Interplay Between Metabolism and Oncogenic Process: Role of microRNAs

Aastha Arora[1,2], Saurabh Singh[1], Anant Narayan Bhatt[1], Sanjay Pandey[1,3], Rajat Sandhir[2] and Bilikere S. Dwarakanath[1,4]

[1]Division of Radiation Biosciences, Institute of Nuclear Medicine and Allied Sciences, Delhi, India. [2]Department of Biochemistry, Panjab University, Chandigarh, India. [3]Dr B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi, India. [4]Sri Ramachandra University, Chennai, India.

ABSTRACT: Cancer is a complex disease that arises from the alterations in the composition and regulation of several genes leading to the disturbances in signaling pathways, resulting in the dysregulation of cell proliferation and death as well as the ability of transformed cells to invade the host tissue and metastasize. It is increasingly becoming clear that metabolic reprograming plays a critical role in tumorigenesis and metastasis. Therefore, targeting this phenotype is considered as a promising approach for the development of therapeutics and adjuvants. The process of metabolic reprograming is linked to the activation of oncogenes and/or suppression of tumor suppressor genes, which are further regulated by microRNAs (miRNAs) that play important roles in the interplay between oncogenic process and metabolic reprograming. Looking at the advances made in the recent past, it appears that the translation of knowledge from research in the areas of metabolism, miRNA, and therapeutic response will lead to paradigm shift in the management of this disease.

KEYWORDS: metabolic reprograming, microRNA, cancer therapy, tumorigenesis, angiogenesis, metastasis, glycolysis, cell signaling

Introduction

Cancer is defined by abnormal and uncontrolled cell division, a phenotype that arises from the alteration of different mechanisms, leading to misregulation of several protein-coding genes. It is nearly 90 years ago that the Nobel laureate Otto Warburg discovered the glycolytic phenotype (aerobic glycolysis) of the cancer cells, where glucose is converted into lactate for energy production rather than performing oxidative phosphorylation (OXPHOS), even in the presence of oxygen. This is widely known as the Warburg's effect and purportedly supports energy production, macromolecular synthesis, and redox balance essential for tumor growth.[1] This metabolic shift, referred to as the metabolic reprogramming, is known to be under the influence of both oncogenic activation and downregulation of tumor suppressor genes.[2] Further, as tumors grow, it becomes increasingly difficult for the innermost cells to obtain oxygen from the blood, creating a hypoxic environment, which accentuates the metabolic reprograming.[3] The high rate of glycolysis and suppressed gluconeogenesis also help to maintain a low concentration of intracellular glucose, creating a gradient favoring the flux of glucose into the cell, and create microenvironmental acidosis compelling evolution of phenotypes with stress resistance and metastatic ability. These alternations enable cancer cells to acquire characteristics different from normal cells: resistance to growth inhibitory factors, proliferation in the absence of exogenous growth factors, evasion of apoptosis, limitless replication potential via the reactivation of telomerase, abnormal angiogenesis, and avoidance of destruction by the immune system, invasion, and metastasis.[4,5] The above essential hallmarks of cancer are intertwined with an altered cell-intrinsic metabolism, either as a consequence or as a cause.[6] This process of metabolic reprograming is linked to the activation of oncogenes and/or suppression of tumor suppressor genes, which are further regulated by either their activation or inactivation dynamics, where the microRNAs (miRNAs) appear to play important roles.[7] Furthermore, numerous studies revealing the involvement of miRNAs in the regulation of the essential cellular homeostatic pathways suggest that miRNAs can play key roles in tumorigenesis, maintenance, and progression of the neoplastic state.[8,9] It is increasingly becoming clear that metabolic reprograming plays a critical role in tumorigenesis and metastasis. Given the essential role of miRNAs in tumor development and their global deregulation, they are ideally suited as either surrogate or therapeutic biomarkers in cancer.[10] Therefore, targeting this phenotype

may be a promising approach for the development of therapeutics and adjuvants.[11]

