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REVIEW

Regulation of Tumor Metabolome by Long Non-Coding RNAs

Revathy Nadhan* and Danny N. Dhanasekaran*,†

Tumorigenesis necessitates enhanced ability for macromolecular biosynthesis, higher energy/ATP levels and co-ordinated redox balance systems within the cancer cells as well as the cellular components of the tumor microenvironment. Cancer cells have adapted several mechanisms to accommodate their growing need for energy and macromolecular building blocks. A critical mechanism that sustains cancer growth and progression is metabolic reprogramming. Metabolic reprogramming refers to the process that changes the pattern of metabolism in these cells that regulates cancer energetics and metabolic biosynthesis. Recent studies have shown a role for long non-coding RNAs (lncRNAs) in the metabolic reprogramming of multiple cell types in cancer tissue. LncRNAs play a decisive role in the reprogramming of glucose, lipid, amino acid, and nucleotide metabolisms to promote tumor growth. Emerging tumorigenic role of lncRNAs and the diverse mechanisms through which they reprogram tumor metabolome is comprehensively discussed here.

Keywords: Cancer; lncRNA; tumor metabolome; metabolomics; targeted therapy

Introduction

Tumorigenesis requires metabolic reprogramming of the cells for meeting their higher energy demands as well as for the production of anabolic intermediates, together which signifies metabolic reprogramming as one of the major cancer hallmarks. The augmented catabolism of glucose, lipids and amino acids facilitate the higher proliferative rates of cancer cells by enhancing the energy supply as well as overpowering the apoptotic signals [1]. Under conditions of nutritional stress or hypoxic conditions, the cells of the tumor microenvironment (TME) also undergo metabolic reprogramming, so as to enable their own survival as well as inducing metabolic changes within other cells favouring tumorigenesis [2]. Recent researches have shown that metabolic reprogramming of the cancer cells and the cells in the tumor stroma remodel the TME into an acidic immunosuppressive environment as well [3]. Metabolomics, which sheds light to metabolic reprogramming, have evolved as a promising arm to decipher novel biomarkers and therapeutic targets empowering the concept of precision medicine for cancers.

Similar to the diverse components such as proteins and mRNAs involved in regulating the cancer cell metabolism, long non-coding RNAs (lncRNAs) are emerging as a major regulator of cancer metabolome [4]. LncRNAs are non-coding RNAs that are greater than 200 nucleotides in length, but cannot be translated into proteins [4]. For a longer time period in the scientific research, lncRNAs were considered to be dark matters of the genome, since it composed larger fractions of the genome than the coding ones and was thought to be not involved in any cellular processes [4]. However, recent studies have unravelled their tremendous potential as a regulatory node which actively takes part in physiological and pathological signaling in the humans [5]. LncRNAs carry out indispensable role in regulating almost all the cancer hallmarks, including metabolic reprogramming [6]. They can act as miRNA sponges, guides, scaffolds and even mediate interactions with several other nucleic acids or proteins to bring about their functions. In this review, we try to portray the major lncRNAs involved in reprogramming of glucose, lipid, amino acid as well as nucleotide metabolisms in numerous cancers, which would strengthen the notions on considering lncRNAs as precise therapeutic targets favouring advancements in cancer therapy.

LncRNAs and Reprogramming of Glucose Metabolism in Cancers

LncRNAs are involved in the regulation of multiple pathways involved in the reprogramming of glucose metabolism in tumor cells (**Figure 1**). The primary energy source for highly proliferating cancer cells is glucose. Under normal physiological conditions, cells utilize glucose through glycolysis and then proceed to the mitochondrial oxidative phosphorylation for production of ATP, in the presence of oxygen. In the absence of oxygen, cells mostly rely on glycolysis for energy production [7]. However, even in

* Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

† Department of Cell Biology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, US

Corresponding author: Danny N. Dhanasekaran (danny-dhanasekaran@ouhsc.edu)

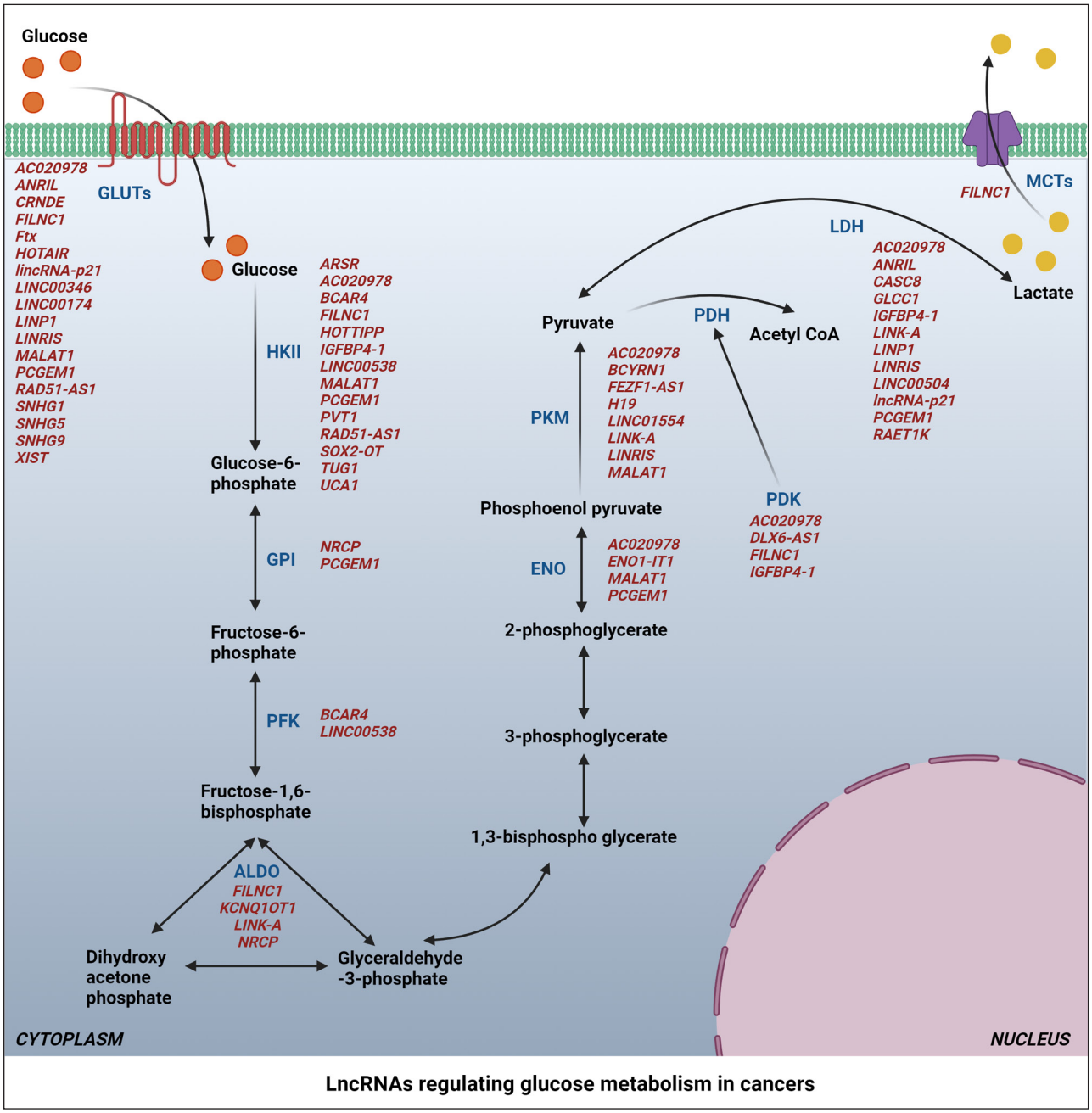

Figure 1: LncRNAs regulating glucose metabolism in cancers. The figure illustrates the representative lncRNAs that regulate various enzymes at different stages of glucose metabolism in cancers. (ALDO-aldolase; ENO-enolase; GLUTs-glucose transporters; GPI-phosphoglucoisomerase; HKII-hexokinase II; LDH-lactate dehydrogenase; MCTs-monocarboxylate transporters; PDK-pyruvate dehydrogenase kinase; PDH-pyruvate dehydrogenase; PFK-phosphofructokinase; PKM-pyruvate kinase).

the presence of oxygen, cancer cells rely on rapid glycolysis for ATP synthesis that fuels the uncontrolled proliferation of the cancer cells. This phenomena is termed as Warburg effect or aerobic glycolysis [8]. Cancer cells employ this mechanism by enhancing their glucose uptake and lactate release. The acidic TME facilitates the cancer progression, as well. Glycolytic intermediates are utilized as substrates for various cellular anabolic processes [9]. Furthermore, utilization of aerobic glycolysis provides additional survival advantage to the cancer cells for the fact that they produce lesser amounts of reactive oxygen species (ROS) that can induce apoptotic signal in cancer cells [10]. LncRNAs regulate glucose metabolism in cancer cells as well as the TME by regulating the pathways at different stages such as enhancing glucose transporters as well as modulating the enzymes involved in diverse glucose metabolic pathways.

