogene, bHLH transcription factor (c-Myc), is a crucial oncogene in MR, extensively substantiated to modulate glucose metabolism and acting as a critical switch in the AG of cancer cells [41, 42]. Studies have found that lncRNAs could affect the MR and activate AG by regulating the expression and stability of c-Myc. LncRNA *AF339830* prevents c-Myc from ubiquitin-mediated degradation by binding to the heat shock 90 kDa protein 1, alpha (HSP90) chaperone

protein, thereby stabilizing c-Myc expression in the cytoplasm. The lncRNA-mediated stabilization facilitates the transcriptional activation of the lactate dehydrogenase (*LDHA*) gene, a key gene in the AG pathway, thus driving CRC malignant development. Furthermore, *AF339830* has been implicated in tumorigenesis, tumor size, and dismal prognostic outcomes in individuals with colorectal cancer (CRC). Thus, targeting the AF339830-c-Myc-LDHA axis and its related pathways by developing metabolic blockade agents may hold considerable therapeutic implications in treating patients with CRC [43]. Similarly, another study on CRC uncovered the interaction between lncRNA *LINRIS* and insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2). The LINRIS-IGF2BP2 axis has been identified as a regulator to enhance AG in CRC cells by upregulating c-MYC expression and repressing the ubiquitination and degradation via the autophagy-lysosome pathway, thus promoting malignant cell proliferation [30].

Phosphoglycerate kinase 1 (PGK1) is a critical metabolic enzyme that influences ATP production during AG and catalyzes the conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate [44]. Studies have shown that a variety of lncRNAs can directly affect the stability, activity and post-translational modification of PGK1. The lncRNA nuclear enriched abundant transcript 1 (*NEAT1*) exhibits elevated expression and imparts pro-oncogenic effects on breast cancer (BC) [45, 46]. NEAT1 provides a scaffold for the glycolytic PGK1-PGAM1-ENO1 multienzyme complex to promote composite stability and intensify the energy release in AG, leading to escalated glycolytic activity and accelerating BC malignant progression. Besides, *NEAT1* enhanced AG and glioma cell proliferation by interacting with the hairpin A structure and M1 domain of PGK1. Because PGK1 contains multiple phosphorylation, ubiquitination, and acetylation sites, its enzymatic activity can be regulated by various lncRNAs through post-translational modifications [47]. For instance, lncRNA *LINC00963* has a dominant role in the post-translational modulation of PGK1 by blocking its ubiquitin-mediated degradation, which, in turn, stabilizes PGK1 levels. This mechanism activates the PI3K-AKT-mTOR signaling cascade, thus fostering a conducive environment for MR and the metastatic activity of non-small cell lung cancer (NSCLC) cells [48]. Other studies have found that the lncRNA *ENST00000425894*, also termed gallbladder cancer (GC) drug resistance-associated lncRNA 1 (*GBCDRlnc1*), is overexpressed in drug-resistant GC cells. Targeted silencing of *GBCDRlnc1* bolsters the therapeutic sensitivity of resistant cells by curbing autophagy. Mechanistically, *GBCDRlnc1* binds to PGK1 and curtails its ubiquitin-dependent degradation. The stabilized PGK1 protein impacts the formation of the autophagy-related ATG5-ATG12 regulatory complex and activates autophagic potential, ultimately leading to chemotherapy resistance of GC cells [49].

Pyruvate kinase M2 (PKM2) is an isoform of pyruvate kinase that catalyzes the conversion of phosphoenolpyruvate to pyruvate and is involved in lactate metabolism during AG in tumor cells [50]. LncRNA *AC020978* and *LINC01554* have been highlighted to orchestrate the stability of PKM2 via a ubiquitin-dependent proteasomal degradation pathway, thereby implicating these lncRNAs in the regulation of AG in cancers. Notably, lncRNA *AC020978* interacts with PKM2 and promotes the stability of the nuclear PKM2-HIF-1α complex, enhancing the transcriptional activity of HIF-1α on target genes and augmenting a tumor-specific glycolytic profile conducive to the accelerated malignancy of NSCLC [51]. Conversely, *LINC01554* accelerates ubiquitin-mediated PKM2 degradation via the AKT-mTOR signaling pathway, thus halting AG and exerting an anti-cancer effect in hepatocellular carcinoma (HCC) [52]. Additionally, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) catalyzes the transformation of fructose-6-phosphate (F6P) into fructose-2,6-bisphosphate (F-2,6-BP) within AG biochemical cascade. Intriguingly, lncRNA actin gamma 1 pseudogene (*AGPG*) has previously been reported to specifically bind to the C-terminal domain of PFKFB3. The binding constrains the ubiquitination and subsequent degradation of PFKFB3 at its Lys302 residue to facilitate the stability of the PFKFB3 protein, thus resulting in AG in esophageal squamous cell carcinoma [29]. Similarly, lncRNA *LINC00538*, also known as YIYA, stimulates PFKFB3 phosphorylation dependent on cyclin dependent kinase 6 (CDK6). This enzymatic modification fosters the metabolic conversion from F6P to F-2,6-BP and ultimately activates MR in BC cells [53]. These findings collectively underscore the promising influence of lncRNAs on the malignant progression of solid tumors by influencing glucose metabolism and orchestrating the MR of tumor cells. Figure 1 summarizes the main processes that lncRNAs modulate MR of solid tumor cells by targeting glucose metabolism.