miRNAs are short, endogenous ~22 nt RNAs that can play important regulatory roles in a variety of biological processes.[12] They demonstrate complementarity with 3′-untranslated region (3′-UTR) of their target messenger RNAs (mRNAs). The miRNA-mediated regulation of gene expression could be either by posttranscriptional 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.[13] The monocistronic or polycistronic miRNA-coding genes are transcribed by RNA polymerase II into long primary transcript of miRNA (500–3000 bases) containing the hairpin structure, which are converted into precursors of miRNAs (pre-miRNA, ~70 bases) by nuclear RNase III Drosha with the aid of cofactor DGCR8.[14,15] Following nuclear processing, the pre-miRNAs are exported to the cytoplasm by a nuclear transport receptor, exportin-5, and Ran-GTP before being processed by the cytoplasmic RNase III Dicer into 21-nt mature miRNAs duplexes.[16] Finally, the single-stranded miRNA are incorporated into an RNA-induced silencing complex to induce translation suppression or degradation of the target mRNAs depending on the degree of complementarity with the 3′ UTR of the target mRNA.[17]

The miRNAs regulate a plethora of cellular processes through various mechanisms, including direct targeting of the key enzymes or transporters of metabolic products and regulating transcription factors.[18] The first evidence showing the involvement of miRNAs in cancer came from studies on chronic lymphocytic leukemia (CLL), which showed that the critical region most frequently deleted in majority of the CLL encoded two tumor-suppressive miRNAs – miR-15 and miR-16-1.[19] It is now well established that miRNAs play a pivotal role in cancer by regulating oncogenes/tumor suppressors and multiple oncogenic signaling pathways, involved in the phenotypic hallmarks of cancer, from the development of autonomous cellular proliferation to acquiring invasive and metastatic capabilities.[20] However, the influence of a few miRNAs appears to be contextual, influencing both progression and suppression of carcinogenesis, although interestingly, majority of the tumor suppressor genes are targets of the miRNAs.[21] As miRNAs are integral nodes in the regulation of important steps of the altered metabolic profile of cancer cells, modulating their activity represents a promising new approach for cancer therapy. The role of miRNA in the general context of cancer including tumor response to various therapies has been extensively reviewed.[22–24]

The role of miRNAs in various human metabolic diseases such as obesity, diabetes, and cancer has recently gained increasing attention resulting in a paradigm shift in our understanding of the regulation of cancer metabolism. Emerging picture based on miRNA profiling in the preclinical samples

and clinical studies shows that miRNAs regulate the metabolism of normal as well as the transformed cells and plays a critical role in cancer progression/tumor development.[25] Available evidences strongly suggest that miRNAs act directly either by targeting key metabolic transporters and metabolic enzymes or by critical signaling pathways by controlling the expression of oncogenes and/or tumor suppressors.[7] Table 1 provides an overview of the miRNAs involved in the metabolic reprograming of cancer cells and their functions. While majority of the studies suggest that miRNAs regulate the glucose metabolism during the process of tumorigenesis, fewer studies have also suggested the potential role of altered glucose metabolism in regulating miRNAs contributing to the disease progression.[26–29] The interplay between oncogenic transformation-driven metabolic reprograming and aberrant miRNAs regulation further establishes their critical role in initiation, promotion, and progression of cancers[30–32] by creating a pro-tumorigenic microenvironment, thus orchestrating processes of evasion of apoptosis, angiogenesis, and invasion/migration as well as metastases (Fig. 1).[20] A plethora of evidences indicating the differential expression of miRNAs in normal and tumor samples suggest that miRNAs could serve as useful tumor profiling tools. The conventional, high-throughput oligonucleotide miRNA microarray technique, along with its multiple numbers of variations, makes it possible to profile substantial sample numbers with relative ease.[33,34] It appears that the expression and activation of glucose metabolism-linked miRNAs can act as biomarker signatures together with the metabolic status and may help in the prediction of disease progression and the design of appropriate therapy in the near future. The roles of miRNA in cancer metabolism in relation to proliferation, cell cycle regulation, and cell death and the potential of miRNA related to metabolic reprograming as therapeutic targets have been reviewed earlier.[22,35] This review focuses mainly on the interplay between miRNA regulation and metabolic reprograming, with an emphasis on their potential to influence various hallmark phenotypes associated with carcinogenesis as well as tumorigenesis, such as proliferation, apoptosis, angiogenesis, migration, invasion, and metastasis.