The initial step involved in regulation of glucose metabolism in cancer cells is through the expression of glucose transporters, GLUTs, which are transmembrane glycoproteins that promotes the glucose entry into the cancer cells. LINC00346 sequesters miR-148a/b to upregulate GLUT1 expression to enhance glucose uptake for aerobic glycolysis in breast cancers [11]. The elevated levels of lncRNA CRNDE has been reported to upregulate the GLUT4 levels that enhances the glucose import into the

cancer cells favouring aerobic glycolysis. In addition, it also enhances the levels of transcription factor MLXIPL (MLX interacting protein like) that subsequently elevates the transcription of several downstream genes involved in glucose metabolism [12]. LncRNA Ftx transcriptionally and post-transcriptionally promotes PPARγ (peroxisome proliferator-activated receptor gamma) expression, which further enhances transcription of GLUT1 and GLUT4 facilitating enhanced glucose import into cancer cells for aerobic glycolysis [13]. In cancer cells, hypoxia induces HIF-1α (hypoxia inducible factor 1 alpha) mediated upregulation of lincRNA-p21, which further interacts with HIF-1α to upregulate transcription of GLUT1 and LDHA (lactate dehydrogenase A) to promote glycolysis [14]. In prostate cancers, lncRNA PCGEM1 activates c-Myc mediated upregulation of GLUT1 to enhance the glucose uptake, along with augmenting the expression of glycolytic genes such as HKII (hexokinase II), GPI (glucose-6-phosphate isomerase), ENO1 (enolase1), and LDHA to favour aerobic glycolysis for tumor progression [15]. Furthermore, lncRNA HOTAIR upregulates GLUT1 expression through activation of mTOR pathway in hepatocellular carcinoma and promotes glucose uptake and glycolysis [16]. LncRNA lncp23154 inhibits miR-378a-3p expression to upregulate GLUT1 levels in oral squamous cell carcinoma [17]. In glioblastoma, lncRNA XIST sequesters miR-126 to upregulate IRS1 (insulin receptor substrate 1) and activate PI3K/AKT signaling, which favours GLUT1 and GLUT3 expression [18]. Similarly, LINC00174, SNHG9, SNHG5 and SNHG1 also facilitates enhanced aerobic glycolysis in glioma through enhancing expression of several glycolytic genes by sequestration of their miRNA targets [19–22].

After the entry of glucose into the cancer cells, the next step is the glycolysis. Hexokinase II (HKII) is the first major enzyme in the glycolytic pathway that catalyzes the conversion of glucose to glucose-6-phosphate. In hepatocellular carcinoma, lncRNA TUG1 enhances miR-455-3p expression by downregulating p21 levels, which acts as transcriptional repressor of miR-455-3p. The elevated levels of miR-455-3p inhibits its target AMPKβ2 (5' AMP activated protein kinase beta 2) mRNA that activates p-mTOR (mammalian target of rapamycin) and subsequent downstream target HKII. This promotes aerobic glycolysis in hepatocellular carcinoma [23]. Furthermore, in gall bladder cancer, lncRNA PVT1 sequesters miR-143 to augment the expression of the miR target HKII, facilitating enhanced glycolysis and tumorigenesis [24]. Hypoxia induced lncRNA HOTTIPP expression in non-small cell lung cancers sequesters miR-615-3p to upregulate HMGB3 (high mobility group box 3) expression that regulates HKII expression as well as glucose uptake, lactate secretion and aerobic glycolysis in these cancer cells [25]. LncRNA TUG1 promotes HKII expression and aerobic glycolysis in osteosarcoma [26]. In bladder cancer cells, lncRNA UCA1 regulates the expression of HKII to facilitate aerobic glycolysis through two independent mechanisms. One is through promotion of HKII transcription via mTOR-STAT3 (signal transducer and activator of transcription 3) signaling and the other is via sequestration of miR-143 and resultant upregulation of miR target HKII [27]. UCA1 has been reported to upregulate HKII expression by sequestering miR-203 in oesophageal cancers, as well [28]. Furthermore, UCA1 enhances radioresistance in cervical cancer cells through promotion of HKII/glycolysis signaling pathways [29]. In colorectal adenocarcinoma, lncRNA RAD51-AS1 is downregulated, which otherwise sequesters miR-29b-3p and miR-29c-3p and upregulates NDRG2 (N-Myc downstream regulated gene 2) expression. During cancerous conditions NDRG2 is downregulated and it enhances expression of GLUT1 and HKII favouring aerobic glycolysis [30]. Furthermore, lncARSR sequesters miR-34a-5p to upregulate HKII expression and subsequent aerobic glycolysis to facilitate tumor progression in colorectal cancers, both *in vitro* and *in vivo* [31]. In hepatocellular carcinoma, lncRNA HOTAIR sequesters miR-130a-3p to upregulate HIF-1α expression, which subsequently promotes transcription of HKII to favour aerobic glycolysis [32].

The next steps in glycolysis involves isomerization of glucose-6-phosphate to fructose-6-phosphate by GPI (glucose-6-phosphate isomerase). Fructose-6-phosphate is phosphorylated to fructose-1,6-bisphosphate by the enzyme phosphofructokinase (PFK). Aldolases splits fructose-1,6-bisphosphate to glyceraldehyde-3-phosphate and dihydroxyacetone phosphate in glycolysis. In ovarian cancers, lncRNA NRCP is overexpressed that binds to STAT1 and RNA Pol II to enhance the expression of glycolysis genes such as GPI as well as aldolases, ALDOA and ALDOC [33]. LncRNA KCNQ1OT1 sequesters miR-34c-5p to promote ALDOA expression and aerobic glycolysis in osteosarcoma [34]. LncRNA LINC00538/YIYA interacts with CDK6 and phosphorylates PFKFB3; active PFKFB3 and HKII promotes aerobic glycolytic pathway in breast cancers [35]. Another lncRNA, BCAR4, transcriptionally induced by yes-associated protein (YAP), also upregulates expression of HKII and PFKFB3 through interaction with GLI2 mediating their transcription to promote glucose uptake and lactate production in triple negative breast cancers (TNBCs) [36].

Enolase (ENO) catalyzes the conversion of 2-phsophoglycerate to phosphoenolpyruvate. In colorectal cancers, the microbiota containing *Fusobacterium nucleatum* activates transcription of lncRNA ENO1-IT1 by enhancing the binding of SP1 transcription factor to its promoter. ENO1-IT1 mediates KAT7, histone acetyltransferase, mediated histone modification to promote the expression of ENO1 that augments the aerobic glycolysis in these cancers [37].

Pyruvate kinase is the rate limiting as well as the final step of glycolysis catalysing the conversion of phosphoenolpyruvate to pyruvate. It is coded by PKM gene which has two isoforms, namely PKM1 and PKM2. PKM2 favours aerobic glycolysis while PKM1 upregulation favours oxidative phosphorylation. In colorectal cancers, lncRNA FEZF1-AS1 binds to and stabilizes the PKM2 expression thereby promoting aerobic glycolysis [38]. In ovarian cancers, lncRNA H19 sequesters miR-324-5p to upregulate PKM2 expression favouring aerobic glycolysis [39]. In non-small cell lung cancers, hypoxic conditions induces lncRNA AC020978 expression that enhances PKM2 expression and activity. Furthermore, PKM2 mediated

HIF-1α transcriptional activity promotes the expression of HIF-1α target genes such as GLUT1, pyruvate dehydrogenase kinase 1 (PDK1), HKII, ENO1 and LDHA that promotes glucose uptake and aerobic glycolysis [40]. In hepatocellular carcinoma, lncRNA LINC01554 is downregulated owing to miR-365a-3p mediated inhibition, which otherwise enhances the proteasomal degradation of PKM2 and lowering its expression to reduce the glycolysis [41]. LncRNA BCYRN1 sequesters miR-149 to upregulate PKM2 expression that favours aerobic glycolysis in non-small cell lung cancers [42]. MALAT1 is overexpressed in hepatocellular carcinoma. MALAT1 activates mTORC1 signaling to activate TCF7L2 (transcription factor 7 like 2) transcription factor that upregulates the transcription of genes involved in aerobic glycolysis such as GLUT1, HKII, ENO1 and PKM2, while reducing the expression of genes coding for gluconeogenesis enzymes such as G6PC (glucose-6-phosphatase) and PCK1 (phosphoenolpyruvate carboxykinase 1) [43]. LncRNA SOX2-OT sequesters miR-195-5p to enhance the expression of HKII, thereby promoting aerobic glycolysis in hepatocellular carcinoma [44].

