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Mini-review

# Non-coding RNAs in the reprogramming of glucose metabolism in cancer

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ABSTRACT

Proliferating cancer cells reprogram their metabolic circuitry to thrive in an environment deficient in nutrients and oxygen. Cancer cells exhibit a higher rate of glucose metabolism than normal somatic cells, which is achieved by switching from oxidative phosphorylation to aerobic glycolysis to meet the energy and metabolites demands of tumour progression. This phenomenon, which is known as the Warburg effect, has generated renewed interest in the process of glucose metabolism reprogramming in cancer cells. Several regulatory pathways along with glycolytic enzymes are responsible for the emergence of glycolytic dependence. Non-coding (nc)RNAs are a class of functional RNA molecules that are not translated into proteins but regulate target gene expression. NcRNAs have been shown to be involved in various biological processes, including glucose metabolism. In this review, we describe the regulatory role of ncRNAs—specifically, microRNAs and long ncRNAs—in the glycolytic switch and propose that ncRNA-based therapeutics can be used to inhibit the process of glucose metabolism reprogramming in cancer cells.



## 1. Introduction

Neoplastic disease is characterised by uncontrolled cell proliferation. Cancer cells adapt their metabolism to meet the energy demands associated with increasing biomass. The unique reprogrammed metabolic phenotype exhibited by tumour cells known as the Warburg effect is characterised by high rates of aerobic glycolysis leading to the production of lactic acid and reduced mitochondrial oxidative phosphorylation (OXPHOS) even in the presence of oxygen [1–3]. Unlike in normal cells, glycolytic dependence in tumour cells generates anabolic macromolecules or intermediates that contribute to tumour growth, such as nicotinamide adenine dinucleotide phosphate (NADPH) and ribonucleotides via the pentose phosphate pathway (PPP); glycogen for glucose storage via the hexosamine pathway; and amino acids via the serine/glycine biosynthesis pathway, which fuels one-carbon metabolism to generate NADPH (see Table 1, Fig. 1).

Processes that induce the glycolytic switch and promote cell proliferation are associated with activation of oncogenes (e.g., Rat Sarcoma viral oncogene homolog [RAS] and Avian myelocytomatosis viral oncogene homolog [MYC]), inactivation of tumour suppressor genes (e.g., tumour protein [TP]53 and phosphatase and tensin homolog [PTEN]), growth-factor mediated signal transduction (e.g., insulin-like growth factor receptor, epidermal growth factor receptor, and human epidermal growth factor receptor 2), and hypoxia-mediated signalling (hypoxia-inducible factor [HIF]-1α) [4–7]. Thus, changes in metabolism can be viewed as a hallmark of cancer [8], and targeting the relevant factors represents a potential strategy for cancer therapy [9]. However, our knowledge of the regulation of cancer cell metabolic reprogramming and the signalling pathways that are involved remains limited.

Non-coding (nc)RNAs are a family of functional RNA molecules that are not translated into proteins but regulate the expression of target genes. NcRNAs can be classified based on their size: small

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**Abbreviations**

| | |
|---|---|
| $^{18}$F-FDG | 2-deoxy-2-fluorine-18fluoro-D-glucose |
| ATP | Adenosine triphosphate |
| BC | Bladder cancer |
| CAFs | Cancer associated fibroblasts |
| COX | Cytochrome c oxidase |
| SCO2 | Cytochrome c oxidase 2 |
| CT | Computed tomography |
| GBM | Glioblastoma multiforme |
| GLUT | Glucose transporter |
| HK | Hexokinase |
| HMIT | $H^+$/myo-inositol transporter |
| HCC | Hepatocellular carcinoma |
| HOTAIR | HOX transcript antisense RNA |
| HIF1 | Hypoxia-inducible factor 1 |
| LDH | Lactate dehydrogenase |
| lncRNA | Long non coding RNA |
| mTOR | Mammalian target of rapamycin |
| mTORC1 | Mammalian target of rapamycin complex 1 |
| mTORC2 | Mammalian target of rapamycin complex 2 |
| MEG3 | Maternally expressed gene 3 |
| mRNA | Messenger RNA |
| miRNA | MicroRNA |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| ncRNA | Non-coding RNA |
| OS | Osteosarcoma |
| OXPHOS | Oxidative phosphorylation |
| PPP | Pentose phosphate pathway |
| PTEN | Phosphatase and tensin homolog |
| $PIP_3$ | Phosphatidylinositol-3,4,5-trisphosphate |
| $PIP_2$ | Phosphatidylinositol-4,5-bisphosphate |
| PEP | Phosphoenolpyruvate |
| PFK1 | Phosphofructokinase 1 |
| PFKFB | Phosphofructokinase 2-F2,6Bpase |
| PGM | Phosphoglycerate mutase |
| PI3K | Phosphoinositide 3-kinase |
| PDPK1 | Phosphoinositide-dependent protein kinase 1 |
| piRNA | PIWI-interacting RNA |
| PET | Positron emission tomography |
| PTENP1 | PTEN pseudogene |
| PKM1 | Pyruvate kinase M1 |
| PKM2 | Pyruvate kinase M2 |
| RAS | Rat Sarcoma viral oncogene |
| RTK | Receptor tyrosine kinase |
| RCC | Renal cell carcinoma |
| STAT3 | Signal transducer and activator of transcription 3 |
| siRNA | Small interfering RNA |
| snoRNA | Small nucleolar RNA |
| TP53 | Tumour protein P53 |
| TIGAR | TP53-induced glycolysis and apoptosis regulator gene |
| tiRNA | Transcription initiation RNA |
| UCA1/CUDR | Urothelial cancer-associated 1 |
| WRAP53 | WD repeat containing antisense of p53 |

