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Review

Emergence of MicroRNAs as Key Players in Cancer Cell Metabolism

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BACKGROUND: Metabolic reprogramming is a hallmark of cancer. MicroRNAs (miRNAs) have been found to regulate cancer metabolism by regulating genes involved in metabolic pathways. Understanding this layer of complexity could lead to the development of novel therapeutic approaches.

CONTENT: miRNAs are noncoding RNAs that have been implicated as master regulators of gene expression. Studies have revealed the role of miRNAs in the metabolic reprogramming of tumor cells, with several miRNAs both positively and negatively regulating multiple metabolic genes. The tricarboxylic acid (TCA) cycle, aerobic glycolysis, de novo fatty acid synthesis, and altered autophagy allow tumor cells to survive under adverse conditions. In addition, major signaling molecules, hypoxia-inducible factor, phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin/phosphatase and tensin homolog, and insulin signaling pathways facilitate metabolic adaptation in tumor cells and are all regulated by miRNAs. Accumulating evidence suggests that miRNA mimics or inhibitors could be used to modulate the activity of miRNAs that drive tumor progression via altering their metabolism. Currently, several clinical trials investigating the role of miRNA-based therapy for cancer have been launched that may lead to novel therapeutic interventions in the future.

SUMMARY: In this review, we summarize cancer-related metabolic pathways, including glycolysis, TCA cycle, pentose phosphate pathway, fatty acid metabolism, amino acid metabolism, and other metabolism-related oncogenic signaling pathways, and their regulation by miRNAs that are known to lead to tumorigenesis. Further, we discuss the current state of miRNA therapeutics in the clinic and their future potential.

Altered cellular metabolism is a hallmark of cancer with modified metabolic features observed across many cancer types *(1)*, supporting cell survival and cell growth, in particular under conditions of oxygen and nutrient stress.

One of the most common hallmarks of cancer cells is their high rate of glucose consumption, which supports rapid tumor growth and adaptation to metastatic environments (Fig. 1) *(2)*. As shown in Fig. 1, glucose is diverted from the tricarboxylic acid (TCA)[3] cycle (green) to glycolysis (red), even under aerobic conditions, resulting in the generation of large amounts of lactate, also known as the Warburg effect. Tumor cells also rely on glutamine metabolism, which provides the carbon and amino-nitrogen biomass needed for protein, nucleotide, and lipid biosynthesis. Lipid metabolism pathways are also important with observations that cancer cells satisfy demands for lipids by either increasing the uptake of exogenous lipids and lipoproteins or upregulating their endogenous synthesis. Many of these metabolic changes are controlled by oncogenic signals such as myelocytomatosis oncogene cellular homolog (MYC), hypoxia-

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[3] Nonstandard abbreviations: TCA, tricarboxylic acid; MYC, myelocytomatosis oncogene cellular homolog; HIF, hypoxia-inducible factor; AKT, protein kinase B; AMPK, 5′ AMP-activated protein kinase; miRNA, microRNA; UTR, untranslated region; PPP, pentose phosphate pathway; GLUT, glucose transporter; PCa, prostate cancer; HK2, hexokinase 2; PFKL, phosphofructokinase, liver type; OXPHOS, oxidative phosphorylation; PKM, pyruvate kinase M1/2; HCC, hepatocellular carcinoma; LDHA, lactate dehydrogenase A; 5-FU, fluorouracil; α-KG, α-ketoglutarate; PDH, pyruvate dehydrogenase complex; PDHX, pyruvate dehydrogenase protein X component; PDK, pyruvate dehydrogenase kinase; IDH, isocitrate dehydrogenase; ASCT2, ASC family transporter 2; GLS, glutaminase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ACLY, ATP citrate lyase; SCD1, stearoyl-CoA-desaturase; SREBP, sterol regulatory element binding protein; SIRT1, sirtuin 1; PHGDH, phosphoglycerate dehydrogenase; SHMT, serine hydroxymethyl transferase; PSAT1, phosphoserine aminotransferase 1; BCAA, branched-chain amino acid; BCKD, branched-chain α-ketoacid dehydrogenase; BCAT1, branched-chain amino acid transaminase 1; CAT, cationic amino acid transporter; DPYD, dihydropropyrimidine dehydrogenase; G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; EMT, epithelial–mesenchymal transition; PRODH/POX, proline dehydrogenase; P5C, Δ(1)-pyrroline-5-carboxylate; LKB1, liver kinase B1; mTOR, mechanistic target of rapamycin; TP53, tumor protein 53; TIGAR, TP53-induced glycolysis and apoptosis regulator; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; NSCLC, non-small cell lung cancer; PTEN, phosphatase and tensin homolog; CAF, cancer-associated fibroblast; IDH3α, isocitrate dehydrogenase 3 complex.