Pyruvate dehydrogenase kinases (PDK) phosphorylates pyruvate dehydrogenase (PDH) and inhibits its activity, thereby preventing entry of pyruvate to TCA cycle and favouring aerobic glycolysis mediated lactate production for ATP synthesis. In gastric cancers, lncRNA DLX6-AS1 sequesters miR-4290 that targets PDK1. Subsequently, PDK1 expression is upregulated and contributes to enhanced glucose uptake and lactate production [45]. Pyruvate is converted to lactate favouring energy production for rapidly proliferating cells and is catalysed by lactate dehydrogenase (LDH), encoded by LDHA and LDHB genes. LncRNA GLCC1 is upregulated in colorectal cancers. It acts as scaffold for the interaction of HSP90 to c-Myc proteins to stabilize the latter and facilitating c-Myc mediated transcription of LDHA favouring higher glycolysis for meeting energy needs [46]. Similar mechanism have been reported for LINC00504 in promoting glycolysis in colon cancer through c-Myc stabilization [47]. In bladder cancer, lncRNA CASC8 is downregulated, which otherwise binds to FGFR1 and prevents the FGFR1 mediated LDHA phosphorylation that activates LDHA activity [48]. While lncRNA ANRIL enhances GLUT1 and LDHA expression via activation of AdipoR1 pathway in acute myeloid leukemia, it activates the same in nasopharyngeal carcinoma via activation of mTOR signaling pathway [49, 50]. However, lncRNA LINP1 enhances GLUT1 and LDHA expression in acute myeloid leukemia through upregulation of HNF4α (hepatocyte nuclear factor 4 alpha) and AMPK (AMP activated protein kinase)/WNT5A signaling cascades [51]. In hepatocellular carcinoma, under hypoxic conditions, HIF-1α promotes lncRNA RAET1K expression which sequesters miR100-5p to upregulate LDHA expression [52]. In TNBCs lncRNA LINK-A interacts with BRK and LRRK2 kinases to phosphorylate and stabilize HIF-1α that further activates the transcription of glycolytic genes such as ALDOA, PKM2 and LDHA to promote aerobic glycolysis [53]. In lung cancer cells, lnc-IGFBP4-1 enhances the expression of glycolytic enzymes HKII, PDK1 and LDHA to promote aerobic glycolysis for tumor progression [54]. In colorectal cancer lncRNA LINRIS interacts with IGF2BP2 (insulin growth factor 2 binding protein 2) and prevents its ubiquitin mediated degradation. IGF2BP2 then binds to c-Myc and stabilizes it further to enhance the transcription of c-Myc regulated glycolytic genes such as GLUT1, PKM2 and LDHA, thereby promoting aerobic glycolysis for tumorigenesis [55].

Cancer cells maintains optimum lactate fluxes mainly through the monocarboxylate transporters (MCTs). In renal cell carcinoma, lncRNA FILNC1 is downregulated, which otherwise binds to AUF1 transcription factor and downregulate c-Myc expression. Lower FILNC1 levels is correlated with higher c-Myc and upregulation of c-Myc regulated glycolysis target gene expressions such as GLUT1, GLUT3, HKII, ALDOC, MCT4 lactate transporter, PDK1, PDK4. Thus, FILNC1 deficiency promotes glucose uptake and lactate production for energy needs in renal cell carcinoma [56].

The circNRIP1, a circular lncRNA, sequesters miR-149-5p to activate AKT1/mTOR signaling, which enhances glucose uptake, lactate and ATP production, indicative of enhanced glycolysis in gastric cancers [57]. In ovarian cancers, the elevated levels of lncRNA GHET1 induces vHL mediated HIF-1α expression under hypoxic conditions that enhances the glucose uptake and lactate production in these cancer cells [58]. In cetuximab resistant colorectal cancer cells, it has been reported that LINC00973 enhanced the aerobic glycolysis and thereby contributing to chemoresistance in these cells as evidenced by augmented glucose uptake and lactate production [59]. In hepatocellular carcinoma DDX11-AS1-miR-195-5p-MACC1 axis promotes glucose uptake and lactate production [60]. In oesophageal cancers, LINC00184 recruits DNMT (DNA methyl transferase) to PTEN promoter and inhibits PTEN expression. This promotes AKT activity which enhances glucose uptake, lactate production and ATP synthesis [61]. LncRNA PDIA3P interacts with c-Myc and promotes transcription of G6PD (glucose-6-phosphate dehydrogenase), thereby promoting pentose phosphate pathway in multiple myeloma [62].

LncRNAs and Reprogramming of Lipid Metabolism in Cancers

Lipids are one of the major cellular macromolecules as it forms the structural part of plasma membrane, plays role in energy production, affects membrane fluidity, mediates post-translational modifications, acts as signaling mediators and even play cardinal role in pathogenesis of cancers. Though there are diverse classes of lipids, studies on lncRNAs associated with fatty acids, triglycerides, cholesterol and sphingolipids are the major ones linking lncRNAs to reprogrammed lipid metabolism in cancers (**Figure 2**).

Though normal cells prefer exogenous fatty acids, cancer cells prefer *de novo* synthesis of fatty acids as it would act as an energy source for proliferating cancer cells. In addition, they could serve as major source for NADPH in volved in the anti-oxidant response that favor tumorigenesis. Major enzymes involved in fatty acid biosynthesis, utilizing citrate from TCA (tricarboxylic acid) cycle, that are