LncRNAs modulate MR of solid tumor cells by influencing lipid metabolism

Lipids are integral molecules comprising the cellular skeleton and serve as critical reservoirs for energy storage and provision within the human body. In a nutrient-deficient microenvironment, lipids generate energy and regulate intracellular redox reactions through NADPH [54]. The complexity and significance of lipid metabolism, including digestion, absorption, synthesis, and degradation of fats, underscore its essential role in sustaining biological functions. Lipid MR facilitates oncogenic processes across a spectrum of tumor-related activities, including metastasis, alterations within the TME, therapy

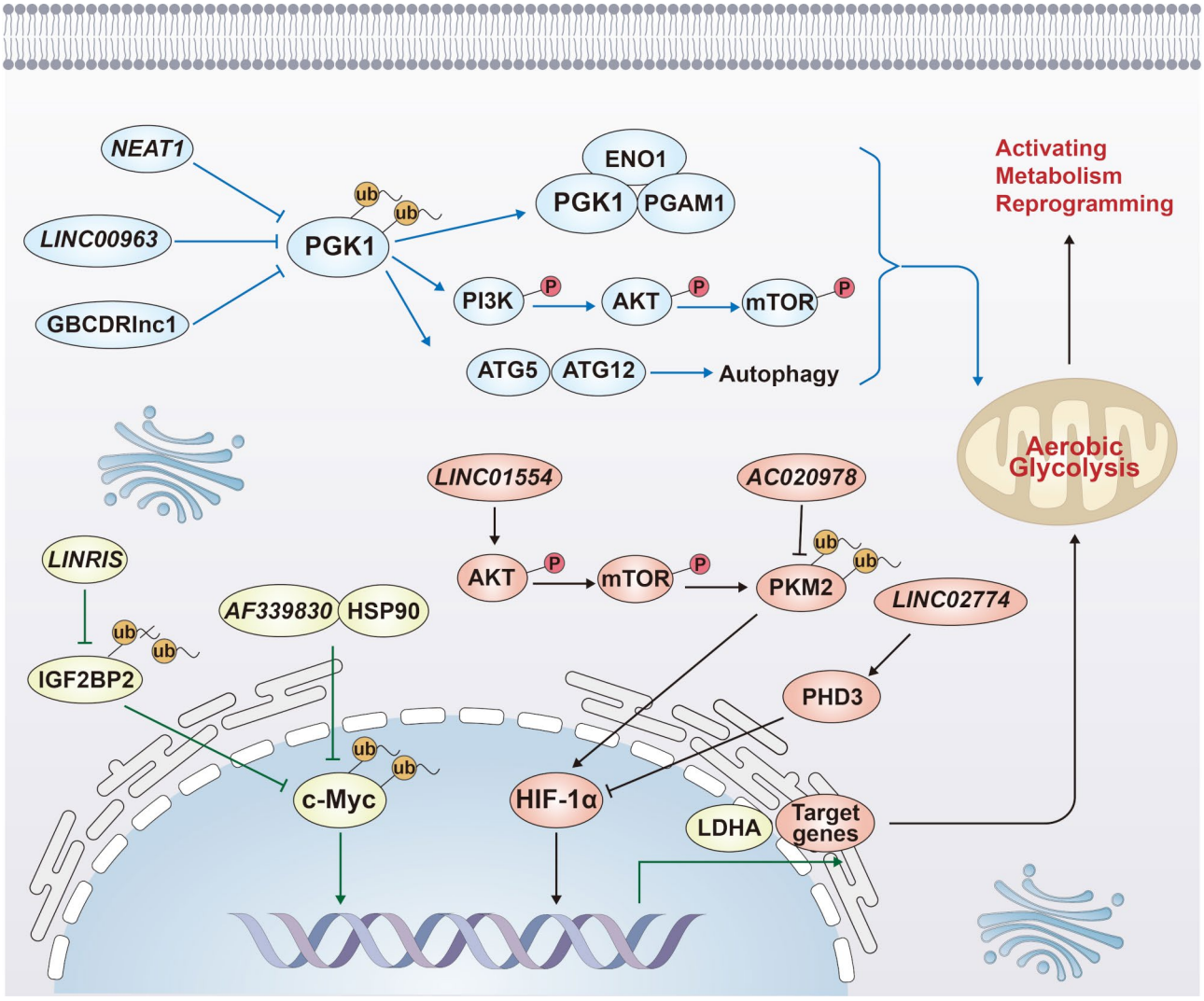

Fig. 1 LncRNAs modulate MR of solid tumor cells by targeting glucose metabolism. LncRNAs orchestrate glucose metabolism by regulating the expression of metabolic enzymes and transporters or interacting with relevant signaling cascades, thereby controlling tumor MR. In this figure, we mainly summarize that lncRNA *AF339830* and *LINRIS* inhibit ubiquitination of c-Myc, increase its' protein stability, then activate the transcription of the *LDHA* gene or other glucose metabolism-related genes. Meanwhile, lncRNA *NEAT1*, *LINC00963*, and GBCDRlnc1 also inhibit the ubiquitination of PGK1, a critical metabolic enzyme in glucose metabolism, which significantly activates aerobic glycolysis of solid cancer cells by related signaling pathways. Besides, lncRNA *AC020978*, *LINC01554* and *LINC02774* significantly affect the function of HIF-1α-related pathway to take action in aerobic glycolysis of solid cancer cells. These findings collectively underscore the promising influence of lncRNAs on MR of solid tumors by influencing glucose metabolism

resistance, energy provision for tumor cells, and redox equilibrium maintenance [32, 55]. Increasing evidence suggests that the hyperactivation of lipid MR is a critical contributor to the continued proliferation of metastatic tumor cells upon their settlement in new organ environments [56]. Lipid MR typically occurs during the increase in fatty acid oxidation (FAO) and lipid synthesis [57], and it is regulated by lncRNAs that modulate FAO-related genes by influencing the stability of their mRNAs through epigenetic mechanisms. These mechanisms trigger crucial lipid metabolism-associated signaling pathways, thereby governing MR of solid tumor cells. For example, p38 MAPK-PPARα, PI3K-AKT, Wnt-β-catenin and Hippo-YAP signaling pathways [58].