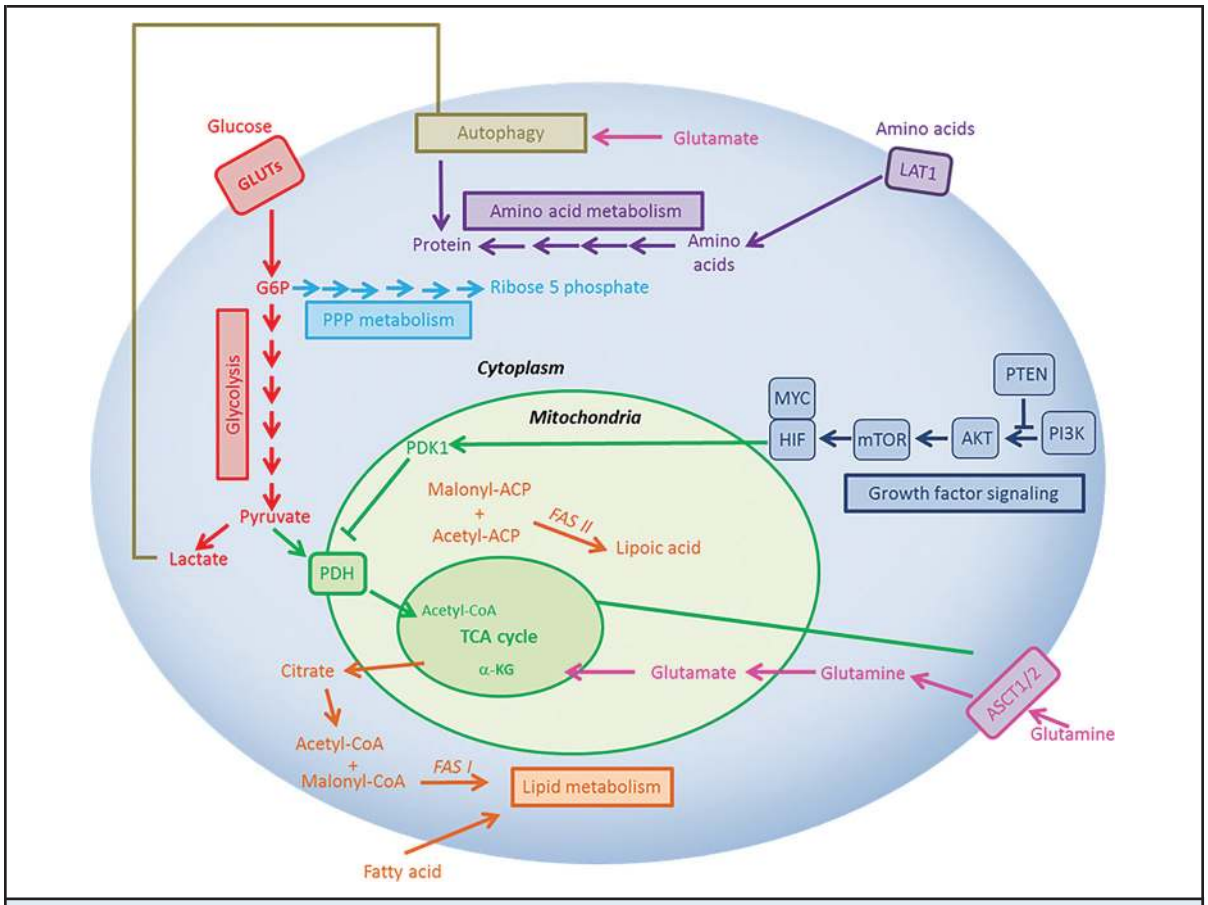

Fig. 1. Overview of the metabolic pathways deregulated in cancer.

Reprogramming of glycolysis, the PPP, TCA cycle, fatty acid synthesis, amino acid synthesis, lipid metabolism and autophagy occurs in cancer, along with the associated oncogenic signaling pathways that directly affect cancer cell metabolism. LAT1, L-type amino acid transporter 1; FAS I/II, fatty acid synthase; ACP, acyl carrier protein.

inducible factor 1-α (HIF-1α), protein kinase B (AKT), and 5′ AMP-activated protein kinase (AMPK) and are supported by scavenging pathways such as autophagy that supplement metabolites to support tumor cell growth.

This review focuses on the role of microRNAs (miRNAs) in cancer-associated metabolic reprogramming. miRNAs, the short noncoding RNAs (20–24 nucleotides), bind to their target mRNAs mostly within the 3′ untranslated region (UTR) but also 5′ UTR and coding regions, and play dual regulatory roles in gene regulation both by translational and mRNA repression and/or by mRNA stabilization *(3)*. Because of their emerging roles as key players in tumor metabolism and progression, here we discuss the evidence that cancer-regulating miRNAs may represent potential biomarkers and new therapeutic targets for cancer.

As miRNAs are known to regulate various metabolic processes either directly or indirectly, we have discussed their diverse roles in the following sections with additional reference to the expression and functional impact of miRNAs in Table 1 of the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol65/issue9.

Direct Regulation of Cancer Metabolism Enzymes by miRNAs

The reprogramming of cancer cells by increased glucose, fatty acid, amino acid, and pentose phosphate pathway (PPP) is a metabolic hallmark that supports tumorigenesis. Many enzymes in these pathways are under the regulation of miRNAs, and a detailed understanding of the role of miRNAs in these pathways may provide promising therapeutic targets for malignant progression as discussed below.

miRNAs TARGET GLUCOSE TRANSPORTERS AND GLYCOLYSIS ENZYMES

The first step in glycolysis is the entry of glucose into cells via glucose transporters (GLUTs). GLUTs are one of the

most important proteins controlling glycolysis and are overexpressed in many tumors. Among the 14 GLUT subtypes, GLUT1 has been the most widely studied in cancer, and its expression is shown to be increased in cancer tissues compared with adjacent normal tissue in prostate and colorectal cancers *(4, 5)*, in addition to a positive correlation with poor prognosis. Increased glucose uptake leading to increased lactate production via glycolysis has been shown to have a positive impact on prostate cancer (PCa) cell growth. In addition, the GLUT1 suppressor, miR-132, has been reported to be downregulated in several cancers, resulting in high GLUT1 expression and enhanced glucose uptake *(6)*. Similarly, other miRNAs, including miR-451, miR-144, miR-340, and miR-148b, suppress GLUT1-mediated glucose uptake, and the GLUT1-targeting miR-218 increased sensitivity of T24 and EJ bladder cancer cells to the chemotherapy agent cisplatin *(7)*.

Like GLUT1, GLUT3 expression, which correlates with poor survival in a number of cancers, is also regulated by cancer-associated miRNAs (see Table 1 in the online Data Supplement). Decreased GLUT3-mediated glucose uptake in T24 bladder cancer cells by miR-195–5p resulted in suppression of cell growth and increased apoptosis *(8)*, and miR-106a, which is frequently downregulated in a number of cancers, has been shown to target GLUT3 in glioma cells, decreasing glucose uptake and cell proliferation *(9)*.

In addition to GLUTs, a cascade of enzymes involved in glycolysis are regulated by miRNAs (see Table 1 in the online Data Supplement and Fig. 2). For example, hexokinase 2 (HK2), the first and rate-limiting enzyme in glucose metabolism that phosphorylates glucose to glucose-6-phosphate, has been shown to be regulated by miRNAs in several cancers. The direct targeting of HK2 by miR-143 altered glucose consumption and lactate production in prostate, lung, and colon cancer cells *(10)*, and miR-181b abrogated glycolysis in PC3 PCa cells, acting as a mediator between enhancer of zeste homolog 2 and HK2 *(11)*. In addition, the dual function of miRNAs in regulating glycolysis via HK2 has been demonstrated with both miR-199a-5p and miR-98 acting as tumor suppressors and miR-155, as an oncogenic miRNA to regulate HK2 *(12)*.

Another important enzyme, downstream of HK2, phosphofructokinase liver type (PFKL), when regulated by the miR-128–PFKL–AKT axis, modified AKT phosphorylation and mediated a metabolic shift from glycolysis to oxidative phosphorylation (OXPHOS) in NCI-H460 lung cancer cells *(13)*. This altered signaling led to decreased glucose uptake and lactate production in addition to increased cellular ATP content. Other glycolysis enzymes regulated by miRs include 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB) family members. PFKFB2 inhibition by miR-421 reduced glycolysis, cell migration, and cell viability in PCa cells, and regulation of PFKFB3 by miR-26b led to reduced proliferation, migration, invasion, and glycolysis in osteosarcoma cells *(14)*.

miRNAs also influence the regulation of pyruvate kinase (PKM). PKM is a rate-limiting glycolytic enzyme that regulates net ATP production with 2 isoforms: PKM1 and PKM2. PKM2 is highly expressed in proliferating cancer cells promoting glycolysis, whereas PKM1 is the predominant isoform in differentiated tissues that predominantly utilize OXPHOS *(15)*. PKM2 downregulation by miR-122 has been shown to decrease the occurrence of metastasis in breast and hepatocellular carcinoma (HCC) cells *(16)*, suggesting a critical role for these changes to glucose metabolism in facilitating metastasis. Further, miR-124 suppressed PC3 PCa cell growth by directly targeting PKM2 *(17)*. A second level of indirect regulation of PKM occurs by miRNAs controlling the expression of PKM alternative splicing protein complex (polypyrimidine tract-binding protein 1/hnRNAPA1/hnRNAPA2), with these splicing proteins shown to be targeted by miR-124, miR-137, miR-340, miR-1, and miR-133b in colon and colorectal cancer *(18)*. miR-133b overexpression has also been shown to resensitize A549 radio-resistant lung cancer cells via downregulating the glycolytic pathway, suggesting miR-133b as a potential therapeutic target for radio resistance *(19)*. Interestingly, miR-326 was upregulated upon resveratrol treatment in cervical, colon, breast, and HCC cell lines, leading to miR-326-mediated inhibition of PKM2, which demonstrates a potential antitumor role of this miRNA *(20)*.