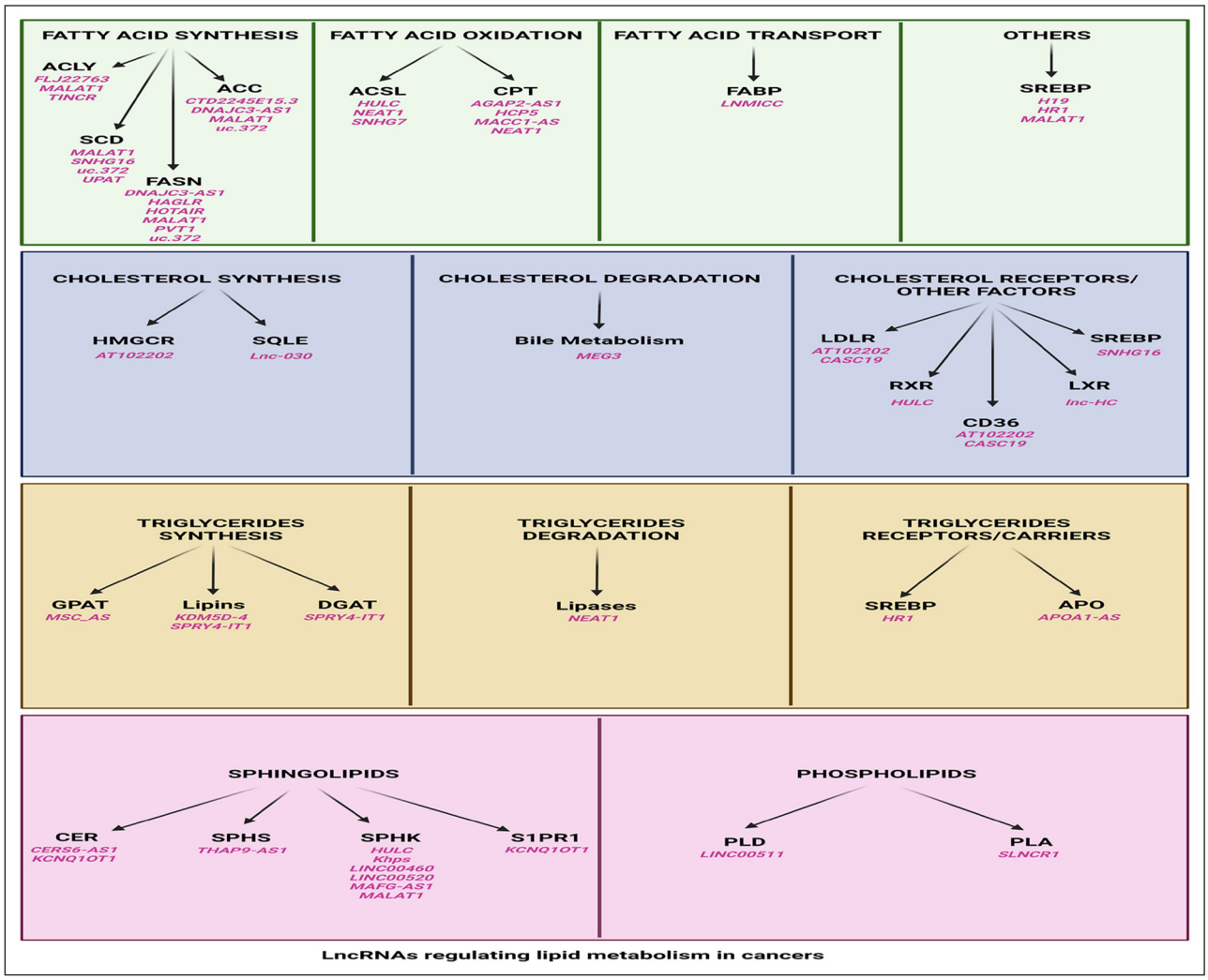

Figure 2: LncRNAs regulating lipid metabolism in cancers. The figure depicts various lncRNAs affecting lipid metabolism in numerous cancers. Lipids undergoing metabolic reprogramming are grouped into four classes namely the fatty acids, the cholesterol, the triglycerides as well as the sphingolipids and the phospholipids. LncRNAs regulate each of these lipid classes in their synthesis, degradation as well as transport and other regulatory stages. (ACLY-ATP citrate lyase; ACC-acetyl CoA carboxylase; FASN-fatty acid synthase; ACSL-acyl CoA synthetase long chain; SCD-stearoyl CoA desaturase; CPT1-carnitine palmitoyltransferase 1; SREBPs-sterol regulatory element binding proteins; HMGCR-3-hydroxy-3-methyl-glutaryl-CoA reductase; FABP-fatty acid binding proteins; SQLE-squalene epoxidase; LDLR-low density lipoprotein receptor; LXR-liver X receptor; RXR-retinoid X receptor; APO-apolipoproteins; GPAT- glycerol-3-phosphate acyltransferase; DGAT-diacylglycerol acyl transferase; CER-ceramidases; SPHK-sphingosine synthase; SIPR1-sphingosine-1-phosphate receptor 1; SPHS-sphingosine synthase; PLD-phospholipase D; PLA-phospholipase A).

upregulated in cancers includes ATP citrate lyase (ACLY), acetyl coA carboxylase (ACC), fatty acid synthase (FASN) and acyl CoA synthetase-long chain (ACSL). Initial step of fatty acid biosynthesis is the conversion to citrate to acetyl CoA in the mitochondria by ACLY enzyme. LncRNA TINCR is upregulated in nasopharyngeal carcinoma, which binds to ACLY to prevent its ubiquitin mediated proteasomal degradation, thereby enhancing fatty acid synthesis and proliferation, chemoresistance and metastasis in these cancers [63]. In human gastric cancer cell lines, it has been reported that lncRNA FLJ22763 is downregulated, which otherwise reduces the ACLY expression and thereby fatty acid biosynthesis. However the exact mechanism is yet to be elucidated [64]. Acetyl CoA is carboxylated to malonyl-CoA in the next step for fatty acid biosynthesis that is catalysed by ACC, which has two isoforms namely ACC1 and ACC2. While ACC1 promotes fatty acid synthesis, ACC2 inhibits fatty acid oxidation. While lncRNA DNAJC3-AS1 activates PI3K/AKT pathway to enhance expression of ACC and FASN in colorectal cancers, lncRNA CTD2245E15.3 activates ACC1 activity by preventing inhibitory phosphorylation at Ser-117 site of ACC1 in non-small cell lung cancers to promote lipogenesis [65, 66]. FASN is the major enzyme involved in synthesis of palmitate in a NADPH dependent mechanism. FASN catalyzes the conversion of acetyl CoA and malonyl coA to palmitate. In human osteosarcoma U2OS cells, the upregulated PVT1 levels sequester miR-195 to enhance FASN expression and favour de novo fatty acid biosynthesis enabling cancer cell proliferation, attenuation of apoptosis

and tumor progression [67]. Over-expression of lncRNAs HAGLR and HOTAIR in non-small cell lung cancers and nasopharyngeal carcinoma respectively has been reported to upregulate FASN expression and fatty acid biosynthesis, which was correlated with higher free fatty acid levels in these cancers promoting tumor progression through an unknown mechanism [68, 69]. Yet another enzyme involved in synthesis of monounsaturated fatty acids is SCD (stearoyl-CoA desaturase) that has two isoforms, namely SCD1 and SCD5. It has been reported that lncRNA SNHG16 promotes c-Myc mediated SCD expression by acting as a competing endogenous RNA to sequester miRNA that targets SCD by forming complex with Ago-HuR proteins in colorectal cancers [70]. In hepatocellular carcinoma, overexpression of lncRNA uc.372 prevents maturation of miR-195 and miR-4668 by binding to their pri-miRNAs. This further relieves the inhibition of these miRNAs on their targets leading to upregulated target expressions such as ACC and FASN for miR-195 and SCD1 and CD36 for miR-4668 contributing to fatty acid synthesis and tumorigenesis [71]. In colon cancers, the lncRNA UPAT is upregulated which binds to UHRF1 (ubiquitin like with PHD and ring finger domains 1) and prevents the ubiquitin mediated proteasomal degradation to enhance UHRF1 stability. SCD1 is a downstream target of PAT and UHRF1, the regulation of which is yet to be elucidated [72]. Fatty acid transporters such as FABPs (fatty acid binding proteins) are also deregulated by lncRNAs to promote fatty acid metabolism in cancers. The lncRNA LNMICC, which is upregulated in cervical cancers, recruits NPM1 (nucleophosmin 1) transcription factor to FABP5 promoter to enhance its expression. Higher levels of FABP5 have shown to promote epithelial to mesenchymal transition (EMT) and metastasis in these cancers through reprogramming of fatty acid metabolism [73]. Not just the fatty acid biosynthesis, lncRNAs also regulate fatty acid oxidation. Fatty acid oxidation produces acetyl CoA, which in turn, produces NADPH through TCA cycle and coupled oxidative phosphorylation. NADPH acts as antioxidant as well as source of energy for the cancer cells. For these, fatty acids are initially converted to fatty acyl CoA by ACSL isoforms that facilitate their entry into mitochondria for oxidation. The upregulated HULC levels in hepatocellular carcinoma induces methylation on the promoters of miR-9, thereby attenuating its expression. Subsequently miR-9 target PPAR-α (peroxisome proliferator-activated receptor alpha) is upregulated, which acts as a transcription factor to enhance the expression of ACSL1 that favours conversion of fatty acids to fatty acyl CoA and fatty acid oxidation that promotes cancer progression [74]. In thyroid cancers, lncRNA SNHG7 is upregulated, which sequesters miR-449a and enhances the expression of miR target ACSL1, thereby promoting fatty acid oxidation in thyroid cancer cells [75]. In docetaxel resistant prostate cancer cells, NEAT1 levels are upregulated. NEAT1 sponges miR-34a-5p and miR-204-5p, which otherwise targets ACSL4 expression. Upregulated NEAT1 and ACSL4 levels contribute to proliferation, migration and docetaxel resistance in these cancers through promoting fatty acid oxidation [76]. CPT1 (carnitine palmitoyltransferase 1) is another major enzyme that regulates fatty acid oxidation and subsequent ATP-NADPH generation process. The mesenchymal stem cell induced lncRNAs HCP5 and MACC1-AS functions through miRNA sequestration to upregulate CPT1 expression in gastric cancer cells. HCP5 sequesters miR-3619-5p and upregulates its target, the transcription factor, PGC-1α (PPARγ coactivator 1 alpha), which further enhances CPT1 expression by activating PGC-1α-CEBPB (CCAAT enhancer binding protein beta) complex at the CPT1 promoter [77]. However, it has also been reported that mesenchymal stem cell secreted TGF-β1 (transforming growth factor-β1) acts through TGF-β receptor and SMAD2/3 pathway to upregulate the lncRNA MACC1-AS that sequesters miR-145-5p to upregulate the expression of miR target, CPT1 [78]. In both these events, CPT1 upregulation, enhances fatty acid oxidation and contributes to stemness as well as chemoresistance in gastric cancers. Furthermore the mesenchymal stem cells induce lncRNA AGAP2-AS1 in breast cancers which enhances CPT1 expression in two ways. One is by stabilizing the CPT1 mRNA through AGAP2-AS1-HuR complex, while the other is by sequestering miR-15a-5p to upregulate CPT1 expression, thereby promoting stemness and trastuzumab resistance in breast cancers [79]. Furthermore, in breast cancer cells, lncRNA NEAT1 sequesters miR-107 to upregulate CPT1 expression to promote fatty acid oxidation and synthesize ATP for energy needs favouring growth and metastasis in breast cancer cells [80]. LncRNAs also effect the expressions of fatty acid synthesis regulatory molecules such as SREBPs (sterol regulatory element binding proteins). SREBP-1a and -1c enhances fatty acid biosynthesis. LncRNAs H19 and MALAT1 are reported to enhance the stability of SREBP-1c and thereby lipid accumulation. H19 acts as a scaffold for the binding of SREBP-1c mRNA to PTBP1, which enhances the stability of SREBP-1c as well as its transcriptional activity in hepatocytes [81]. However, MALAT1 enhances nuclear SREBP-1c protein stability by direct interaction through the ubiquitin mediated proteasome signaling in hepatoma. Subsequently SREBP-1c targets such as SCD1, FASN, ACC1 and ACLY are upregulated that promotes fatty acid biosynthesis and insulin resistance [82]. In addition, lncRNAs HR1 and Gm16551 have been identified as repressors of SREBP-1c that adversely affects fatty acid biosynthesis in hepatic cells; however their roles in human cancers are yet to be elucidated [83, 84].