interfering RNAs, PIWI-interacting RNAs, transcription initiation RNAs, and micro (mi)RNAs are smaller than 200 nucleotides (nt); small nucleolar RNAs are of about 60–300bp in size; and long non-coding (lnc)RNAs are longer than 200 bp. MiRNAs are transcribed as long primary transcripts, which are then processed by enzyme Drosha to form ~70 nt precursor-miRNAs. These precursors are further processed by enzyme Dicer into 19–25 nt mature miRNAs that regulate gene expression by targeting mRNA transcripts. The post-transcriptional level interference leads to target gene silencing via translational repression or mRNA degradation [10]. LncRNAs are transcribed and processed similarly to mRNAs. Functionally lncRNAs have a diverse mechanism of action in a cell, ranging from direct transcriptional regulation, histone modification, to modulating transcription of regulatory factors acting as decoy binding sites. LncRNAs have also been known to regulate miRNAs by acting as sponge and thereby preventing miRNAs from binding to their target mRNAs. Gene expression profiling indicates that lncRNAs are expressed in a tissue-type or cell-type specific manner and hence have a varied expression to different pathophysiological conditions [11,12].

NcRNAs have been implicated in a variety of cancers; miRNAs and lncRNAs are known to function as oncogenes and tumour suppressors, and act on receptor tyrosine kinases (RTKs) and hypoxia-mediated pathways [13,14]. Recently, there has been increased interest in the role of miRNAs and lncRNAs in aerobic glycolysis as it relates to cancer metabolism. Accumulating evidence has shown that ncRNAs can alter glucose metabolism either directly by targeting glucose trafficking and consumption, or indirectly by modulating cancer-associated signalling pathways. In this review, we discuss the current state of knowledge on the role of miRNAs and lncRNAs in the regulation of glucose metabolism.

## 2. Glucose trafficking and consumption

### *2.1. NcRNAs regulate glucose trafficking in cancer cells by altering GLUT levels*

Tumour cells compensate for the inefficiency in Adenosine Tri-Phosphate (ATP) production (two ATPs generated by glycolysis vs. ~38 by OXPHOS) by upregulating the expression of glucose transporters (GLUTs), which increases glucose uptake into the cytoplasm [15,16]. This property has been exploited for the non-invasive diagnostic imaging of human cancer in positron emission tomography with a radiolabelled glucose analogue as a reporter (2-deoxy-2-fluorine-$^{18}$fluoro-D-glucose) combined with computed tomography [17,18]. Glucose transport across the cell membrane along a concentration gradient is an energy-independent process. The passive transport of glucose is facilitated by solute carrier 2A (SLC2A) and GLUT family proteins. Among the 14 GLUT isoforms [19,20], GLUT1 is known to be overexpressed in cancer. NcRNAs have been implicated in the regulation of GLUT1 expression. The lncRNA *neighbour of BRCA1 gene (NBR)2* promotes cell survival by upregulating GLUT1 expression in response to phenformin treatment in renal cell carcinoma (786-O) and breast cancer cell lines (MDA-MB-231). Phenformin treatment increases glucose uptake via overexpressed GLUT1, while *NBR2* knockdown abrogates GLUT1 expression, thereby rendering 786-O and MDA-MB-231 cells susceptible to phenformin-induced cell death [21]. Additionally, the *GLUT1* gene is a target of miR-1291; transfection of miR-1291 mimic in human renal cell carcinoma (RCC) cells reduced *SLC2A1* mRNA and GLUT1 protein expression [22]. Notably, miR-1291 was downregulated in RCC as compared to adjacent non-cancerous kidney tissue.