The lncRNA *LINC00924* is a pro-oncogenic factor that fosters invasive and metastatic capacities of gastric cancer by modulating lipid MR [59]. Metabolomic investigations reveal that *LINC00924* overexpression substantially enhances FAO and fatty acid uptake. These processes are indispensable for the sustenance of cells and spheroid formation of gastric cancer cells once the cells dislodge from their original matrix [60–62]. Furthermore, *LINC00924* overexpression in gastric cancer cells prominently diminishes the accumulation of various lipids, including triglycerides, fatty acids, and diglycerides. Meanwhile,

it upregulates the expression of fatty acid transport-related proteins, such as carnitine palmitoyltransferase 1 A (CPT1A), fatty acid binding protein 4 (FABP4), and CD36. Mechanistically, *LINC00924* modulates the alternative splicing of the MAPK interacting serine/threonine kinase 2 (*MNK2*) precursor mRNA by binding with heterogeneous nuclear ribonucleoprotein C (HNRNPC). This interaction downregulates Mnk2a splicing, which, in turn, regulates the p38 MAPK-PPARα signaling pathway, ultimately affecting the lipid metabolism of gastric cancer cells [59]. The regulatory role of lncRNAs in lipid metabolism has received considerable attention in the context of HCC. The lncRNA *NEAT1* promotes HCC proliferation by upregulating the expression of adipose triglyceride lipase (ATGL), a central enzyme in lipid catabolism. It catalyzes triglyceride hydrolysis to yield diacylglycerol and free fatty acids (FFAs), both of which are crucial intermediates in lipid metabolism. Evidence of the molecular dynamics in this modulation shows that *NEAT1* potentiates the peroxisome proliferator-activated receptor alpha (PPARα) signaling pathway directly *via* ATGL or indirectly through the metabolic intermediates diacylglycerol and FFAs, increasing FAO to regulate lipid MR in HCC [63]. The PPARα protein is an essential transcription factor that regulates the expression of lipid metabolism genes and is closely associated with inflammation, FAO, tumorigenesis, and anti-tumor therapy resistance [64–66]. Another study in HCC demonstrated that lncRNA *HUCL* upregulates the expression of long-chain acyl-CoA synthetase family member 1 (ACSL1), a protein pivotal for enhancing fatty acid uptake and FFA biosynthesis. This regulatory mechanism contributes to the notable accumulation of cholesterol and triglycerides in HCC cells, thus impacting tumor cell lipid MR [67]. The lncRNA *LNMICC* facilitates the nuclear translocation of the nucleophosmin 1 (NPM1) transcription factor to bind to the promoter region of fatty acid binding protein 5 (FABP5), stimulating its transcription and consequently bolstering fatty acid metabolism and lymph node metastasis in cervical cancer [68]. The lncRNA *ROPM* is also implicated in modulating BC cells' MR via lipid metabolism alterations and accelerating its metastatic potential. Specifically, the lncRNA *ROPM*, identified as a novel lipid metabolism-associated lncRNA, targets the phospholipid metabolism-related phospholipase A2, group XVI (*PLA2G16*), a gene overexpressed in adipose tissue that enhances lipolysis and impacts lipid metabolism. The activity of *PLA2G16* is robustly implicated in the proliferative capacity and metastatic spread of solid tumors [69–73]. The lncRNA *ROPM* is ubiquitously expressed across various molecular subtypes of BC and is localized in the cytoplasm. It exhibits elevated expression in BC cell lines characterized by higher invasive capabilities relative to BC cell lines with low invasiveness. Mechanistically, *ROPM* influences phospholipid MR by upregulating *PLA2G16* expression and enhancing FFA production, especially arachidonic acid production, which activates critical oncogenic signaling pathways, including PI3K-AKT, Wnt-β-catenin, and Hippo-YAP. Such activation fosters stemness in BC cells and encourages their capacity for distant metastasis [74]. Additionally, heightened *ROPM* expression correlates with reinforced tumor malignancy, recurrence, resistance to chemotherapy, and adverse prognostic outcomes in patients with BC [74]. These insights affirm the pivotal role of lncRNA-mediated lipid metabolism in MR of solid tumor cells, highlighting a significant contributory factor to the pathogenesis and progression of solid tumors. Figure 2 presents the main processes that lncRNAs modulate MR of solid tumor cells by influencing lipid metabolism.

LncRNAs modulate MR of solid tumor cells by affecting mitochondrial function

The disruption of cellular energy balance has long been recognized as a defining feature of cancerous transformations [75, 76]. Mitochondria are pivotal organelles in the cellular energy landscape extensively involved in biosynthesis and signal transduction. The structural and functional integrity of mitochondria is indispensable for the maintenance of energy homeostasis and metabolic flux within cells. Mitochondrial dysfunction is a fundamental requirement for tumorigenesis and a primary characteristic of tumor cell metabolism [77–79]. Evidence implies that alterations in mitochondrial function, exemplified by oxidative phosphorylation, substantially affect tumor aggressiveness and metastatic capacity [80]. As key regulators of cellular metabolism, lncRNAs also exert a pronounced regulatory effect on mitochondrial function [1, 81, 82]. Mitochondria-associated lncRNAs potentially collaborate with transcription factors and epigenetic modulators to co-regulate the expression of mitochondria-related genes, influencing mitochondrial function [33]. Nuclear genome-encoded lncRNAs control mitochondrial function by entering mitochondria after binding with RNA transport proteins [83], whereas mitochondrial genome-encoded lncRNAs shuttle to the nucleus via RNA transport proteins to regulate nuclear genome function. Emerging evidence underscores the significant impact of lncRNA dysregulation on metabolic aberrations in tumor cell mitochondria [84].