Cholesterol and triglycerides are the next class of lipids, which mainly acts as storage lipids and are cardinal for energy production as well as signaling processes. HMGCR (3-hydroxy-3-methyl-glutaryl-CoA reductase) catalyzes the first rate limiting step in cholesterol biosynthesis which utilizes acetyl CoA to synthesize mevalonate. Studies on hepatocyte cell line, HepG2, shows that knocking down of lncRNA AT102202 enhances HMGCR expression and cholesterol synthesis [85]. SREBP2 is the transcription factor that facilitates HMGCR and LDL (low density lipoprotein) receptor expression. LncRNA SNHG16, which is upregulated in pancreatic cancers, sequesters miR-195 and enhances the expression of SREBP2, thus promoting cholesterol metabolism for energy needs [86]. Mevalonate

is converted sequentially to isoprenoids and then to squalene, which cyclizes to lanosterol by action of SQLE (squalene epoxidase). Lanosterol acts as the immediate precursor for cholesterol biosynthesis. In breast cancer stem cells, lnc-030 binds to PCBP2 (poly rC-binding protein 2) to stabilize the SQLE mRNA, which enhances cholesterol biosynthesis as well as downstream PI3K/AKT signaling pathways to facilitate stemness [87]. The upregulated levels of lncRNA HULC acts through miR-9-PPARA-ACSL1 axis to enhance cholesterol biosynthesis, which acts as a feedback loop for enhancing HULC expression through activation of RXRA (retinoid X receptor alpha) receptors in hepatocellular carcinoma [74]. LDL receptors are involved in the exogenous cholesterol uptake into the cells during cholesterol insufficiency. In non-small cell lung cancers, the elevated levels of lncRNA CASC19 sequesters miR-301b-3p to upregulate LDL receptor expression that promotes exogenous cholesterol uptake by the cancer cells favouring cancer cell proliferation and metastasis [88]. In addition, cholesterol efflux transporters mediate cholesterol transport from the cells, which are anti-tumorigenic signals. Under conditions of surplus cholesterol, LXRs (liver X receptors) are activated that promote the expression of ABC transporters to facilitate cholesterol export. High cholesterol levels in hepatocytes induces transcription factor CEBPB mediated upregulation of lncRNA-HC, which in turn binds to ribonucleoprotein, hnRNPA2B1 to form a complex. This complex binds to mRNA of CYP7A1 or ABCA1 (ATP binding cassette transporter A1) transporters that facilitate cholesterol efflux from the cells [89]. In addition to the cholesterol export, excess cholesterol accumulation in cells are resolved by conversion to bile acids mediated by bile acid sensor, FX receptors and its target genes involved in synthesis of bile acids, such as CYP8B1 and CYP7A1. Cholestasis is a pathological condition seen during liver diseases, including liver cancers, where in defective bile acid secretion results in its accumulation in liver leading to liver injury. In hepatocellular carcinoma, lncRNA MEG3 is downregulated, which otherwise would acts as a scaffold for the binding of PTBP1 (polypyrimidine tract binding protein 1) with SHP (small heterodimer partner) mRNA, leading to the SHP mRNA decay. SHP attenuates bile acid synthesis and prevents cholestasis. However, since MEG3 levels are low, it leads to enhanced SHP levels which enhances bile acid synthesis and cholestasis, as shown in liver cancers, both *in vitro* and i*n vivo*. Furthermore, higher SHP levels prevents the binding of CREBP (cAMP response element binding protein) to the MEG3 promoter to inhibit the MEG3 expression, reciprocally [90]. Though direct studies reporting reprogramming of cholesterol transport in cancers are still under research, several studies have correlated the roles of prominent oncogenic lncRNAs upregulated in cancers and their roles in regulating this factor in significant cellular components of cancer milieu such as monocytes, macrophages or even human hepatocytes, which is correlated with enhanced cholesterol metabolism and associated inflammations. One of the oncogenic lncRNAs mostly upregulated in cancers is NEAT1. In a study on human macrophage cell line THP-1, NEAT1 has been reported to play role in cholesterol metabolism. Oxidized LDL induces NEAT1 expression and paraspeckle formation which is mediated through p38 and NF-κB signaling pathways. Furthermore, NEAT1 also mediates the oxidized LDL induced TNFα (tumor necrosis factor alpha) secretion through regulation of MAPK (mitogen activated protein kinases) and NF-κB (nuclear factor-κB) pathways as well as adversely affecting the CD36 expression by affecting mRNA stability. These events inhibit the lipid uptake by macrophages [91]. In addition, in human monocyte derived macrophages, the upregulated levels of lncRNA RP11-728F11.4 promotes FXYD6 (FXYD domain containing ion transport regulator 6) expression, which enhances the CD36 levels and thereby the lipid uptake and accumulation in these cells [92].

Triglycerides are prominent lipid molecules serving as storage lipids as well as signaling intermediates. Fatty acids are converted sequentially to fatty acyl CoA, LPA (lysophosphatidic acid), phosphatidate, diacylglycerol and then finally to triglycerides. Fatty acyl CoA is converted to LPA by GPAT (glycerol-3-phosphate acyltransferase) enzyme. In lung adenocarcinoma, lncRNA MSC-AS sequesters miR-33b-5p to upregulate the miR target GPAT and facilitate triglyceride synthesis [93]. Conversion of phosphatidate to diacylglycerol is catalysed by phosphatidic acid phosphohydrolases (PAPs) or lipins. Diacylglycerol and fatty acyl CoA are then esterified to triglycerides by diacylglycerol acyl transferase (DGAT). LncRNA SPRY4-IT1 is upregulated in melanomas, which inhibits the activity of lipin2 as well as DGAT2, thereby lowering the triglyceride synthesis in these cancer cells. The study also shows that silencing of SPRY4-IT1 enhances lipid accumulation and lipotoxicity mediated apoptosis in these cancer cells [94]. In hepatocellular carcinoma, silencing of lnc-KDM5D-4 enhances lipin2 activity favouring lipid biosynthesis, though the mechanism is yet unknown [95]. The regulatory elements SREBP-1c also effects triglyceride levels in cancer cells. Exogenous supplementation of lncRNA HR1 in liver cancer cells inhibited AKT phosphorylation and resultant translocation of FOXO1 (forkhead box O1) from nucleus. Nuclear accumulation of FOXO1 antagonizes LXR elements in SREBP-1c promoter to downregulate its expression and prevent triglyceride synthesis as well as accumulation for energy supply to inhibit tumor progression [96]. Triglyceride degradation to free fatty acids are carried out by lipases namely ATGL (adipose triglyceride lipase), HSL (hormone sensitive lipase) and MAGL (monoacylglycerol lipase). In hepatocellular carcinoma, lncRNA NEAT1 is upregulated that sequesters miR-124-3p to enhance expression of ATGL and promote triglyceride catabolism in cancers [97]. Apolipoproteins (APO) are class of lipid binding proteins in circulation, and APOA1 is one of the prominent high density lipoproteins. In hepatocellular carcinoma cells, lncRNA APOA1-AS mediates interaction between SUZ12 and APO gene favouring H3K27 trimethylation and upregulation of APOA1 expression [98].