Lactate dehydrogenase A (LDHA) catalyzes the final step of glycolysis converting pyruvate to lactate (Fig. 2). This is a junction of the glucose fate, where pyruvate can either be converted to lactate to yield 2 ATPs or enter the TCA cycle to ultimately yield 36 ATPs. Flux through this pathway will be affected by how much of the glucose in tumor cells will be shunted into biosynthetic pathways such as pentose phosphate and serine synthesis pathways, as we will discuss later in the review. Nevertheless, there is still a high level of lactate production that has been linked to enhanced tumorigenesis and therapy resistance, highlighting the critical regulation of LDHA in tumor cells. LDHA has been shown to be regulated by miRNAs such as miR-34c, miR-369–3p, miR-374a, miR-4524a/b, and miR-34a *(21)*. Whereas overexpression of miR-34a resulted in LDHA downregulation and reduced lactate production in colorectal cancer cells, upregulation of miR-34a led to resensitization of fluorouracil (5-FU)-resistant DLD-1 colon cancer cells by reducing lactate production through direct regulation of LDHA, as well as resensitization of radio-resistant HepG2 HCC cells *(21–23)*. These studies provide further data that miRNAs could be a potential target for overcoming chemotherapy and radiotherapy resistance in cancer.

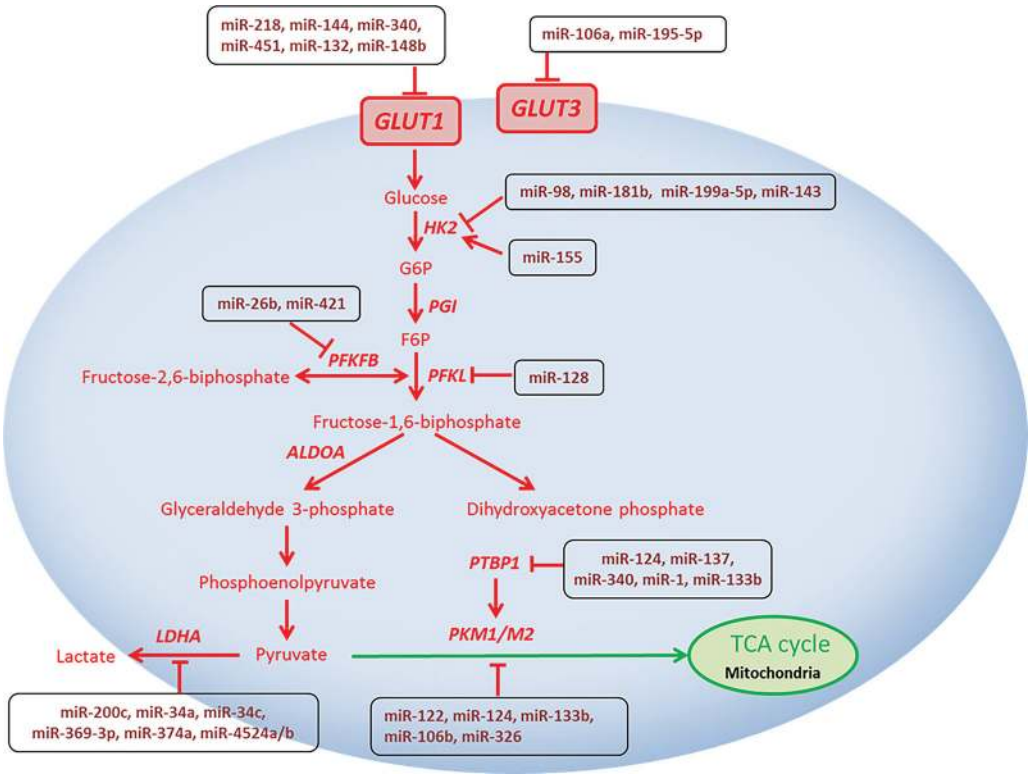

Fig. 2. Overview of miRNAs involved in glucose uptake and glycolysis.

Glucose transporters GLUT1 and GLUT3 are negatively regulated by miRNAs altering glucose uptake in the cell. Other genes, such as *HK2, PFKL, PFKB, PTBP1, PKM,* and *LDHA,* are also negatively regulated by miRNAs, although miR-155 positively regulates *HK2* (see also Table 1 in the online Data Supplement). Human genes: *ALDOA,* aldolase; *HK2,* hexokinase 2; *LDHA,* lactate dehydrogenase A; *PFKFB,* 6-phosphofructo-2-kinases/fructose-2,6-biphosphatases; *PFKL,* phosphofructokinase, liver type; *PGI,* phosphoglucose isomerase; *PKM,* pyruvate kinase M1/2; *PTBP1,* polypyrimidine tract binding protein 1.

miRNAs TARGETING THE TCA CYCLE

Although many cancer cells have upregulated glycolysis and lactate production, mitochondrial OXPHOS via the TCA cycle remains an important metabolic pathway. In addition to ATP, the TCA cycle is supplemented by glutamate conversion to α-ketoglutarate (α-KG), producing critical intermediates such as citrate, which is used in the biosynthesis of lipids. Current evidence indicates that miRNAs regulate the TCA cycle both directly and indirectly (see Table 1 in the online Data Supplement and Fig. 3).

