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Regulation of Aerobic Glycolysis by microRNAs in Cancer

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Abstract

One of the most common and profound biochemical phenotypes of animal and human cancer cells is their ability to metabolize glucose at high rates, even under aerobic conditions. Such alterations lead to establishment of tumor-specific metabolic machinery that is sufficient for supporting the biosynthetic and energy requirements of the tumor cells for facilitating rapid tumor growth and adaptation to new metastatic niches. These changes entail rapid glycolysis by the tumor cells, shifting the flux of glucose from tricarboxylic acid (TCA) cycle to glycolysis, resulting in generation of vast amounts of lactate, which is then secreted outside the tumor cells. This phenomenon is also termed as Warburg effect, as originally described by Otto Warburg. Several oncogenes and tumor suppressors have been implicated in altering tumor cell metabolism in order to facilitate tumor growth and metastasis. MicroRNAs mediate fine-tuning of the cancer-associated glycolytic pathways either directly or at the level of oncogenes. This article intends to review the mechanisms and pathways by which miRNAs regulate the aerobic glycolysis in cancer.

Keywords

miRNA; Aerobic glycolysis; Cancer Metabolism

Introduction

Under the normal conditions, most cells metabolize glucose by mitochondrial oxidative phosphorylation to maximize ATP production. Only under reduced oxygen state, cells switch to anaerobic glycolysis, which results in low ATP and high lactate production. Interestingly, cancer cells, regardless of oxygen availability, prefer anaerobic glycolysis, which produces excessive amounts of lactate and low ATP. This metabolism is referred as Warburg effect, which was observed by Otto Warburg in 1920s (1). This adaptive response

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Conflicts of Interest

No potential conflicts of interest to disclose.

is required to meet the high demand of various building blocks, such as nucleotides, fatty acids, lipids and amino acids, for rapidly proliferating cells while still supplying sufficient energy (2). A fall in energy further activates compensatory catabolic pathways along with increased glucose uptake and metabolism. A shift towards catabolic pathways forces cancer cells to oxidize molecules other than glucose through mitochondrial Krebs's pathway. This replacement is generally achieved with glutamine, which furnishes lipid synthesis and Krebs's cycle intermediates in the rapidly dividing cells. Also, amino acids such as, arginine and glycine and some fatty acid intermediates are metabolized through the same pathway in some context. This altered metabolism confers several advantages to cancer cells such as adequate energy supply, biosynthesis of required molecules, invasiveness due to high lactate production and also protection against the apoptotic stimuli (3). Metabolic reprogramming of cancer cells is a complex interplay of PI(3)K, mTOR, AMPK and HIF-1 α . Oncogenes and growth factors upstream of these molecules equally govern the changes in the energy metabolism of cancer cells.

MicroRNAs (miRNAs) are short noncoding RNAs, 18 to 25 nucleotides in length, which regulate gene expression. They demonstrate complementarity with 3'-untranslated region (3'-UTR) of their target mRNAs. The miRNA-mediated regulation of gene expression could be either by post-transcriptional regulation of gene expression leading to target mRNA degradation or repression of its translation with consequent decrease in the particular protein levels or even by upregulation of the targets. miRNAs regulate a vast majority of oncogenes and tumor suppressor genes (4–6). Recent evidences implicate altered miRNA regulation in the pathogenesis of cancers of multiple origins (7, 8). Changes in the miRNA expressions and consequent alterations in signaling networks have been observed in a variety of human solid cancers, including lung (9, 10), breast (11–13), colorectal (14, 15), pancreatic (16–19), ovarian (20), renal (21, 22), prostate (23, 24), cervical (25, 26), gastric (27), bladder (28), liver (29), esophageal (30), head and neck (31), and thyroid cancer (20).

Multiple studies have revealed that the altered metabolic pathways in cancers are tightly regulated by miRNA. The downstream targets of a number miRNAs are directly or indirectly connected to the metabolic regulation. Given the crucial role of miRNAs in cell growth and development processes, it is not surprising that alteration in the activity of these non-coding small RNA could lead to changes in metabolic pathways. Hence, above findings warrant a detailed understanding of the role played by miRNAs in cancer cell metabolism.