Sphingolipids are important structural components of plasma membrane and their metabolites such as sphingosine-1-phosphate and ceramides serve as signaling intermediates. Conversion of dihydrosphingosine to

dihydroceramide is catalysed by CERSs (ceramide synthases). In breast cancers, the anti-sense lncRNA CERS6-AS1 binds to IGF2BP3 (insulin like growth factor 2 binding protein 3) to maintain the stability of CERS6 mRNA [99] and enhances CERS6 activity promoting tumor progression [99]. Ceramides can be converted to sphingomyelin by sphingomyelin synthase. In oesophageal squamous carcinoma, elevated levels of lncRNA THAP9-AS1 sequesters miR-335-5p to upregulate sphingosine synthase 2 expression favouring tumor progression [100]. Ceramide can be converted to sphingosine-1-phosphate by ceramidases. In hepatocellular carcinoma, lncRNA KCNQ1OT1 sequesters miR-146a-5p to upregulate ACER3, (alkaline ceramidase 3) expression to attenuate apoptosis and radiosensitivity in these cancer cells [101]. Furthermore, in hepatocellular carcinoma, lncRNA KCNQ1OT1 sequesters miR-149 to upregulate S1PR1 (sphingosine-1-phosphate receptor1) expression that facilitates migration and invasion of cancer cells, *in vitro* and *in vivo* [102]. In addition to ceramidases, sphingosine kinases (SPHK) also convert ceramide to sphingosine-1-phosphate. Several lncRNAs regulate SPHK expressions through sequestration of miRNAs in diverse cancers. While lncRNA MALAT1 sequesters miR-124-3p in osteosarcomas, lncRNA MAFG-AS1 sequesters miR-125b-5p in bladder cancer to upregulate SPHK1 expression [103, 104]. LncRNA Khps, which is antisense to SPHK1 is upregulated in osteosarcoma. Khps binding upstream to SPHK1 promoter that facilitates the binding of p300/CBP (CREB binding protein) histone acetyl transferase complex to the promoter site and open the chromatin. This leads to transcription of both Khps and SPHK1 favouring tumor progression [105]. Furthermore, in hepatocellular carcinoma, lncRNA HULC sequesters miR-107 to upregulate transcription factor E2F1 expression and facilitate its recruitment to SPHK1 promoter to augment its expression that favours angiogenesis [106]. LncRNA LINC00460 sequesters miR-613 to upregulate SPHK1 expression in colorectal cancers [107]. However, in papillary thyroid carcinoma, LINC00460 and LINC00520 sequesters miR-613 and miR-577 respectively to upregulate SPHK2 expression [108, 109].

Phospholipid metabolism are also regulated by lncRNAs in cancers. Phospholipases are enzymes that catalyse the hydrolysis of acyl and phosphate esters of numerous phospholipids. Phospholipase D (PLD) hydrolyses phosphatidyl choline to phosphatidic acid. In cervical cancers, LINC00511 facilitates binding of RXRA transcription factor to PLD1 promoter, to upregulate PLD1 expression, thereby favouring cancer cell proliferation [110]. Phosphatidic acid is further hydrolysed to free fatty acids and lysophospholipids by phospholipase A1 (PLA2). In non-small cell lung cancers, lncRNA SLNCR1 interacts with secretory PLA2 to regulate migration and invasion of cancer cell lines [111].

LncRNAs and Reprogramming of Amino Acid Metabolism in Cancers

Several lncRNAs coordinate the reprogramming of amino acid metabolism in tumor cells (**Figure 3**). Amino acids serve as the building blocks of proteins. They form the essential components of diverse signaling cascades that facilitate the maintenance of cellular homeostasis as well as disease pathogenesis. Amino acids are transported into the cells through membrane bound transporters. In cancers, amino acid metabolism as well as the levels of amino acid transporters are altered to favour tumorigenesis. Amino acids also serve as an alternate source of energy for the rapidly proliferating cancer cells. Glutamine is one of the most abundant amino acids in the human body. Cancer cells utilize higher amounts of glutamine as its serves as an energy source, helps nucleotide synthesis as it serves as source of nitrogen, facilitates synthesis of non-essential amino acid biosynthesis and also serves as source of carbon source for entering into TCA cycle. Exogenous glutamine enters into the cells through ASCT2 transporters, which are then deaminated to glutamate by glutaminase (GLS) enzyme. There are two isoforms namely GLS1 or KGA (glutaminase kidney isoform) and GLS2 or GAC (glutaminase isoform C). Glutamate catabolism is further carried out by glutamate dehydrogenase (GDH) or glutamate transaminases, namely GPT (glutamate pyruvate transaminase) and GOT (glutamate oxaloacetate transaminase). These reactions are accompanied with production of NADH, NADPH, ammonium and biosynthesis of non-essential amino acids. Glutamine also serves as substrate for glutathione synthesis that mediates ROS homeostasis. Hence the major reprogramming within the amino acid metabolism occurs for glutamine in cancer cells.

GLS is one of the most deregulated enzymes in cancers that affects glutamine metabolism. In prostate cancers, lncRNA PCGEM1 acts as a co-activator of c-Myc to transcriptionally induce the GLS expression, which favours the deamination of glutamine to glutamate for tumorigenesis [15]. Furthermore, lncRNA CCAT2 has been identified of exhibiting allele specific activity in regulating the alternate splicing of GLS in colorectal cancers. CCAT2 acts as a scaffold to facilitate the interaction between GLS pre-mRNA with cleavage factor CFIm. This enhances the alternate splicing favouring the production of GAC isoform over KGA to promote cancer cell proliferation and metastasis in colorectal cancers, both *in vitro* and *in vivo* [112]. The role of lncRNA HOTTIPP in regulating glutamine metabolism has been studied in hepatocellular carcinoma. The study reports that miR-192 and miR-204 antagonizes HOTTIP and attenuates its functions. However, HOTTIPP, which is upregulated in hepatocellular carcinoma, also regulates GLS1 expression to enhance glutaminolysis in this cancer favouring tumorigenesis [113]. The circular lncRNA circ0000517 is upregulated in non-small cell lung cancer which sequesters miR-330-5p to upregulate YY1 (ying yang 1) protein and thereby upregulate the GLS expression to promote glutaminolysis in non-small cell lung cancer [114]. Similarly circ-PITX1 also induced enhanced glutaminolysis in non-small cell lung cancers as evidenced by the extracellular acidification rates by seahorse metabolic assays [115]. LncRNA HOTAIR is upregulated in glioma and it sequesters miR-126-5p to enhance the GLS expression that favour glutaminolysis and tumor progression. In addition, since glutamate acts as precursor for glutathione, it enhanced glutathione production,