In the first step of the TCA cycle, pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase (PDH). This enzyme acts as a gatekeeper to pyruvate entering the TCA cycle via a highly regulated multi-unit enzyme containing 3 catalytic and 2 regulatory subunits tethered by a noncatalytic E3 binding protein called pyruvate dehydrogenase protein X component (PDHX) *(24)*. The activity of PDH is primarily regulated via phosphorylation by pyruvate dehydrogenase kinases 1 through 4 (PDK1–4) *(25)*. Four isomeric forms of PDKs are expressed in a tissue-specific manner in mammals: PDK1 is exclusively expressed in heart and pancreatic islet; PDK2 is found in all tissues but mostly in the kidney and liver; PDK3 is found in liver and testis; and PDK4 is mostly expressed in liver, heart, and skeletal muscle. In tumors, PDK1 has been reported to be upregulated in gastric cancer, HCC, melanoma, and renal cell carcinoma; PDK2 is upregulated in breast cancer; PDK3 is overexpressed in colon cancer; and PDK4 is upregulated in glioblastoma. Upregulation of PDKs is associated with poor prognosis of various cancers. PDHX has been shown to be regulated by miR-26a in HCT116 colorectal cancer cells, where it inhibited PDHX expression by directly targeting the 3′ UTR *(26)* and reduced the conversion of pyruvate to acetyl-CoA. In this manner, miR-26a can inhibit the key rate-limiting step of glycolysis entry into the TCA cycle, adding another layer of control

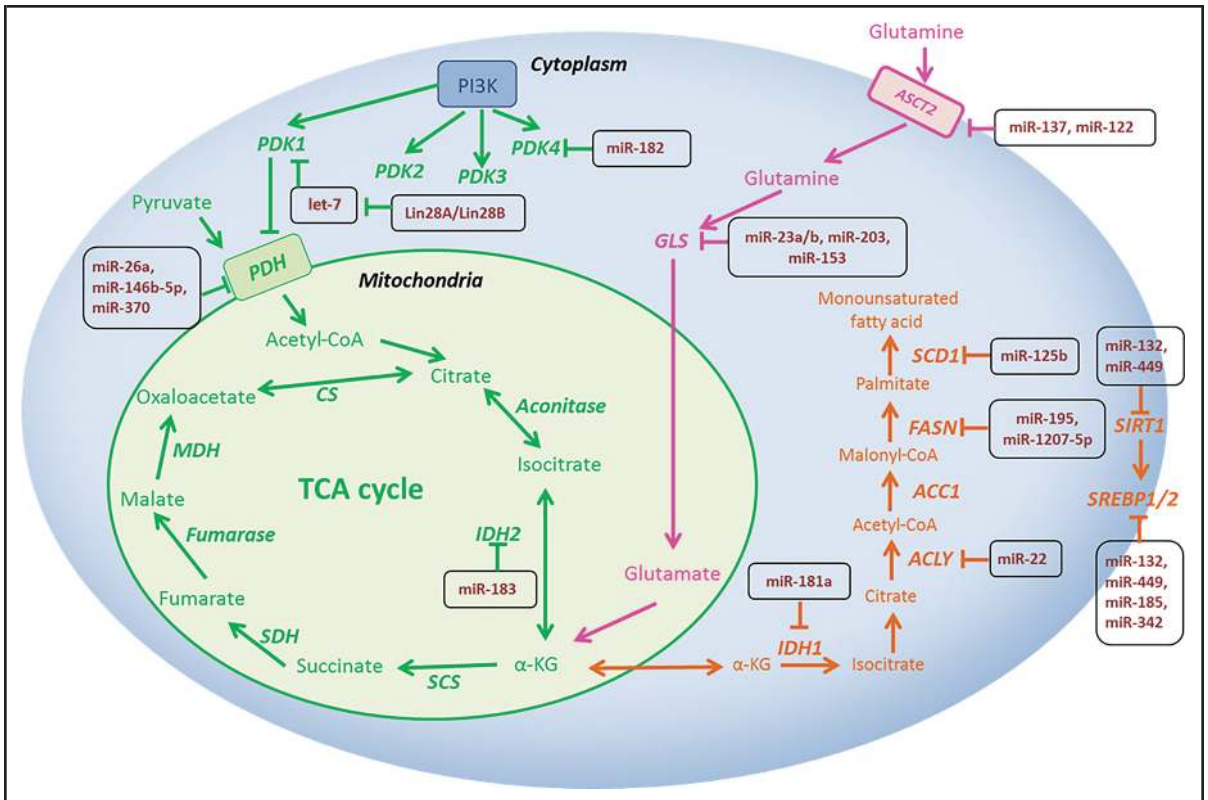

Fig. 3. The steps in the TCA, glutamine, and lipogenesis cycle regulated by miRNAs.

miRNAs can regulate the TCA, glutamine, and lipogenesis cycle by modulating the expression of PDH, PDKs, ASCT2, GLS, IDH, SDH, SREBP1/2, ACLY, FASN, IDH1, SCD1, and SIRT1. PDH, PDK1, PDK4, GLS, IDH2, ASCT2, IDH1, ACLY, SCD1, FASN, SREBP1/2, and SIRT1 are negatively regulated by miRNAs, whereas PDK1 is indirectly positively regulated by LIN28A/28B (see Table 1 in the online Data Supplement). CS, citrate synthase; MDH, malate dehydrogenase; SCS, succinyl coenzyme A synthetase; SDH, succinate dehydrogenase.

of glucose metabolism *(26)*. Other subunits of PDH are known to be regulated by miRNAs, including PDHB, which is down-regulated by miR-146b-5p and miR-370, contributing to the malignant development of colorectal and melanoma cancer *(27, 28)*. Other PDH subunits such as PDHA1 and PDHB are part of a group of enzymes directly regulated by Lin28A/Lin28B, including HK1 and PDK1 also indirectly via let-7, which together promote Warburg-like metabolic reprogramming *(29)*. In contrast, let-7 activates the PDH complex by directly suppressing PDK1 *(29)*. PDK4 has also been shown to be inhibited by miR-182, which promoted lung tumorigenesis via modulation of PDH activity, and an inverse correlation between miR-182 and PDK4 expression in human lung adenocarcinomas was reported *(30)*. Citrate, an important component of the TCA cycle, is either exported to the cytoplasm or converted to isocitrate by aconitase and α-KG by the enzyme isocitrate dehydrogenase (IDH) (Fig. 3). Suppression of IDH2 by miR-183 has been shown to decrease the cellular levels of α-KG, leading to an increase in aerobic glycolysis in glioma cells *(31)*.

Glutamine anaplerosis (intermediates) can supplement α-KG, and high amounts of glutamine are consumed by proliferating cells, providing a major source of energy for cancer cells with the glutamine transporter, ASC family transporter 2 (ASCT2), frequently upregulated in tumors. miR-137 has been shown to inhibit ASCT2, leading to reduced glutamine metabolism and affecting cell survival in colorectal carcinoma, glioblastoma, prostate, and pancreatic cancers, and ASCT2 was regulated by miR-122 in 293T cells *(32)*. Once inside the cell, glutamine is converted to glutamate by the enzyme glutaminase (GLS) and then subsequently converted into α-KG (Fig. 3). c-Myc-mediated repression of miR-23a and miR-23b resulted in higher expression of their target protein, GLS, which enhanced glutamine metabolism in B-cell lymphoma and PCa cells, leading to increased proliferation of the cancer cells *(33)*. In contrast, overexpressing miR-23a in leukemic cells inhibited

the expression of GLS protein and induced cell death *(33)*, highlighting the importance of this pathway. Further, miR-153 controlled glutamine utilization, and glutamate generation targets GLS in U87MG and U373MG glioblastoma cells *(34)*. Recent studies indicate that miRNAs play a role in chemosensitization via regulation of glutamine metabolism demonstrated by overexpression of miR-203, which sensitized HT144 malignant melanoma cancer cells to the chemotherapy drug temozolomide via the inhibition of GLS *(35)*.