Regulation of the Glycolytic Flux by miRNAs

Glycolysis, glutaminolysis, and de novo lipid biosynthesis form a stereotypic platform supporting cancer cell proliferation (Fig. 2).[36] Cancer cell proliferation can only proceed as metabolites accumulate to ensure an ample supply of building blocks such as reduced nicotinamide adenine dinucleotide phosphate (NADPH), acetyl-CoA, and ribose for DNA, RNA, protein, lipid, and complex carbohydrates to prepare for mitosis.[37] The emerging cancer cell rewires its metabolic program to support growth, evade death (through apoptosis), and maintain favorable redox balance. Metabolic reprograming of cancer cells is a complex interplay of regulatory networks involving phosphoinositide 3-kinase (PI3K), mechanistic target of rapamycin (mTOR), Akt, phosphatase and tensin homolog (PTEN), and

Table 1. List of miRNAs involved in metabolic reprograming of cancer cells and their function.

miRNA	TARGET GENES	FUNCTION	OBSERVED PHENOTYPE (HALLMARK OF CANCER)	REFERENCES
A. Upregulated miRNAs				
miR-155	Up-regulation of HK2, GLUT1, PFK2, PKM2, LDHA	Suppresses miR-143; enhances glucose consumption and lactate production, regulates EMT	Proliferation, migration, invasion and angiogenesis	61,104,106–108
miR-26a	PDHX, PTEN	Inhibits TCA cycle by targeting PDHX mRNA; regulates PTEN	Metastasis and angiogenesis	35,149–151
miR-378*	SuFu and FUS-1, ERRγ, GABPA	Reduces TCA cycle gene expression and oxygen consumption, enhances lactate production via the PGC-1β/ERRγ transcriptional pathway	Proliferation, Angiogenesis	45
miR-23a	PGC-1α	Suppression of PGC-1α to enhance aerobic glycolysis	Proliferation	46–48
miR-21	PTEN, HIF-1α, VEGF	Suppresses the activation of caspases; inhibits PTEN; activates PI(3)K/Akt pathway; induces tumor neo-vascularization by increasing HIF-1α and VEGF expression	Evasion of apoptosis, Angiogenesis	26,74–77,91,165
miR-181a	PTEN, AKT, CYCLIN-D1	Inhibits PTEN; activates PI(3)K/Akt pathway; up-regulates Cyclin D1	Evasion of apoptosis	155
miR-451	LKB1/AMPK, CAB39	Suppresses the activation of LKB1/AMPK pathway	Evasion of apoptosis, Proliferation	84,85,158
miR-33	SIRT-6, AMPKα1, IRS-2	Inhibition of AMPKα1, Sirtuin 6, Insulin receptor substrate 2	Proliferation	161
miR-424	CUL2	Stabilizes HIF-1α under hypoxic conditions	Angiogenesis	166
miR-210	ISCU1/2, COX-10, EPHRIN-A3	Inhibition of mitochondrial respiration and TCA cycle by repressing ISCU1/2, COX-10	Proliferation, Angiogenesis, Migration	50–52,134
Lin-28a/b	Let-7 miRNA family	Activated by c-myc; repress the let-7 miRNA family members; activates insulin/PI3K/mTOR signaling cascade leading to enhanced glucose tolerance	Proliferation	87–89,133,177
miR-25, miR-30d, miR-504	P53	Negatively regulate p53 activity and response through direct reduction in p53 protein levels	Evasion of apoptosis	188
miR-125b	BAK1, P53	Targeting Bak1; directly reduces p53 levels by targeting its 3'UTR	Evasion of apoptosis	73,188
miR-17-92	PTEN, AKT, RB2, THBS1	Up-regulated by myc and inhibited by p53; activates PI(3)K/Akt/mTOR pathway; suppresses PTEN and RB2	Evasion of apoptosis, Angiogenesis	65,78–80,101,128
B. Downregulated miRNAs				
miR-195-5p	GLUT3	Inhibits GLUT3 expression	Proliferation	32
miR-143	HK2, AKT	Inhibits expression of HK2 and Akt signaling	Proliferation	33,34,61
miR-326	PKM2	Tumor suppressor; targets PKM2	Proliferation	44
miR-125b	HK2, ACSS1, PDK1	Repression of transcripts encoding enzymes in glucose, glutathione and lipid metabolism	Proliferation	49
miR-1	G6PD, TKT, 6PGD	Inhibits multiple enzymes within the PPP	Apoptosis	53,54
miR-15	BCL2	Negatively regulates the anti-apoptotic gene, BCL2	Apoptosis	70
miR-122	BCL-W	Down-regulates Bcl-w	Apoptosis	71,72
miR-16-1	BCL2, KRAS, CDK6	Activated by p53; induces cell cycle arrest; negatively regulates the anti-apoptotic gene BCL2	Apoptosis	70,187
miR-126	PI3K, VEGF	Inhibits PI(3)K/Akt pathway; inhibits tumor angiogenesis through regulation of VEGF-A signaling	Angiogenesis	59,97–100
miR-199a-3p	mTOR1, C-MET	Repression of mTOR1 and c-Met	Proliferation	60
miR-199a	HIF-1α	Inhibits HIF-1α	Proliferation	129
miR-22	HIF-1α, VEGF	Suppresses HIF-1α translation and VEGF expression; regulates tumor angiogenesis	Angiogenesis	167