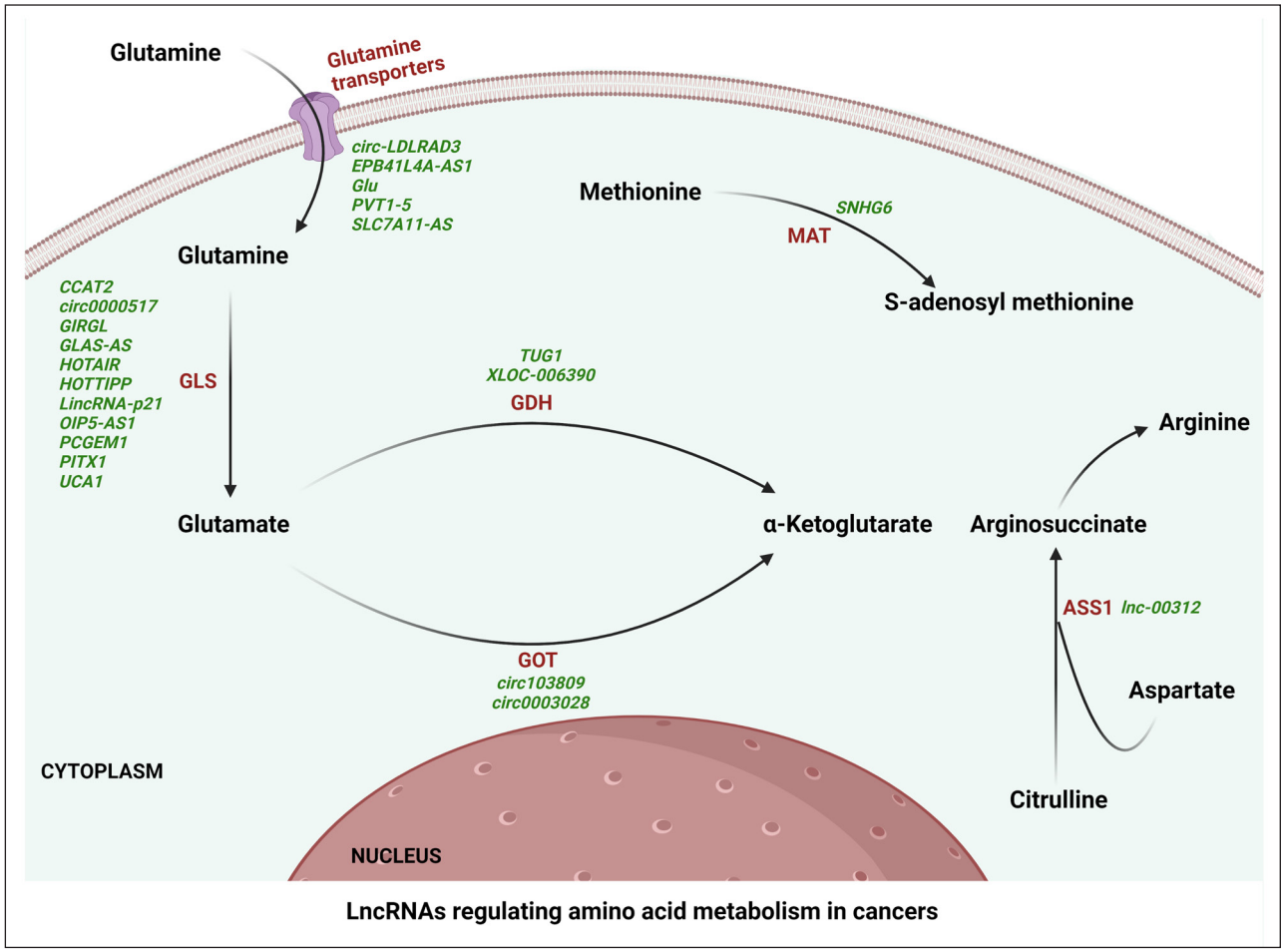

Figure 3: LncRNAs regulating amino acid metabolism in cancers. The figure presewnts an overviee of various lncRNAs that affect the metabolic reprogramming of amino acids namely glutamine, arginine and methionine in cancers. (ASS1-arginine succinate synthase 1) GDH-glutamate dehydrogenase; GLS-glutaminase; GOT-glutamine oxaloacetate transferase; MAT-methionine adenosyltransferases).

as well [116]. Furthermore, lncRNA UCA1 plays cardinal role in reprogramming the glutamine metabolism in bladder cancers. The upregulated UCA1 sequesters miR-16 and enhances the expression of miR-16 target GLS2, which in turn favours ROS homeostasis, redox balance and promotion of mitochondrial glutaminolysis [117]. LincRNA-p21 is a tumor suppressor which is downregulated in bladder cancers. Though the exact mechanism is not known yet, exogenous supplementation of lincRNA-p21 lowers GLS levels and glutaminolysis, thus regulating the glutamine metabolism [118]. The antisense lncRNA, OIP5-AS1 promotes glutaminolysis in melanoma by sequestering miR-217, thereby upregulating the miR target GLS. Thus, OIP5-AS1 enhances glutamate, α-ketoglutarate and ATP levels, in addition to glutamine consumption in melanoma [119].

Certain lncRNAs express during glutamine stress conditions to help the cancer cells to adapt during the stress by downregulating GLS expression. Two such lncRNAs are GLAS-AS and GIRGL. During glutamine deficiency or stress in pancreatic cancers, the lncRNA GLS-AS, which is antisense to GLS is downregulated. GLS-AS, otherwise, inhibits GLS by binding to the mRNA post-transcriptionally. It also attenuates GLS-c-Myc binding which affects c-Myc stability adversely. Under conditions of glutamine stress, c-Myc cannot bind to GLS-AS promoter to attenuate GLS-AS expression. Thus, GLS-AS-GLS-c-Myc axis acts reciprocally to favour the tumor progression under conditions of glutamine stress in pancreatic cancers [120]. In colorectal cancers, under conditions of glutamine deficiency, c-Jun mediated upregulation of lncRNA GIRGL occurs. GIRGL binds to stress protein CAPRIN1 (cell cycle associated protein 1) thereby affecting the stability of GLS1 mRNA by inducing liquid-liquid phase separation of this complex into stress granules. These processes favours cancer cells to adapt to glutamine deficiency [121].

Glutamine metabolism also involves activity of GOT1 and GOT2 enzymes as these transaminases help in the production of α-ketoglutarate which supplements resources to TCA cycle. The circ-103809 and circ-0003028 sequesters miR-377-3p and miR-1298-5p to upregulate the expressions of GOT1 and GOT2 respectively in non-small cell lung cancers to promote glutamine metabolism favouring tumor progression [122, 123]. GDH is also regulated by lncRNAs. In intrahepatic cholangiocarcinoma, the lncRNA TUG1 is upregulated, which sequesters miR-145. This in turn enhances the expression of miR-145 target SIRT3 (sirtuin 3) which augments the GDH activity and thereby glutamine consumption as well as ATP production to promote cancer [124]. LncRNA XLOC-006390-c-Myc axis regulates

GDH expression in pancreatic cancers. This lncRNA interacts with c-Myc to enhance its stability by preventing ubiquitin mediated degradation, thus making c-Myc available at the promoter of GDH to enhance the GDH expression and glutaminolysis in pancreatic cancers [125].

Glutamine or glutamate transporters are also regulated by lncRNAs to favour deregulated glutamine metabolism in cancers. LncRNA EPB41L4A-AS1 is downregulated in liver cancers and is regulated by p53 and PGC-1α (peroxisome proliferator activated receptor gamma coactivator 1-alpha). Lower expression of this lncRNA or its deletion in cancers renders HDAC2 (histone deacetylase 2) free of its interaction with EPB41L4-AS1in nucleolus and facilitates its entry to nucleoplasm. HDAC2 then epigenetically repress vHL and VDAC1 (voltage dependent anion channel 1) expressions through histone modifications. ROS was increased, which leads to transcriptional activation of ATF4 (activating transcription factor 4) /P-eIF2α and subsequent enhancement of SNAT5 (system N amino acid transporter 5) glutamine transporters. These events enhances glutamine consumption by the cancer cells, increases glutaminolysis and glutamine dependency. Other than SNAT5, upregulation of transporter ASCT2 (alanine serine cysteine transporter 2), GLS as well as ME1/2 were also observed that contributed to altered glutamine metabolism. Furthermore, the study has also shown that depletion of this lncRNA enhances sensitivity of these cancers to GLS inhibitors [126]. The circ-LDLRAD3 lncRNA enhances glutamine metabolism by sequestering miR-137 to upregulate SLC1A5, mitochondrial glutamine transporter expression. This favours glutamine dependent ATP synthesis and glutathione production favouring tumor progression in non-small cell lung cancers [127]. In addition, lncRNAs PVT1-5 and MINCR also exhibit similar mechanism of action by sequestering miR-126 to upregulate glutamine transporter SLC7A5 to promote glutaminolysis in lung cancers and non-small cell lung cancers respectively [128, 129]. In triple negative breast cancers, 17-β estradiol activates the G-coupled estrogen receptor to downregulate lncRNA Glu expression, which otherwise would bind to VGLUT2 (vesicular glutamate transporter 2). Lnc-Glu binds to VGLUT2 to inhibit the latter and thereby attenuating glutamate secretion from the TNBC cells. However, in TNBCs, active VGLUT2 promotes glutamate secretion to promote cancer cell invasion and metastasis [130].

Yet another amino acid whose metabolism is deregulated in cancers is arginine. Arginine succinate synthase 1 (ASS1) is the central enzyme indispensable for arginine synthesis, regulation of the urea cycle and in addition, regulation of aspartate to urea conversion. In renal cell cancers, lncRNA00312 is downregulated, which otherwise sequesters miR-34a-5p to upregulate ASS1 expression [131]. The amino acid cysteine acts as rate-limiting factor for glutathione synthesis and hence is cardinal for maintaining redox balance in cancer cells. One of the major transporters for extracellular cysteine is SLC7A11, which also transports the intracellular glutamate, thus favouring glutathione synthesis. The antisense lncRNA SLC7A11-AS is downregulated in epithelial ovarian cancers, which otherwise would inhibit the SLC7A11 expression. The higher levels of SLC7A11 contributes to enhanced redox homeostasis through glutathione production and also regulates glutamine metabolism in cancer cells to favour tumor progression [132]. LncRNAs also regulate the methionine cycle in cancers. LncRNA SNHG6 sequesters miR-1297, thereby upregulating the expression of miR target MAT2A, which codes for methionine adenosyltransferases in hepatocellular carcinoma. These enzymes catalyse the synthesis of S-adenosylmethionine through methionine cycle affecting global genome methylation that favours hepatocarcinogenesis [133].