REGULATION OF FATTY ACID METABOLISM/LIPOGENESIS

Solid tumors require high levels of energy in the form of lipids for growth and membrane synthesis and to provide precursors for promoting signal transduction. However, changes in lipid metabolism also contribute to cell survival under stress and chemoresistance. Some tumors, e.g., PCa, mainly depend on lipid oxidation rather than glucose utilization as their main energy source *(36)*.

The synthesis of de novo fatty acids starts from acetyl-CoA and NADPH, which are synthesized from the TCA cycle and the PPP (Fig. 3). In addition, acetyl-CoA is carboxylated by acetyl-CoA carboxylase (ACC) forming malonyl-CoA, and the malonyl-CoA, along with the acetyl-CoA condensation reaction, is catalyzed by fatty acid synthase (FASN) to produce palmitic acid (Fig. 3). Several lines of evidence demonstrate miRNA-mediated regulation of the lipogenic enzymes, such as ACC, FASN, ATP citrate lyase (ACLY), and stearoyl-CoA-desaturase (SCD1).

Sterol regulatory element binding proteins (SREBPs) are a family of transcription factors that regulate cholesterogenesis and lipogenesis by controlling expression of a range of genes that are involved in lipid metabolism. There are 3 isoforms for SREBP—1a, 1c, and 2—which have diverse roles in lipogenesis *(37)*. Sirtuin 1 (SIRT1), a NAD^+-dependent deacetylase, regulates a series of genes involved in the regulation of lipids, and miR-132-mediated inhibition of SIRT1 and SREBP-1c expression in U251 and U87 glioma cells suppresses their target genes, including 3-hydroxy-3-methylglutaryl-CoA reductase and FASN *(38)*. Similarly, miR-449 in hepatoma cells and miR-185 and miR-342 in PCa suppress SIRT1 and SREBP-1c expression *(39, 40)*. Further downstream, overexpression of miR-1207–5p and miR-195 exerts antitumor effects in HCC and PCa by inhibiting FASN *(41, 42)*, demonstrating multiple regulation mechanisms in malignancy.

Another cytoplasmic enzyme, IDH1, is an important contributor of lipid synthesis. The miR-181a–IDH1 interaction decreases expression of genes involved in lipid synthesis and increases expression of genes involved in β-oxidation, ultimately reducing lipid accumulation. In addition, ACLY, the key enzyme involved in de novo lipid synthesis, is upregulated in cancer cells *(43)*, and miR-22 inhibited of ACLY in osteosarcoma, prostate, cervical, and lung cancer cells *(43)*, demonstrating the dependence of a wide range of cancers on lipid metabolism. The enzyme SCD-1 catalyzes the conversion of mono-unsaturated fatty acids from saturated fatty acids, and inhibition of its activity by miR-125b impairs lipid desaturation. In vivo studies showed that injection of miR-125b significantly reduced hepatic triglyceride concentration *(44)*.

Despite the current research focus on glucose metabolism in cancer, the studies above (see Table 1 in the online Data Supplement and Fig. 3) underline the importance of miRNA-mediated regulation of fatty acid absorption, elongation, and oxidation in a wide range of cancers. It is likely that other miRNAs will be identified in future that target additional rate-limiting enzymes in lipid metabolism with emerging roles in cancer.

REGULATION OF AMINO ACID METABOLISM

As mentioned above, tumor cells have an increased, sometimes exquisite, requirement for amino acids to facilitate rapid growth and control oxidative stress. Serine and glycine are essential for synthesis of nucleotides, and the deprivation of these 2 amino acids inhibits tumorigenesis *(45)*. Although cells can generally acquire serine via synthesis or uptake, recent literature suggests a subset of tumors are dependent on de novo serine synthesis, regardless of extracellular availability *(45)*. This has sparked a renewed interest in defining the molecular features of these cells and the design of inhibitors to target key enzymes in this pathway, including phosphoglycerate dehydrogenase (PHGDH) and serine hydroxymethyl transferase (SHMT). De novo synthesis of both serine and glycine starts from 3-phosphoglycerate and ends with the conversion of 3-phosphoglycerate to serine. Serine is further converted to glycine by SHMT consisting of 2 isoforms, SHMT-1 and SHMT-2, which are expressed in the cytoplasm and mitochondria, respectively *(46)*. Although targeting of SHMT2 by miR-193b reduces MCF-7 breast cancer cell growth (see Table 1 in the online Data Supplement and Fig. 4), a strong negative correlation was also observed between overexpression of miR-198 and SHMT1 expression in lung adenocarcinoma *(47)* with significant inhibition of cell proliferation, increased cell apoptosis, and induced cell cycle arrest both in vitro and in vivo *(47)*. Similarly miR-340 was observed to directly regulate phosphoserine aminotransferase (PSAT1) in an esophageal squamous cell carcinoma xenograft mouse model *(48)*.

Amino acids are largely imported into the cell through a series of specific and nonspecific transporters and antiporters. The branched-chain amino acids (BCAAs) leucine, isoleucine, and valine play important roles in insulin secretion and protein turnover and have a putative role in amino acid regulation in cancer cells. For