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is a lncRNA encoded by the nuclear genome and exhibits notable enrichment within the mitochondria of HCC cells. It functions as a messenger transcript in the epigenetic crosstalk between the nucleus and mitochondria, modulating MR essential for HCC progression. A targeted depletion of *MALAT1* precipitates structural

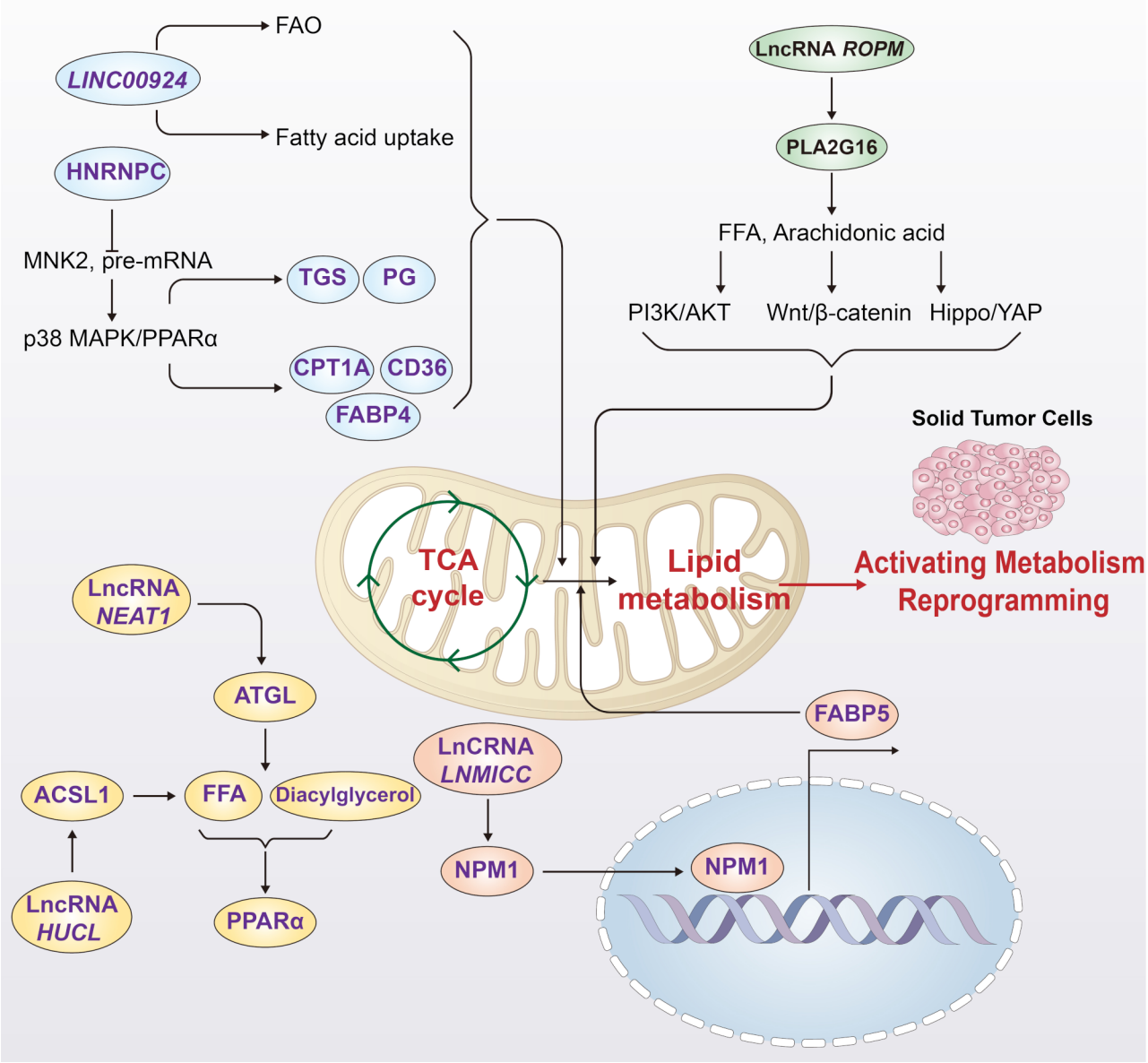

Fig. 2 LncRNAs modulate MR of solid tumor cells by influencing lipid metabolism. LncRNAs significantly regulate the mRNA stability of FAO-related genes and lipid synthesis-related genes through epigenetic mechanisms. These mechanisms trigger crucial lipid metabolism-associated signaling pathways, thereby governing MR of solid tumor cells. In this figure, we mainly summarize that lncRNA *LINC00924* substantially enhances FAO, fatty acid uptake and upregulates the expression of fatty acid transport-related proteins. Mechanistically, LINC00924 modulates the alternative splicing of the MNK2 precursor mRNA by binding with HNRNPC. This interaction downregulates Mnk2a splicing, which, in turn, regulates the p38 MAPK-PPARα signaling pathway. Meanwhile, lncRNA *NEAT1* upregulates the expression of ATGL, which catalyzes triglyceride hydrolysis to yield diacylglycerol and FFAs to potentiate the PPARα signaling pathway. LncRNA *HUCL* also upregulates the expression of ACSL1 to activate above pathway. Furthermore, lncRNA *LNMICC* facilitates the nuclear translocation of NPM1 transcription factor to bind to the promoter region of FABP5, stimulating its transcription and consequently bolstering fatty acid metabolism. Besides, the lncRNA *ROPM* influences phospholipid MR by upregulating PLA2G16 expression and enhancing the production of FFA and arachidonic acid, which activates critical oncogenic signaling pathways, including PI3K-AKT, Wnt-β-catenin, and Hippo-YAP. At last, all these lncRNAs related pathways influence lipid metabolism to modulate MR in solid tumor cells