Direct regulation of the key enzymes involved in aerobic glycolysis by miRNAs

Regulation of glucose uptake receptors (GLUTs) by miRNAs

GLUT family of receptors are involved in facilitated transport of glucose across the plasma membrane. Among the members of GLUT receptor family (GLUT1–4), GLUT1 and GLUT3 are mostly upregulated in most cancers (32). While GLUT1 and GLUT3 function independent of insulin, GLUT4 activity is regulated by insulin or insulin-like growth factor (IGF) signaling, which regulates the plasma membrane trafficking of the GLUT4 receptors (33–35). Although a number of miRNAs have been predicted to regulate the expression levels of GLUT1 and GLUT3, none of those have been experimentally verified to regulate the mRNA levels of GLUT1 or GLUT3. However, GLUT4 expression is regulated by miR-223 and miR-133 in cardiomyocytes (36, 37). To what extent GLUT4 expression levels contribute to the metabolic phenotype in cancer remains to be studied.

Regulation of glycolytic enzymes by miRNAs

Several glycolytic enzymes are direct targets of miRNAs (Table 1). Hexokinases (HKs), which transfer a phosphoryl moiety from ATP to the 6-hydroxyl of glucose to produce glucose-6-phosphate (G6P), represent the first step in the glycolytic pathway. The glucose phosphorylation reaction carried out by HKs maintains the concentration gradient necessary for facilitative glucose transporters (GLUTs) to move glucose into the cell. Till date no miRNAs have been identified to regulate HKs. Phosphoglucose isomerase, which is also associated with invasion and metastasis of cancer cells, has been shown to be regulated by miR-200 family, which includes miR-200a, miR-200b, and miR-200c (38). Aldolase A (ALDOA) has been shown to be regulated by miR-122 mimetics in human and rat liver cells (39). miR-17-92 cluster regulates the levels of phosphoglycerate kinase 1 (PGK1), enolase 1 (ENO1), ENO2, and triosephosphate isomerase 1 (TPI1) (40). However, these genes lack potential target sites for the miRNAs comprising the miR-17-92 cluster. Most the effects of the miR-17-92 cluster on these glycolytic genes seem to be due to regulation of HIFs by the cluster (40). TPI1 is one of the predicted targets for the miR-195, which is significantly downregulated in the bladder cancer (41). However, a direct relationship remains yet to be validated. miR-15a/16-1 cluster, which is significantly downregulated or lost in B cell chronic lymphocytic leukemias (CLLs), seems to regulate TPI1 and ALDOA, as identified in a proteomic screen in MEG-01 leukemic cells (42). Out of these, TPI1 is a predicted direct target of the miR-15a/16-1 cluster. The miR-15a/16-1 cluster also regulates aldehyde dehydrogenase 6 family, member A1 (ALDO6A1) in CLL, as identified in a microarray screen (42). miR-29a modulates the expression of target genes, phosphoglucomutase (PGM1), ENO1 and phosphoglycerate kinase 1 (PGK1) in invasive DLKP-A lung cancer cell line, as identified by proteomic analysis (43). ENO2 also seems to be significantly downregulated by miRNA-mediate mechanism in HepG2 hepatocarcinoma cell line as knockdown of Dorsha significantly upregulates the levels of ENO2 (44). However, the exact miRNAs targeting ENO2 are not known yet. Pyruvate kinase M2 (PKM2), which is significantly overexpressed in cancer cells, is a direct target of miR-326 (45). miR-133a and miR-133b also target PKM2 in solid tumors (46).

Regulation of lactate production in cancer cells by miRNAs

During the aerobic glycolysis in cancer cells, most of the pyruvate gets converted into lactate instead of getting converted into the acetyl-CoA that would enter the Krebs's cycle in mitochondria. The lactate thus made in the cytosol is then secreted outside the cells by the monocarboxylate transporters (MCTs). Most of the lactate thus secreted, can then be taken up by the liver where it is converted into glucose and recycled back to the tumors. However, lactate has also been hypothesized as an energy source for the tumor or stromal cells under aerobic conditions. No major cancer-associated miRNAs are known to regulate the enzyme lactate dehydrogenase (LDHA), which converts pyruvate into lactate. However, three miRNAs, miR-29a, miR-29b and miR-124, selectively target both human and mouse MCT1 3'-UTRs, thus potentially regulating the ability of the tumor cells to secrete lactate (47). Out of these, miR-29b is associated with a region that is frequently amplified in breast cancer (48), while miR-124 is frequently downregulated in medulloblastoma (49). The plasma membrane levels of MCT1 and MCT4 are regulated by CD147, a broadly expressed plasma membrane glycoprotein (50). The expression levels of CD147 are regulated by let-7b, a tumor suppressor miRNA that represses cancer cell proliferation and migration as well as tumor metastasis (51).