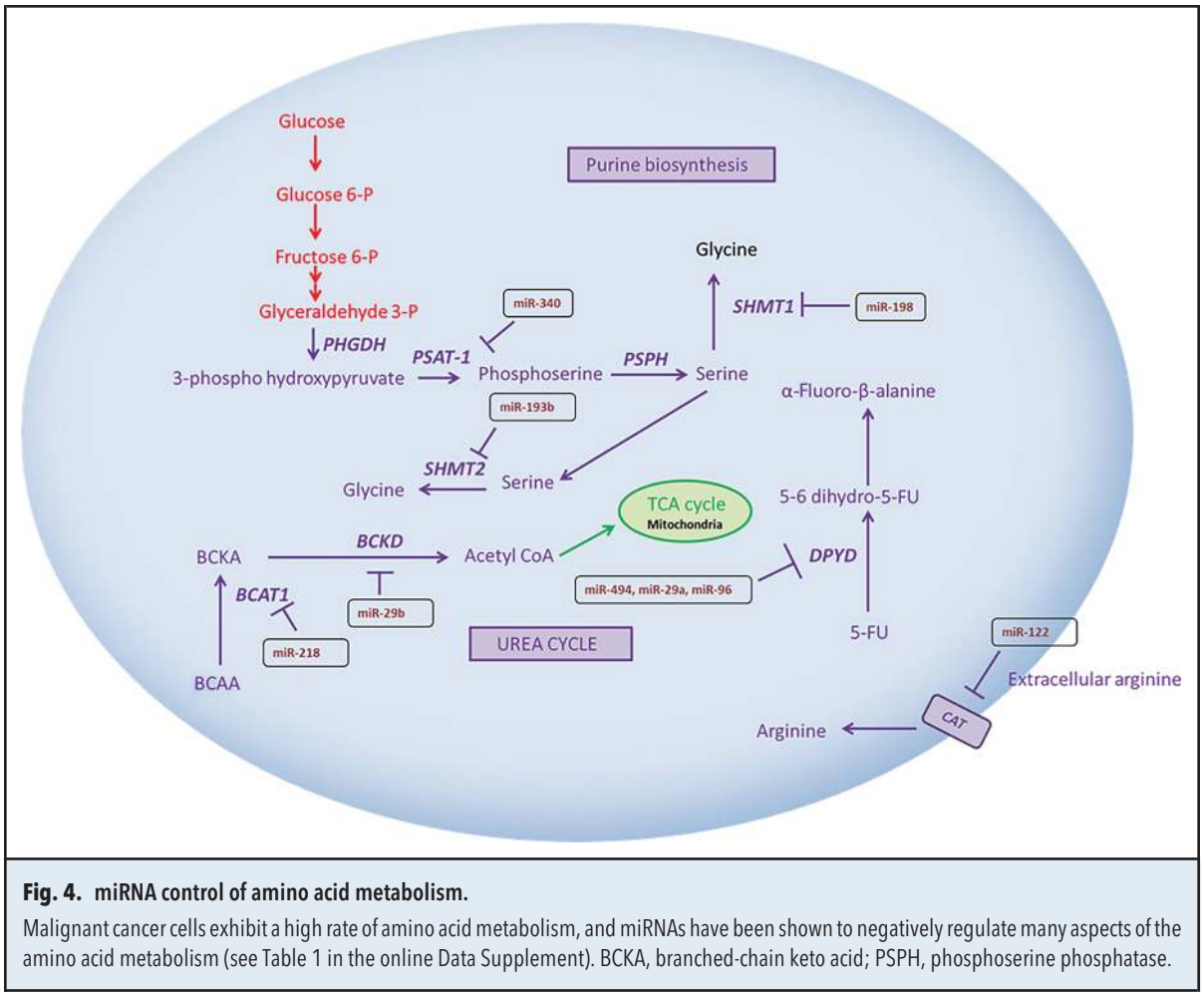

Fig. 4. miRNA control of amino acid metabolism.

Malignant cancer cells exhibit a high rate of amino acid metabolism, and miRNAs have been shown to negatively regulate many aspects of the amino acid metabolism (see Table 1 in the online Data Supplement). BCKA, branched-chain keto acid; PSPH, phosphoserine phosphatase.

example, branched-chain α-ketoacid dehydrogenase (BCKD) catalyzes the irreversible step in BCAA catabolism. miR-29b targets the mRNA for the dihydrolipoyl branched-chain acyltransferase component of the BCKD complex and prevents its translation in mammals *(49)*. In addition, Zhu et al. reported that miR-218 negatively regulates branched-chain amino acid transaminase 1 (BCAT1) protein expression and contributes to the increased sensitivity to cis-diaminedichloroplatinum treatment in PC3 and DU145 PCa cells *(50)*. In addition, cationic amino acid transporter (CAT-1) mRNA is translationally repressed by miR-122, thus regulating amino acids in Huh7 HCC cells *(51)*. Further evidence suggests that miR-494 sensitizes the colon cancer cell line, SW480, to 5-FU treatment by targeting dihydropyrimidine dehydrogenase (DPYD), an enzyme involved in amino acid metabolic pathways including that of β-alanine metabolism *(52)*. miRNAs miR-29a and miR-96 target DPYD and are known to be involved in amino acid metabolism *(53)* (Fig. 4). In particular, miR-21 and miR-30d are predicted to target valine, leucine, isoleucine, alanine, aspartate, and glutamate pathways, resulting in reduced sensitivity to 5-FU chemotherapy for colorectal cancer *(53)*. Overall, these data suggest that miRNAs have the capacity to regulate one or multiple genes involved in amino acid metabolism, and this has the potential to open up context-driven translational opportunities.

REGULATION OF THE PPP

The PPP is initiated by conversion of glucose to glucose-6-phosphate (G6P) by hexokinases sequestered from glycolysis. PPP activity has been reported to be upregulated in many cancers *(54)*. Tumor cells utilize pentose phosphates for their high rate of nucleic acid synthesis, with NADPH providing precursors for both the synthesis of fatty acids and contributing to cell survival as a scavenger of reactive oxygen species. The high activity of this pathway in cancer cells in part accounts for the typically high glucose consumption.

Expression of glucose-6-phosphate dehydrogenase (G6PD), which is involved in the first reaction of PPP,