and functional shifts in mitochondria, including changes in mitochondrial copy number, oxidative phosphorylation (OXPHOS), ATP production, cell apoptosis, and mitochondrial autophagy [85]. Autophagy is a critical mechanism for maintaining mitochondrial integrity in cells [86, 87], and those with *MALAT1* expression deficiency often exhibit reduced expression of known mitochondrial autophagy markers: PTEN induced kinase 1 (PINK1), sequestosome 1 (SQSTM1/p62) nuclear domain 10 protein 52 (NDP52), BCL2 interacting protein 3 (BNIP3), and the microtubule-associated protein 1 light chain 3 beta (LC3B)-II/I ratio. Concurrently, lysosome

labeling suggests that the number of stained lysosomes significantly decreases upon *MALAT1* silencing, indicating that *MALAT1* is crucial for regulating autophagy in HCC cells. Upon translocating to the mitochondria, *MALAT1* binds to multiple sites on mitochondrial DNA to alter the DNA methylation status and instigate retrograde and anterograde signaling, modifying mitochondrial metabolism and regulating tumor cell MR [85]. Glutamine is an abundant and functionally significant non-essential amino acid that directly enters the mitochondrial citric acid cycle through the glutaminolysis pathway. It participates in aerobic respiration and synthetic metabolism to maintain the cellular redox balance, providing the materials and energy required for synthetic metabolism. In tumor tissues, glutamine supports the rapid growth and proliferation of tumor cells [88–90]. The nuclear-enriched antisense lncRNA of glutaminase (*GLS-AS*) associated with glutaminase has been pinpointed as a key metabolic regulator in pancreatic cancer (PCa). The expression of *GLS-AS* is notably diminished in PCa specimens, and its attenuation is linked to enhanced tumor cell proliferation and invasive capabilities. Moreover, *GLS-AS* suppresses glutaminase expression by forming double-stranded RNA with the pre-mRNA of glutamine through ADAR/Dicer-dependent RNA interference at the post-transcriptional level, affecting the mitochondrial metabolic function of PCa cells. Under nutritional stress, MYC transcriptionally downregulates GLS-AS to induce the expression of glutaminase. Conversely, GLS-AS can also reduce the GLS-mediated MYC protein stability to diminish its protein levels, then the MYC-GLS-AS reciprocal feedback is established, which regulates the unusual expression of glutaminase to achieve homeostatic glutaminase levels [91]. These findings suggest that *GLS-AS* governs MR in PCa by influencing glutaminase functionality in mitochondria. The main processes that lncRNAs modulate MR of solid tumor cells by affecting mitochondrial function are also summarized in Fig. 3.

LncRNAs orchestrate MR in solid tumor cells by influencing interactions between tumor and non-tumor cells in TME

TME is a complex network of tumor, immune, and inflammatory cells surrounding stromal tissues, microvasculature, and a milieu of cytokines and chemokines [92–94]. Carcinogenesis and progression of malignant tumors fundamentally rely on the neoplastic