miRNA-mediated regulation of signaling pathways that regulate aerobic glycolysis

miRNAs regulate mTOR expression/activity

Target of rapamycin, (TOR), critically governs the cellular growth and metabolic processes of all eukaryotic cells by precisely integrating the extracellular stimuli with amino acid availability and intracellular energy (52). mTOR activation leads to enhanced expression of several of the glycolytic enzymes, including GLUT1, LDHB and PKM2 (53–56). Existing in two complexes, the mammalian TOR complex 1 (mTORC1) and complex 2 (mTORC2) in mammalian systems, mTOR directly enhances the translational machinery by phosphorylating eIF4E binding proteins (4E-BPs) and the ribosomal protein S6 kinases (57, 58). mTOR1 activity is essentially driven by the growth factors, mitogens and hormones through PI(3)K/AKT/Ras-like GTPase Rheb signaling (59). Activation of mTOR signaling leads to increase in protein synthesis of HIF1 α in response to growth factors and PI3K/Akt signaling, and thus, leads to enhanced expression of glycolytic enzymes (60, 61). Recent findings suggest critical role of miR in mTOR regulation through PI(3)K/AKT dependent and independent pathways. In a recent study, Nagaraja et al. demonstrated mTOR as a direct target of miR-100, which actively inhibits mTOR signaling in clear cell ovarian cancer (CCOC) (62). Functional consequences of this inhibition were reflected in the reduced phosphorylation of mTOR substrate and enhanced sensitivity of miR-100 over-expressing CCOC towards rapamycin analog RAD001. Another study by Fornari et al. revealed an inverse correlation between miR-193a-3p and mTOR (63). In this study direct translational repression of mTOR1 and c-met by miR-193a-3p was observed in hepatocellular carcinoma that resulted in cell cycle modulation, invasiveness, and sensitization towards doxorubicin treatment and to hypoxia-induced apoptosis. In another study, Goa et al. reported that miR-126 impedes tumor cell growth by targeting p85 β subunit of PI(3)K (64). As PI(3)K/AKT triggers downstream signals to mTOR for cellular growth and proliferation, loss of miR-126 facilitates tumor growth. Similarly, Pineau et al. showed the negative correlation between miR-221 and expression level of PI3K/AKT/mTOR pathway regulator, DDIT4, in liver cancer cell lines (65).

Against this background, a number of miRNAs indirectly activate the mTOR activity through the negative regulation of mTOR inhibitors such as PTEN, AMPK1 and LKB1. miR-21 increases the tumor cell migration, proliferation and invasiveness by inhibiting PTEN in human hepatocellular carcinoma (66). Similarly, miR-451 promotes glioma cell proliferation and migration in response to glucose through targeting LKB1-associated protein CAB39 (67). Both of these suggest the indirect activation of mTOR signaling through the suppression of its inhibitors.

Regulation of KRAS expression by miRNAs

RAS family of proteins (H-, N-, and KRAS) plays an important role in transducing growth-promoting signals from the cell surface receptors towards nuclear targeted genes and thus, regulates cellular growth, differentiation and survival (68). According to estimates, approximately 20% of all tumors have mutated RAS protein, predominantly in the K (Kirsten) member of RAS family (69). Mutated KRAS mediates several aspects of oncogenesis through its constitutive expression and constant activation of downstream pathways such as Raf/MEK/ERK and PI3K/Akt (69). Apart from promoting tumor growth and survival, emerging findings suggest direct correlation between KRAS and cancer metabolism through HIF-1 activation (70). It has been suggested that glucose deprivation leads to mutations in KRAS gene that eventually lead to enhanced expression of GLUT1 and other glycolytic genes (71). Given the important role of the RAS mutations in tumor progression, numerous studies investigated the possible link between miRNA regulation and