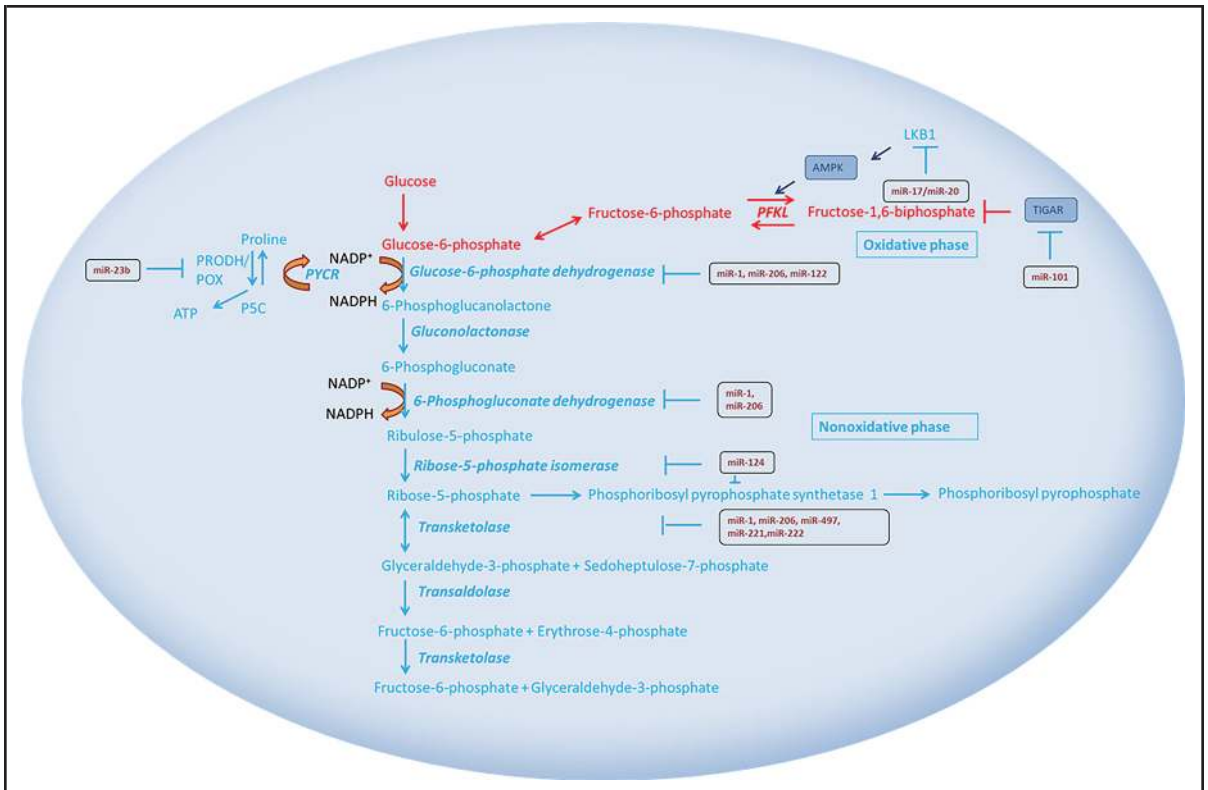

Fig. 5. miRNA regulation of PPP metabolism.

miRNAs negatively mediate the PPP by directly or indirectly regulating the expression of enzymes that are involved in the PPP (see Table 1 in the online Data Supplement). PYCR, P5C reductase.

has been shown to be negatively regulated by miR-1, miR-122, and miR-206 *(54)* (Fig. 5). The downstream effects of these miRs significantly impaired NADPH production and ribose synthesis, in addition to decreased in vivo tumor growth. Fulvestrant-resistant MCF7-FR breast cancer cells transfected with antisense to miR-221 showed increased expression of PPP-related enzymes, suggesting that miR-221 may target this pathway. The data also suggest that PPP may play a role in drug resistance in breast cancer *(55)*. Further, a study has demonstrated that miRNA plays a role in the epithelial–mesenchymal transition (EMT) via PPP enzymes. EMT is a key determinant of metastasis and activates metabolic rewiring in cancer cells. miR-200b has been shown to be modulated by G6PD, which resulted in downregulation of EMT through downregulation of E-cadherin and suppression of lung carcinoma cell migration *(56)*.

Proline dehydrogenase (oxides, PRODH/POX) catalyzes the first step in the proline degradative pathway linked to tumorigenesis. The proline cycle formed by the interconversion of proline and Δ(1)-pyrroline-5-carboxylate (P5C) between mitochondria and cytosol connects with the PPP. Moreover, proline is sequentially converted by PRODH/POX and P5C dehydrogenase to glutamate, a starting material of α-KG, linking proline metabolism with the TCA cycle. miR-23b directly targets PRODH/POX, leading to reduced protein levels and deregulation of the TCA cycle and PPP *(57)*.

The miR-17 seed family (abundant with miR-17, miR-20, and miR-92) is involved in metabolic reprogramming through negative regulation of the serine/threonine kinase, liver kinase B1 (LKB1) tumor suppressor. Studies have shown that suppression of LKB1 alters the PPP via downstream effects on AMPK and mammalian target of rapamycin (mTOR) signaling in lymphoma cells *(58)*. Another metabolism-related miRNA, miR-497, modulates chemosensitivity in HeLa cervical cancer cells through targeting transketolase *(59)*, which is a thiamine-dependent enzyme playing a key role in the channeling of excess glucose phosphates to glycolysis in the PPP *(59)*. Further, miR-124 suppresses DNA synthesis and proliferation by inhibiting multiple PPP enzymes in colorectal cancer cells *(60)*. As tumor protein 53 (TP53)-induced glycolysis and apoptosis regulator (TIGAR) increased the PPP levels in tumor cells, overexpression of miR-101 decreased G6PD expression and

NADPH levels and enhanced cisplatin-induced DNA damage in PCa cells by regulating TIGAR *(61)*. The dramatic phenotypes observed by PPP modulation suggest that targeting PPP by miRNAs could be a potential therapeutic opportunity to limit drug resistance and metastasis in various cancers.

Indirect Regulation of Metabolism by miRNAs

This section covers the principal indirect pathways that are involved in the reprogramming of metabolism, including signaling pathways such as HIF, TP53, MYC, AMPK, and AKT. Many important components of these pathways are shown to be indirectly regulated by miRNAs.

miRNAs REGULATION OF HIF-1α

Hypoxia is common in several types of solid tumors, as tumor cells under hypoxic conditions begin to adapt to low oxygen by activating several signaling pathways, including HIF-1α. Under hypoxic conditions, HIF-α subunits form heterodimers with HIF-1β that in turn regulate the expression of several miRNAs, which in turn are the direct mediator of metabolic adaptation. HIF-1α regulation by miRNAs is supported by many studies, and further details are discussed in the online Data Supplement.

REGULATION OF THE PI3K/AKT/MTOR/PTEN PATHWAY

AMPK is a major cellular energy regulator. AMPK activates AKT by regulating phosphatidylinositol-3 kinase (PI3K), and the PI3K family plays a major role in metabolism. The serine/threonine kinase AKT, which is located downstream of PI3K, gets phosphorylated upon activation of PI3K and targets multiple metabolic pathways.

miR-451 inhibited the PI3K/AKT signaling pathway in glioma cells *(62)*. In that study, AKT was shown to directly target glycolysis by regulating the localization of GLUT1 and suppressing the proliferation and invasion of glioma cells (see Fig. 1 in the online Data Supplement). Moreover, miR-30a-5p and miR-342–3p target the epidermal growth factor receptor and insulin-like growth factor receptor 1 signaling pathways and reduce epidermal growth factor receptor inhibitor resistance via regulating the PI3K/AKT signaling pathway in non-small cell lung cancer (NSCLC) and HCC cell lines *(63, 64)* (see Fig. 1 in the online Data Supplement). Furthermore, overexpression of miR-21 decreased phosphatase and tensin homolog (PTEN), increased p-AKT, and consequently increased HIF-1α expression, leading to autophagy in cervical cancer cells *(65)*. Similarly, miR-130b acts as an oncomir in HCC and breast cancer by regulating the PTEN/p-AKT/HIF-1α signaling pathway and promoting proliferation and EMT-induced metastasis *(65)*. Another miRNA, miR-370, inhibited gastric cancer metastasis through targeting PTEN and also inhibited apoptosis signaling and cell proliferation in cervical cancer cells. PTEN was also found to be directly regulated by miR-92a and miR-21 in NSCLC and colorectal cancer, respectively *(66, 67)*. Further, an anticancer effect of curcumin inhibited MCF-7 breast cancer cell growth by downregulating miR-21, leading to activation of PTEN *(68)*, and overexpression of miR-21 was found to induce a metabolic shift in bladder cancer cells by targeting PTEN. Thus, the accumulating evidence suggests that the PI3K/AKT/mTOR/PTEN pathway is both positively and negatively regulated by various miRNAs in a variety of cancers.