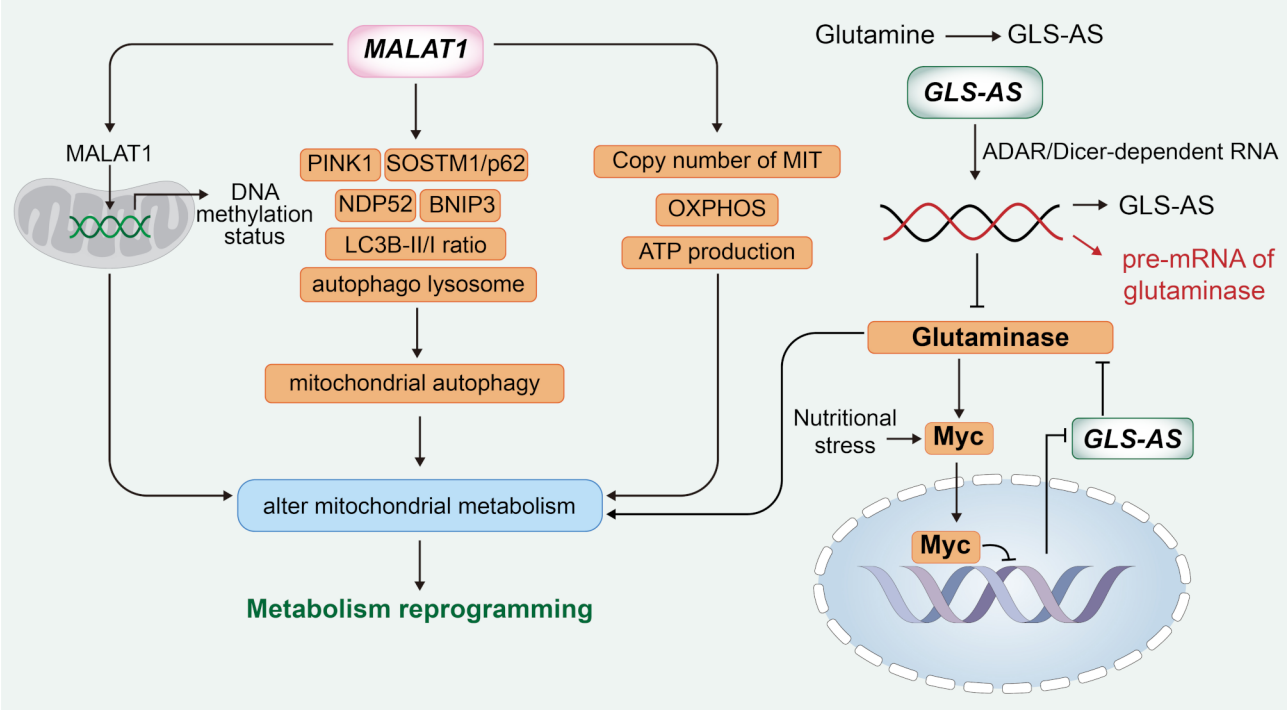

Fig. 3 LncRNAs modulate MR of solid tumor cells by affecting mitochondrial function. Mitochondria-associated lncRNAs potentially collaborate with transcription factors and epigenetic modulators to co-regulate the expression of mitochondria-related genes, influencing mitochondrial function, as a result, modulating MR. In this figure, we mainly summarize that lncRNA *MALAT1*, significantly alters the DNA methylation status of mitochondrial DNA, mitochondrial autophagy, mitochondrial copy number, OXPHOS, ATP production, and other important mitochondrial functions to alter mitochondrial metabolism of solid cancer cells. Meanwhile, the nuclear-enriched antisense lncRNA of glutaminase (*GLS-AS*), effectively regulate the glutaminase level in mitochondria by ADAR/Dicer-dependent RNA interference and MYC-GLS-AS reciprocal feedback. This process also alters mitochondrial metabolism, then affects MR of solid tumor cells

transformation of tumor cells and their interaction with the TME. Under stressful conditions, such as severe nutrient deprivation and hypoxia, notable MR changes occur in the tumor, immune, and stromal cells within the TME [95–97]. Tumor-associated macrophages (TAMs), which are also important components of the tumor microenvironment, are often regulated by MR. With immunometabolic interaction between HCC and TAMs, TAMs can deliver carcinogenic lncRNA related to macrophage polarization, named *lncMMPA*, via exosomes. In addition, *lncMMPA* can also increase the mRNA level of ALDH1A3 as microRNA sponge by interacting with miR-548, which further enhances glucose metabolism and AG, thus influences MR and promotes the proliferation of liver cancer cells [98]. The MR shifts in tumor cells fulfill their immediate survival demands and reciprocally influence the metabolic state of surrounding non-tumor cells through various mechanisms. Meanwhile, the MR alterations in the non-tumor cells bear significant implications for cancer initiation, proliferation, metastatic dissemination, and resistance to therapeutic interventions [99]. In this context, lncRNAs directly impact the functions of tumor and non-tumor cells within the TME and establish intercellular signaling pathways that modify it, regulating tumor cell MR and ultimately promoting the malignant progression of tumors [37, 100, 101].

Specifically, the dynamic processes of tumor infiltration, metastasis, and angiogenesis are strongly associated with alterations in the expression profiles of lncRNAs in the TME. In contrast, these expression changes in lncRNAs facilitate metabolic shifts in glucose, lipid, amino acid, and lactate pathways, which, in turn, modulate the phenotypic and functional attributes of immune cells within the TME. Such phenotypic and functional alterations in immune cells exert a reciprocal impact on the MR of tumor cells, thus establishing a feedback mechanism substantially contributing to the malignant advancement of solid tumors. Song et al.. uncovered that tumor-associated macrophages (TAMs) affect BC cells in the TME by secreting a unique lncRNA HIF-1α-stabilizing lncRNA (*HISLA*) through extracellular vesicles (EVs). HISLA stabilizes and upregulates HIF-1α, a critical transcription factor under hypoxic conditions within the TME. Enhanced HIF-1α expression mediates AG alterations to sustain the malignant growth of tumors by activating the transcription of glucose transporter 1 (*GLUT1*) and lactate dehydrogenase A (*LDHA*) mRNAs [102–104]. Multiple other lncRNAs, such as *LINK-A*, *CASC9*, *lincRNA-P21*, and *PCED1B-AS1*, have been identified to modulate HIF-1α expression through various epigenetic mechanisms, such as phosphorylation, ubiquitination, or direct mRNA interaction, thereby promoting AG in associated solid tumors [104–107]. A focused exploration into *HISLA* revealed its AG-promoting underlying mechanism in BC cells. Specifically, the transcript represses HIF-1α hydroxylation and subsequent degradation by obstructing the interaction between prolyl hydroxylase domain 2 (PHD2) and HIF-1α, thus facilitating AG in BC cells. Conversely, This process is further augmented by a reciprocal interaction where substantial lactate production by glycolytic BC cells induces *HISLA* expression in macrophages, thus activating TAMs and creating a forward feedback loop that reinforces tumorigenic activities. Furthermore, the inhibition of *HISLA* transmission via EVs has been shown to suppress AG and counteract chemotherapy resistance in BC cells in vivo [100]. This research underscores the pivotal role of lncRNAs as signaling molecules in the communicative exchange between immune and tumor cells, modulating MR through the interactions between these two cell types in the TME. Further affirmation of this vital function comes from investigations into cancer-associated fibroblasts (CAFs), essential constituents of the TME known for their role in nurturing tumor cells via paracrine signaling mechanisms, including the provision of nutrients and the secretion of chemokines [108–111]. Specifically, the chemokine CXCL14, produced by CAFs, has been identified to enhance the invasion and metastasis of ovarian cancer (OC) cells by upregulating lncRNA *LINC00092*. Mechanistically, *LINC00092* activates glycolysis in OC cells by binding the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 (PFKFB2) to facilitate OC cell metastasis [34]. These insights collectively highlight that lncRNAs facilitate the regulatory dynamics between tumor and non-tumor cells in the TME to affect tumor cell MR and finally contribute to the malignant progression. The main processes that lncRNAs orchestrate MR in solid tumor cells by influencing interactions between tumor and non-tumor cells in TME are also shown in Fig. 4.