RAS-induced transformation. As a first report, Johnson et al. demonstrated reciprocal relation between, let-7 miRNA and RAS protein in the lung tumors (72). Similarly, another group showed inverse correlation between ectopic expression of miR-96 and KRAS protein in pancreatic cancer (73). Their results revealed reduced AKT signaling and heightened apoptosis post KRAS inhibition in the same cell types. In the later studies, miR-143 was found to target KRAS translation, which notably inhibited ERK1/2 phosphorylation and cancer growth in colorectal cancer cells (74). Similar results were observed in prostate cancer cells (75). Interestingly, KRAS mediates miR-143/145 regulation through RAS-responsive element-binding protein 1 (RREB1) in pancreatic cancer cells (76). The overabundance of miR-143/145 directly targets KRAS and hence suggested the feed forward circuit of KRAS regulation in pancreatic cancer cells. Recently, two more miRNAs, miR-18* and miR-217 have been identified to directly targets KRAS protein (77, 78). Through KRAS inhibition, miR-18* impedes proliferation and anchorage-independent growth of human cancer cells. In line with this, miR-217 was also found to regulate the tumor cell growth and anchorage-independent colony formation through KRAS inhibition in pancreatic ductal adenocarcinoma.

Regulation of p53 expression/activity by miRNAs

p53, the most commonly mutated gene in the human cancers, essentially regulates the cellular pathways in response to DNA damage and maintains genomic stability (79, 80). In response to stress stimuli, p53 upregulates selective genes and controls the propagation of damaged cells through cell cycle arrest and apoptosis. p53 enhances the expression of *TP53*-induced glycolysis and apoptosis regulator (TIGAR), while inhibiting the expression of PGM, resulting in the inhibition of glycolysis (81). TIGAR functions by potentially inhibiting PFK-2/FBPase-2 that regulates both the synthesis (through PFK-2) and the degradation (through FBPase-2) of intracellular fructose-2,6-bisphosphate (Fru-2,6-P₂), a potent positive allosteric effector of 6-phosphofructo-1-kinase (PFK-1), which stimulates glycolysis (82). p53 also induces Synthesis of Cytochrome c Oxidase 2 (SCO2) and glutaminase 2 (GLS2) to enhance mitochondrial respiration, and induces p53R2 to maintain mitochondrial DNA (81). Furthermore, p53 represses the transcriptional expression of GLUT1 and GLUT4, and inhibits the NF- κ B pathway to reduce the expression of GLUT3 to reduce glycolysis (81). Thus, p53 inhibits glycolysis and enhances mitochondrial respiration in cells. The role of p53 in cancer metabolism has been clearly highlighted through the discovery of p53-mediated upregulation of SCO2 protein (83). SCO2 plays crucial role in the assembly of components for cytochrome c oxidase complex 11 and promotes aerobic respiration in the cell. Any mutation in p53 significantly downregulates SCO2 protein and drives the cells towards respiratory failure. In tumors where p53 is highly mutated and SCO2 is low, glycolysis is the safest option to meet the high-energy demand of proliferating cells. This finding further strengthens the role of p53 as a guardian angel of the genome and also stresses the direct link between the energy metabolism and stress response in tumor cells.

Taken the diverse role of p53 in tumor prevention, various groups actively studied the role of miRNAs in this context. Studies suggest that p53 directly targets some of the miRNAs in respond to DNA damage. It activates the transcription of miR-34a and miR-194/miR-215 cluster, which function as effectors in the p53 signaling pathway (84). p53 also suppress the transcription of some tumorigenic miRNAs such as miR-17-92 family (85). Interestingly, some miRNAs are post-transcriptionally controlled by p53 under conditions of DNA damage where p53 directly associates with Dorsha and enhance the miRNA processing activity (86). Activation of such miRNAs, miR-16-1, miR-143 and miR-145, further controls the cellular division through cell cycle arrest by targeting KRAS and CDK6. These

miRNAs thus represent additional mechanism of defense provided by p53 against tumor progression.