miRNAs AND AUTOPHAGY: ESTABLISHING THE LINK

Autophagy is a cellular catabolic degradation process that plays an essential role in tumor progression. Stress-induced autophagy leads to degradation of cellular organelles and proteins by lysosomes and provides energy to support cellular metabolism. A large number of studies have highlighted the importance of miRNAs in autophagy regulation. In our article, regulation of autophagy by miRNAs is discussed in detail in the online Data Supplement. In essence, the emerging evidence indicates that miRNA-targeting autophagy-related genes mainly play a role in drug resistance, indicating that the autophagy-related miRNA axis may be an attractive target for therapeutic interventions in cancer.

miRNAs AND METABOLIC REGULATION IN THE TUMOR MICROENVIRONMENT

Tumor stromal cells are composed of matrix, fibroblasts, immune cells, and endothelial cells. A major component of tumor stroma is adipocytes, and the metabolic interactions between adipocytes and tumor cells could drive cancer progression *(69)*. Metabolic cross talk promoted fibroblast-tumor lactate shuttling, lipolysis, and fatty acid oxidation in various cancer cells. Intercellular interaction increased expression of glucose transporter GLUT1, lactate production, and lactate shuttling by MCT4. Also, transfer of glutamine from cancer-associated fibroblasts (CAFs) to breast and pancreatic cancer cells promoted proliferation with reciprocal metabolic reprogramming, in addition to fostering glutamine synthesis and glutamine catabolism in cancer cells. The process of adipogenesis is also known to be partially regulated by miRNAs, as they have been implicated in adipocyte differentiation and adipocyte functions such as lipolysis, glucose uptake, and therapeutic resistance. For example, overexpression of miR-128 induced adipogenic differentiation of human mesenchymal stem cells by suppressing the vascular endothelial growth factor pathway *(70)*.

Furthermore, CAFs were shown to induce docetaxel resistance in PCa cells via OXPHOS metabolic shift, and

reexpression of miR-205 resulted in the shift from OXPHOS to a Warburg metabolism, thereby increasing docetaxel toxicity in PCa cells *(71)*. Moreover, isocitrate dehydrogenase 3 complex (IDH3α) is an important enzyme in glycolysis, and overexpression of IDH3α prevents fibroblasts from transforming into CAFs. Interestingly, miR-424 degraded IDH3α during CAF formation and stabilized HIF-1α protein, which promoted glycolysis by increasing the uptake of glucose in colon cancer cells *(69)*. Another study showed the downregulation of miR-205 in PC3 PCa cells upon tumor fibroblast stimulation by direct repression of HIF-1α *(65)*. Subsequent overexpression of miR-205 in PCa cells reduced cell invasion, tumorigenicity, and metastasis. Further, miR-205 inhibited tumor-induced activation of surrounding fibroblasts by reducing proinflammatory cytokine secretion. miR-210 was shown to convert normal fibroblasts into CAF-like cells to promote cancer cells via EMT, to support angiogenesis, and to recruit monocytes/macrophages *(65)*. Fibroblasts activated by miR-210 can supply cancer cells with L-lactate and ketone bodies to support cancer growth. miR-335 and miR-21, found to be upregulated in CAFs, modulated the secretion of senescence-associated secretory phenotype factors and induced cancer cell motility in cocultures by suppressing the expression of PTEN *(72)*. CAFs enhanced glucose uptake to promote tumor growth and enzymes involved in glucose uptake, such as PKM and HK2, which were found to be increased in CAFs. Cancer cell-secreted miRNA miR-122 suppressed glucose uptake in breast cancer by downregulating the glycolytic enzyme, PKM. Moreover, overexpression of miR-182 degraded both HK2 mRNA and protein in CAFs *(73)*.

Therapeutic Potential of miRNAs Regulating Cancer Metabolism

miRNAs can act either as tumor suppressors by targeting oncogenes or as oncomirs by targeting tumor suppressor mRNAs. Based on the dual functional characteristics of miRNAs, current approaches for miRNA therapy involve using either anti-miRNAs or miRNA mimics. Antisense oligonucleotides targeting miRNAs, locked nucleic acids, antagomirs, miRNA sponges, and small molecule chemical compounds may be used as the agent for anti-miRs *(74)*. Similarly, miRNA mimics and miRNA expression vectors agents can be used for miRNA expression restoration *(75)*. Currently, there are several clinical trials using miRNAs to manage various types of malignancies. Anti-miR strategy is being used to target miR-10b, miR-21, miR-155, and miR-221, whereas for let-7, miR-16, miR-29, and miR-34, a miRNA mimics strategy is used to deliver miRNAs in various human malignancies *(76)*. Notably, these miRNAs are also currently in preclinical and clinical trials. For instance, miR-34a, which has been intensively studied in brain, prostate, pancreatic, lung, liver, and colon tumors, functions as a tumor suppressor and plays a role in the regulation of glycolysis, the TCA cycle, and autophagy, and is already in phase 1 clinical trials (NCT01829971) for the management of multiple solid tumors *(77)*. Furthermore, miR-16, which is also involved in the regulation of autophagy pathways in mesothelioma and NSCLC, has progressed into phase 1 clinical trials *(75)*. These findings indicate the potential of miRNAs as therapeutic strategies in inhibiting tumor progression.

Conclusion and Future Challenges

There is little doubt that miRNAs have emerged as versatile players in regulating different aspects of cancer metabolism. Several lines of evidence have identified that miRNAs have the ability to act either as oncomirs or tumor suppressors, which make them attractive targets for dissecting cancer pathophysiology. We have highlighted how their functions vary in different tumors, making it necessary to know the correct tumor state and tumor type to understand the specific role of miRNAs in tumor metabolism. Regulation of cancer metabolism by miRNAs either enhances or suppresses tumorigenic processes such as proliferation, migration, invasion, apoptosis, angiogenesis, autophagy, and metastasis. Therefore, identifying the specific role of a miRNA at a particular stage of tumorigenesis may open up avenues for miRNA-based personalized or precision medicine in cancer. Encouragingly, several miRNAs have been well studied in various cancers and have shown promising results in preclinical studies. Thus, this is an exciting time in miRNA therapeutic advances to modulate cancer cell metabolism and other pathways in the search for more efficacious treatments to prolong patient survival and improve their quality of life. However, the clinical translation of miRNA-based therapies has been plagued by many unanswered questions. These include finding the best miRNA for a particular tumor type, suitable delivery system, treatment velocity, and avoiding off-target effects. Another challenge is that a single miRNA may have multiple targets that could control metabolism as well as other cellular processes; therefore, targeting a specific miRNA could lead to unwanted side effects. Notwithstanding, miRNA-directed regulation of metabolic pathways appears to be tumor- and stage-specific; therefore, accurate identification of the exact role of miRNAs could pave the way for development of novel therapeutics. More research is clearly warranted in this area.

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tion of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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