Summary and future research directions

MR is one of the ten hallmarks of cancer, and its aberrant activation is a crucial driver of malignant progression in solid tumors. LncRNAs are critical regulators of the aberrant MR activation in solid tumors, and their contribution to the aberrant activation of MR in solid tumors has garnered increasing empirical support. As discussed in this review, lncRNAs orchestrate MR of solid tumor cells by modulating diverse biological processes, such as glucose and lipid metabolism, mitochondrial function, and the crosstalk between tumor and non-tumor cells within the TME, thereby facilitating the malignant progression of solid tumors. The clinical significance of lncRNAs in various tumors and its important role in tumor MR make lncRNAs have multiple potentials in tumor diagnosis and treatment, including as biomarkers for early diagnosis and prognosis assessment of tumor, targeting lncRNAs

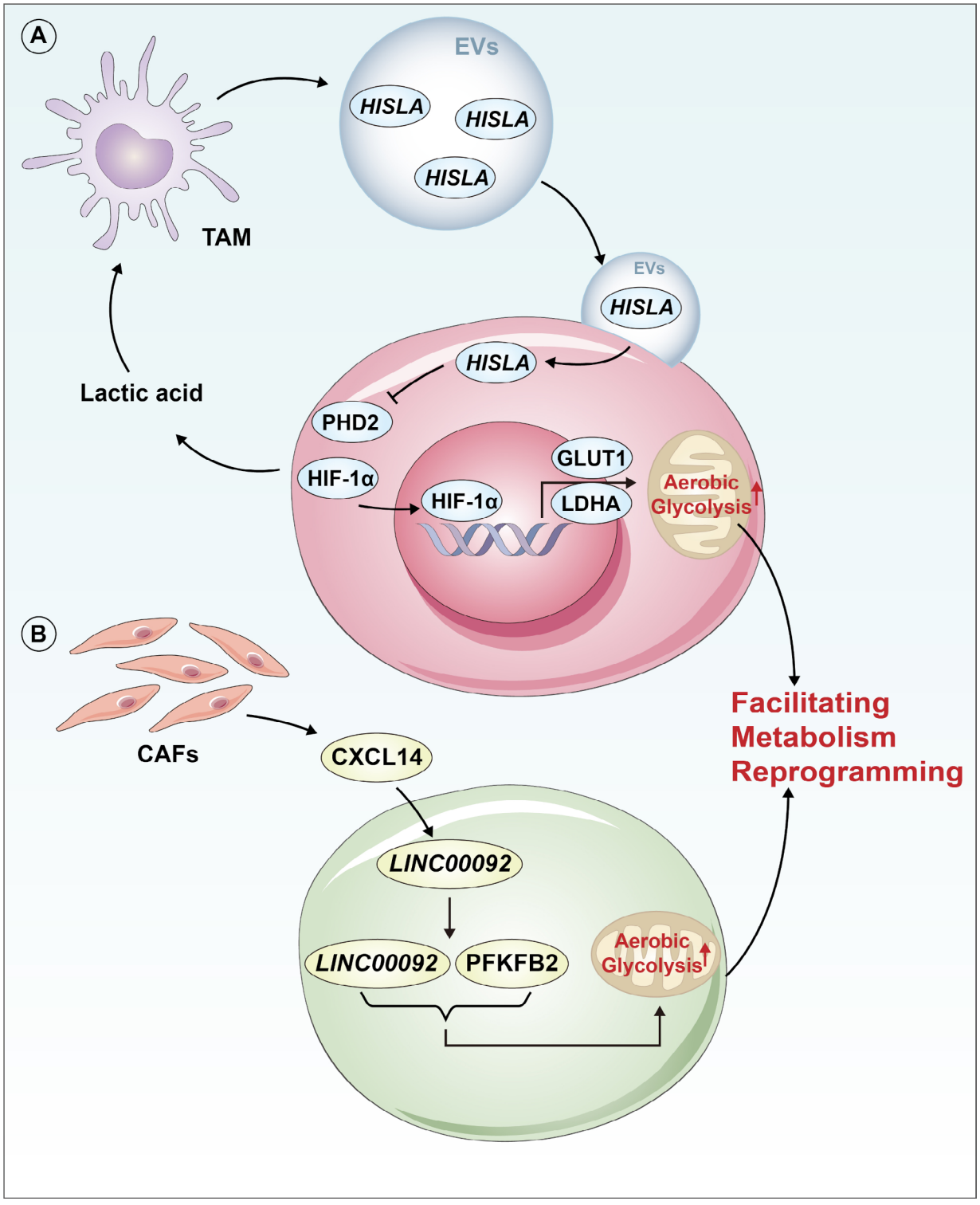

Fig. 4 LncRNAs orchestrate MR in solid tumor cells by influencing interactions between tumor and non-tumor cells in TME. LncRNAs directly impact the functions of tumor and non-tumor cells within the TME and establish intercellular signaling pathways that modify it, regulating tumor cell MR and ultimately promoting the malignant progression of tumors. In this figure, we mainly summarize that: (**A**) TAMs secret EVs which containing lncRNA *HISLA* to stabilize and upregulate HIF-1α in tumor cells. Enhanced HIF-1α expression mediates AG alterations to sustain the malignant growth of tumors by activating the transcription of *GLUT1* and *LDHA* mRNAs. This process is further augmented by a reciprocal interaction where substantial lactate production by glycolytic tumor cells induces *HISLA* expression in macrophages, thus activating TAMs and creating a forward feedback loop that reinforces tumorigenic activities. (**B**) The chemokine CXCL14, produced by CAFs, has been identified to upregulate the expression of lncRNA *LINC00092*. Further, *LINC00092* activates glycolysis in tumor cells by binding the PFKFB2 to facilitate MR of tumor cells

for tumor therapy, etc. However, the research in this field is still in the exploratory stage and the application of lncRNAs in clinical treatment still faces many challenges.