Recently a group of miRNAs regulating P53 activity has been identified. miR-25, miR-30d, miR-504 and miR-125b directly target p53 3'-UTR and hence, impair p53 response and promotes tumorigenicity through direct reduction in p53 protein levels (87–89). A study by Papagiannakopoulos et al. demonstrated indirect regulation of p53 by miR-21 in glioblastoma cells (90). miR-21 activation negatively suppress p53 response by directly targeting p53 homologues and p53 activators such as JMY, TOPORS, TP53BP2, DAXX and HNRPX. miR-34a indirectly activates p53 by downregulating SIRT1, which negatively regulates p53 through deacetylation (91). miR-122 enhances p53 activity through downregulation of cyclin G1, which forms a complex with PP2A phosphatase and enhances MDM2 activity to inhibit p53 (92). miR-29 down-regulates p85a, a regulatory subunit of PI3K, and thereby enhances p53 activity through the negative loop between PI3K-AKT-MDM2 and p53 (93).

Regulation of c-myc by miRNAs

c-Myc, a transcription factor encoded by MYC oncogene, regulates the expression of genes involved in the biogenesis of ribosomes and mitochondria, and regulation of glucose and glutamine metabolism (94). In concert with E2F1, c-Myc induces genes involved in nucleotide metabolism and DNA replication, whereas in association with HIF-1 α it programs the adaptive response of cells to hypoxic conditions. Deregulated expression of c-myc has been observed in a variety of tumors. According to an estimate, approximately 40% of all the tumors are associated with increased expression of c-myc (95). Study indicates that over expression of c-myc directly alters glucose metabolism in tumor cells (96).

The cross talks between c-myc and miRNA essentially regulates cell cycle progression, survival, metabolism, angiogenesis and vascularization in tumors (97). c-Myc regulated cancer metabolism has garnered much interest in the recent years. A number of upcoming studies strongly point to the integrated role of c-myc and miRNAs in reprogramming the cancer metabolism. miR-17-92 cluster, which accelerates the effects of c-myc on cell survival and metastasis, is also associated with abnormal glucose metabolism in cancer cells (98, 99). miR-19, a component of miR-17-92 cluster activates the Akt-mTOR pathway, thereby functionally antagonizing Pten to promote cell survival and metabolism (100). Downstream target of miR-17-92 cluster, PI(3)K signaling, strongly promotes the glucose metabolism and fatty acid synthesis by upregulating glucose transport and glycolytic enzyme activity and inhibition of this pathway essentially changes the metabolic fate of a normal cell (100).

Regulation of HIFs by miRNA

Under conditions of low oxygen tension or hypoxia, mammalian cells elicit an array of cellular processes to maintain their survival by enhancing glycolysis. The induction of genes under hypoxia is triggered mostly by Hypoxia-Inducible Factor 1 alpha (HIF1 α), which is a basic helix-loop-helix transcription factor of the PAS family (101). The transcription factor is functional as a heterodimer of HIF1 α and HIF1 β . While both HIF1 α and HIF1 β are constitutively transcribed and translated, only HIF1 α protein is rapidly degraded under conditions of oxygen availability (normoxia) by ubiquitin-proteasomal pathway. The Von Hippel-Lindau (VHL) tumor suppressor binds to oxygen-dependent degradation domain and causes polyubiquitination and hence, degradation of HIF1 α . However, interaction of VHL with HIF1 α is dependent on prolyl hydroxylation of HIF1 α by HIF prolyl-4-hydroxylases (PHDs), which require oxygen, iron and 2-oxoglutarate as cofactors. Under hypoxic conditions the PHDs are inactive and HIF1 α is unhydroxylated, thus resulting in diminished

interaction with VHL and enhanced protein stability. The stable HIF1 α , in complex with HIF1 β , occupies hypoxia-responsive elements (HREs) and drives the transcription of hypoxia-responsive genes. One of the key cellular programs driven by HIF1 α is the induction of glycolysis in the tumor cells, which is triggered by HIF1 α -dependent upregulation of genes involved in glucose uptake (GLUT1), glycolysis, lactate production (LDHA), secretion of lactate (LDHA) and blockage of entry of glucose into the TCA cycle (PDK1) (102). Hence, miRNA-mediated changes in the expression levels of any of the genes, which regulate HIF levels, result in alterations in the HIF activity and hence, the flux of glucose through glycolytic or TCA cycle pathways.