LncRNAs and Reprogramming of Nucleotide Metabolism in Cancers

Nucleotides that includes both purines and pyrimidines constitute the genomic material are cardinal for the uncontrolled cell proliferation seen in cancers. Though there are significant advances in research on reprogramming on glucose or lipid or amino acid metabolisms in cancer, the data on nucleotide metabolic reprogramming is scarce. Similar to the interconnected glucose/lipid/amino acid metabolisms in cancer, certain reports have also shown how amino acid and nucleotide metabolisms are in par with each other. It has been shown that under conditions of glutamine starvation, in glioblastoma, the upregulation of glutamine synthetase provides glutamine prototrophy to the cells and enhances the purine biosynthesis, favouring de novo nucleotide synthesis for cancer cell proliferation. This has been proved by the *in vitro*, orthotopic glioblastoma model as well as patient data [134]. It has been reported that over 30% of cytoplasmic glutamine undergoes catabolism to glutamate that aids nucleotide biosynthesis. Another study explains an elaborated genome scale metabolic model created by analysis of uptake and release fluxes in the cellular level proves that enhanced release of cytoplasmic glutamate to the ECM enhances the nucleotide metabolism, especially the pyridine biosynthesis in liver cancers to sustain their cellular proliferation and tumor growth [135]. These data serves as a treatise on predicting the possible roles of those lncRNAs affecting GS expression to regulate nucleotide metabolism as well (**Figure 4**).

Thymidylate synthase (TS) acts as a major enzyme in DNA synthesis by catalysing the rate limiting step involving reductive methylation of dUMP to dTMP. In colorectal cancers, lncRNA XIST is upregulated and induces the expression of TS enzyme through an unknown mechanism, so as to enhance pyrimidine biosynthesis facilitating DNA replication in the proliferating cancer cells. The higher levels of XIST induced TS also confers resistance to 5-FU therapy in these cancers [136]. In addition, the lncRNA TUG1 also enhances TS expression by sequestering miR-197-3p and thereby conferring 5-FU resistance in colorectal cancer cells [137]. In colorectal cancers, yet another mechanism was shown wherein lncRNA HOTAIR epigenetically silenced miR-218 expression to activate VOPP1 (vesicular over-expressed in cancer pro-survival protein 1) expression and NF-κB signaling. These subsequently enhanced TS expression to confer 5-FU resistance in these cancers

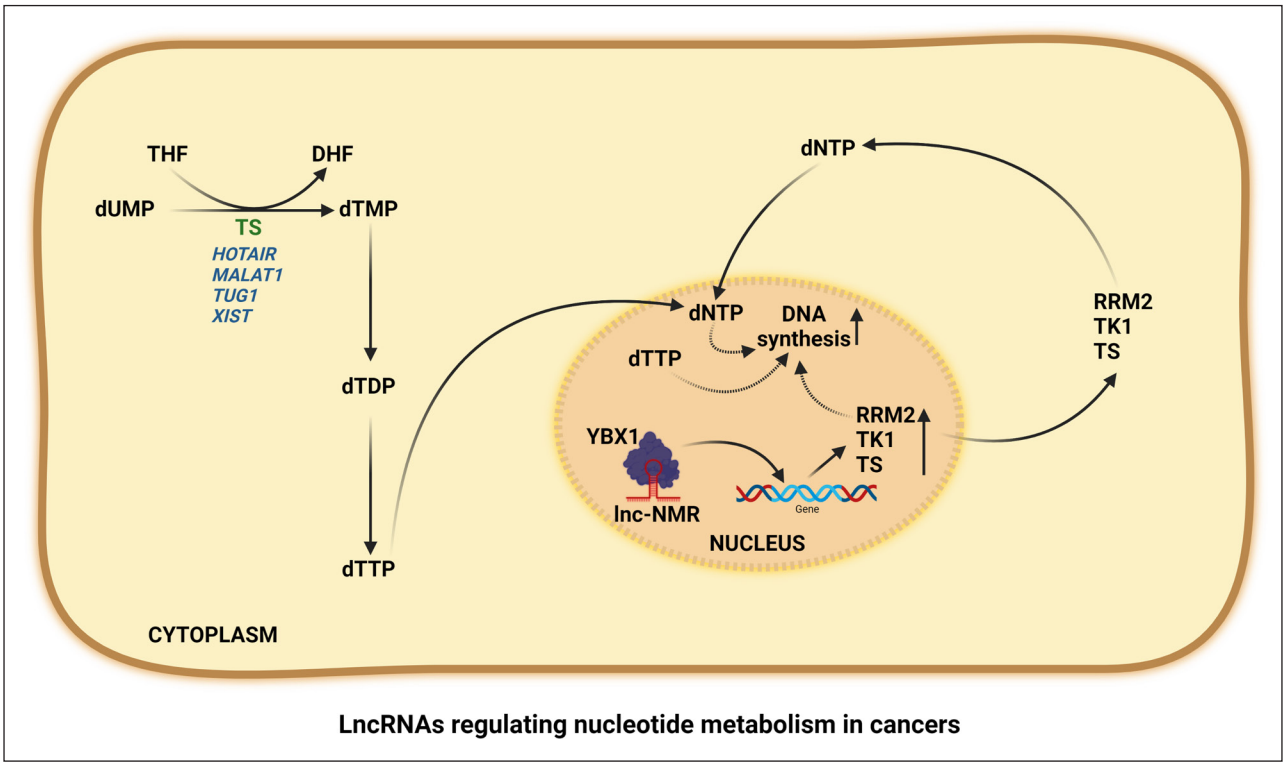

Figure 4: LncRNAs regulating nucleotide metabolism in cancers. The figure presents a summary of mechanisms by which different lncRNAs modulate the reprogramming of nucleotide metabolism in cancers. The major enzymes involved in nucleotide metabolism that are regulated by lncRNAs includes TS (thymidylate synthase), TK1 (thymidylate kinase 1) and RRM2 (ribonucleotide reductase subunit 2).

[138]. In glioblastoma multiforme, lncRNA MALAT1 is over-expressed. MALAT1 sequesters miR-203a-3p, thereby upregulating its target TS. This signaling axis confers resistance to temozolomide in glioblastoma [139]. These reports explore the roles of lncRNAs such as XIST, TUG1, HOTAIR and MALAT1 in regulating the TS expression and thereby the nucleotide metabolism in cancers.

An elaborated report on the effect of lncRNAs in regulating the nucleotide metabolism in cancers have been reported through unveiling the role of lncRNA, linc-NMR, in hepatocellular carcinoma [140]. Linc-NMR is upregulated in hepatocellular carcinoma. It interacts with the transcriptional factor, YBX1 (Y-box binding protein 1), and regulates YBX1 activity. Linc-NMR-YBX1 complex is recruited to the promoters of the genes coding for three major enzymes indispensable for nucleotide biosynthesis, namely, RRM2 (ribonucleotide reductase subunit 2), TK1 (thymidylate kinase 1) and TS. Elevated levels of these enzymes increases the dNTP levels in the cancer cells leading to enhanced cell proliferation and tumorigenesis. Thus, linc-NMR-YBX1-RRM2-TK1-TS axis regulates proliferation-senescence axis in hepatocellular carcinoma, which can serve as an ideal therapeutic target for numerous cancers [140].

Conclusion

Cancer cells reprogram their macromolecular metabolism to sustain their uncontrolled proliferation and tumorigenic attributes. The reprogrammed metabolisms serves as a better energy source for the rapidly proliferating cells in cancers. They also enable the cells with surplus metabolic intermediates that can facilitate cellular biosynthesis. LncRNAs form a critical group of regulatory molecules that reprogram various cellular metabolisms for cancer progression. In this review, we have detailed on the role of various lncRNAs in reprogramming of glucose, lipid, amino acid and nucleotide metabolisms in diverse cancers. Ranging from basic research to clinical trials, lncRNAs serve as potent therapeutic targets for cancers. The review provides us a concise knowledge of employing several of these lncRNAs as diagnostic, prognostic or therapeutic cancer biomarkers. Further advancements in employing lncRNAs are therapeutic targets would bring about betterments in personalized cancer therapy.

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Competing Interests

The authors have no competing interests to declare.

Author Contributions

Conceptualization: D.N.D.; Writing—original draft preparation: R.N.; Writing, revising, and editing: D.N.D. and R.N. All authors have read and agreed to the published version of the manuscript.

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