Firstly, lncRNAs can participate in the regulation of tumor process through various mechanisms, including enhancing or inhibiting gene expression, regulating chromatin modification and histone modification. Due to the complex mechanism of lncRNAs, it may be very difficult to carry out precise targeted therapy for tumor according to specific mechanisms. Secondly, there is no doubt that lncRNAs mediated gene regulation has added new dimensions to the central rule in many aspects. However, the expression and activity of lncRNAs can not be specifically regulated because of their natural flexibility and structural heterogeneity. In addition, the existing evidence shows that the function mediated by lncRNAs and the effect as a clinical therapeutic target are convincing. Still, the cross species conservation of lncRNAs is weak. The phenotype of targeting lncRNAs may depend on different tissue environments, therefore, the application of lncRNAs in vivo remains extremely challenging.

In view of the above bottlenecks, on the one hand, it is necessary to further reveal the biological functions and mechanisms of lncRNAs. For example, based on existing studies, the characteristics of lncRNA and its subcomponents were analyzed in a spatio-temporal manner in normal, developmental and tumor environments. The temporal and spatial patterns of different lncRNAs subtypes were distinguished by dynamic analysis of transcriptomics and long reading sequencing combined with new tools [112–114]. The in-depth elucidation of the space-time specific molecular mechanism of lncRNAs will further deepen researchers' systematic understanding of the cellular process of tumor MR. On the other hand, it is necessary to take corresponding strategies to reduce the drug toxicity in vivo when targeting lncRNAs and avoid the potential off-target effects. Considering the construction of a safe and efficient carrier, lncRNAs can be packaged in the drug delivery system to directly target tumor cells, which can reduce toxic side effects in vivo and drug loss in blood circulation [115–117]. In order to effectively deal with the off-target effects of lncRNAs in tumor targeted therapy, targeted molecules with higher specificity can be designed, such as small interfering RNAs (siRNAs) or antisense oligonucleotide (ASO) with higher specificity and binding affinity. Furthermore, the gRNA optimization design of CRISPR/cas9 system was used to simultaneously target multiple lncRNAs with similar functions [118–120].

In conclusion, despite the abundant evidence elucidating the mechanistic underpinnings of lncRNAs in modulating MR during solid tumor progression, translating most research findings into clinical practice remains a significant bottleneck for lncRNA research in the context of cancer metabolism. The understanding of the life cycle and mechanisms of lncRNAs is still in its infancy. This entails grasping "when" specific lncRNAs are transcribed, "who" they are, "where" they are localized, "how" they exert their effects, and ultimately "what" their functions are [121]. Investigating the role of lncRNAs in functional plasticity, the deregulation of lncRNA-mediated pathways in cancer and other diseases and how they operate in dynamic assemblies with other macromolecules will be the focus of future research. The application of sequencing and imaging technologies, the use of live animal and organoid models, the advancements in mass spectrometry, and computational structural biology modeling are poised to accelerate the comprehension of unique pathways, molecular mechanisms, and phenotypes of specific lncRNAs in gene regulation, which will avoid the effects of conditions and tissue specificity or cell type specificity. These technologies open up new avenues for lncRNAs research. Therefore, future research should focus on constructing tumor metabolic regulatory networks centered on lncRNAs, exploring mechanisms of solid tumor MR targeting lncRNAs, and developing new clinical therapeutic approaches targeting lncRNA-mediated MR. It is hoped that these efforts will provide new targets and open new avenues for the clinical treatment of solid tumors in the future.

Abbreviations

MR	Metabolic reprogramming
lncRNAs	Long non-coding RNAs
mRNAs	Messenger RNAs
TME	Tumor microenvironment
AG	Aerobic glycolysis
CRC	Colorectal cancer
HSP90	Heat shock 90 kDa protein 1
LDHA	Lactate dehydrogenase
IGF2BP2	Insulin-like growth factor 2 mRNA binding protein 2
NEAT1	Nuclear enriched abundant transcript 1
PGK1	Phosphoglycerate kinase 1
NSCLC	Non-small cell lung cancer
GC	Gallbladder cancer
GBCDRlnc1	Gallbladder cancer drug resistance-associated lncRNA 1
PKM2	Pyruvate kinase M2
HCC	Hepatocellular carcinoma
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
AGPG	Actin gamma 1 pseudogene
CDK6	Cyclin dependent kinase 6
PHD3	Prolyl hydroxylase domain 3
PSMA1	Proteasome 20 S subunit alpha 1
PGK1	Phosphoglycerate kinase 1
FAO	Fatty acid oxidation
CPT1A	Carnitine palmitoyltransferase 1 A
FABP4	Fatty acid binding protein 4
MNK2	MAPK interacting serine/threonine kinase 2
HNRNPC	Heterogeneous nuclear ribonucleoprotein C
ATGL	Adipose triglyceride lipase
FFAs	Free fatty acids
PPARα	Peroxisome proliferator-activated receptor alpha
ACSL1	Acyl-CoA synthetase family member 1
NPM1	Nucleophosmin 1
FABP5	Fatty acid binding protein 5
PLA2G16	Phospholipid metabolism-related phospholipase A2, group XVI

MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
OXPHOS	Oxidative phosphorylation
PINK1	PTEN induced kinase 1
SQSTM1/p62	Sequestosome 1
NDP52	Nuclear domain 10 protein 52
BNIP3	BCL2 interacting protein 3
LC3B	Light chain 3 beta
GLS-AS	Antisense lncRNA of glutaminase
PCa	Pancreatic cancer
TAMs	Tumor-associated macrophages
HISLA	HIF-1α-stabilizing lncRNA
EVs	Extracellular vesicles
GLUT1	Glucose transporter 1
PHD2	Prolyl hydroxylase domain 2
CAFs	Cancer-associated fibroblasts
OC	Ovarian cancer
PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2
siRNAs	Small interfering RNAs
ASO	Antisense oligonucleotide

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Declarations

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