HIF1 α expression is a direct target of miR-199a. Overexpression of miR-199a completely abolishes HIF-1 α levels under hypoxia (103). Under normoxia conditions, miR-199a can also cause upregulation of HIF-1 α by targeting and degrading Sirtuin (Sirt)1, which is also a direct target of miR-199a and is responsible for downregulating prolyl hydroxylase 2, required for stabilization of HIF-1 α . Several other miRNA-mediated mechanisms are also involved in the stabilization of HIF1 α . miR-200b, miR-200c, and miR-429 target PHD 2 and demonstrate significant neuroprotective effect induced early in ischemic preconditioning or focal cerebral ischemia (104). Another example of miRNA-mediated regulation of HIF1 α activity is observed in chronic lymphocytic leukemia (CLL), which express constitutive levels of HIF-1 under normoxia (105). Such stabilization of HIF1 α is caused by miRNA, miR-92-1 that targets VHL mRNA for degradation. Several other miRNAs, whose levels are altered in multiple cancers, are predicated to target VHL, namely, miR-20a, miR-20b, miR-21, miR101, miR-106a, miR-106b, miR150, and miR-200b (106). miR-424, a hypoxia-inducible miRNA, targets cullin 1 (CUL2), a scaffolding protein critical to the assembly of ubiquitin ligase system, and hence, stabilizes HIF1 α (107). Recent studies by Kelly et al. identified enzyme glycerol-3-phosphate dehydrogenase 1-like (GPD1L) as a novel regulator of HIF-1 α stability and a direct target of miR-210. HIF-1 α levels are stabilized by decreased levels of GPD1L, in response to miR-210 expression, resulting in an increase in HIF-1 α target genes. The hypoxia-induced miR-210 represses GPD1L, and increases of HIF-1 α protein levels by contributing to suppression of PHD activity (108). Most of the effects of HIF1 α on transcription of metabolic genes are direct, however, HIF1 α also regulates a number of miRNAs, including miR-210, which regulate a plethora of genes involved in diverse physiological functions. miR-210 is significantly overexpressed in multiple cancers (109–112). Under hypoxic conditions, miR-210 represses ISCU1/2 and thus, decreases the activity of prototypical iron-sulfur proteins controlling mitochondrial metabolism, including Complex I and aconitase (113). Hence, miR-210 represses mitochondrial respiration and might indirectly facilitate aerobic glycolysis in cancer.

Some miRNAs can influence overall glucose homeostasis in the body by mechanisms independent of aerobic glycolysis. miR-375 is one such miRNA that regulates glucose homeostasis in the body by modulating insulin secretion. Its overexpression in beta cells inhibits insulin exocytosis by mechanisms that are independent of alterations in the transmembrane Ca²⁺-fluxes and intracellular Ca²⁺-signaling (114). Independent studies have indicated that the regulation of glucose homeostasis by miR-375 could be mediated by modulation of PI3kinase signaling pathway in pancreatic beta cells (115). The expression levels miR-375 are significantly downregulated in pancreatic adenocarcinoma cells (116, 117). However, the exact effect of the downregulation on glucose metabolism, and the potential targets in the tumor cells are not yet known.

Future Perspectives

miRNAs have emerged as very significant regulators of glucose metabolism. However, most of the miRNA predictions yet need to be verified. Several questions persist as to how

miRNAs modulate the metabolism to facilitate changes in the metabolic profile of tumor cells as they leave the sites of primary tumor and migrate through the blood stream to colonize and metastasize at a distant site. Also, the functional significance of mutations in the 3'-UTRs of oncogenes to render them unresponsive to the tumor suppressor miRNAs, is only beginning to be understood. Ongoing and future studies will determine the therapeutic efficacies of targeting miRNAs to reverse the metabolic phenotype of the tumor cells.

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Table 1

miRNAs that directly target genes involved in aerobic glycolysis.

Metabolic Function	miRNA	Target gene	Reference
Glucose uptake	miR-223	GLUT4	(36)
	miR-133	GLUT4	(37)
Glycolysis	miR-200 family	PGI	(38)
	miR-122	ALDOA	(39)
	miR-15a/16-1 cluster	TPI1, ALDOA, ALDO6A1	(42)
	miR-29a	PGM1, ENO1, PGK1	(43).
	miR-326, miR-133a, miR-133b	PKM2	(46)
Lactate secretion	miR-29a, miR-29b and miR-124	MCT1	(47)
	let-7b	CD147	(51)