(Continued)

Table 1. (*Continued*)

miRNA	TARGET GENES	FUNCTION	OBSERVED PHENOTYPE (HALLMARK OF CANCER)	REFERENCES
Let-7	KRAS, NRAS, MYC and HMGA2, MCT	Negatively regulates the translation of oncogenes (KRAS, NRAS, MYC and HMGA2) and MCTs; represses insulin-PI3K-mTOR pathway	Proliferation	87–89,178,183
miR-34a	P21, PUMA, CD44	Activated by and activates p53; induces cell cycle arrest (p21) and apoptosis (PUMA); inhibits metastasis and angiogenesis by repressing glycolysis and directly targeting CD44	Apoptosis, Angiogenesis, Metastasis	135,136,140,185
miR-124, miR-137, miR-340	PKM alternative splicing proteins (PTB1/hnRNAPA1/hnRNAPA2)	Switch PKM gene expression from PKM2 to PKM1	Proliferation	41
miR-23a	GLS	Inhibits glutaminolysis	Proliferation	100,173

adenosine monophosphate-activated protein kinase (AMPK) and can be traced to a "triad" of transcription factors: hypoxia-inducible factor-1 (HIF-1), c-MYC, and p53. The underlying mechanisms leading to the Warburg phenomenon/aerobic glycolysis include mitochondrial changes, upregulation of rate-limiting enzymes/proteins involved in glycolysis and intracellular pH regulation, hypoxia-induced switch to anaerobic metabolism, and metabolic reprograming associated with loss of p53 function.[38] Figure 3 provides an overview of the miRNAs involved in the regulation of metabolism achieved by targeting key metabolic enzymes and multiple oncogenic signaling pathways.

The first step in energy metabolism is the entry of glucose into the cells. miRNAs can directly regulate the intracellular glucose levels by modulating gene transcription and expression of glucose transporters. Glucose transport (GLUT) receptors are responsible for the transport of glucose by cancer cells along the concentration gradient. miRNA-195-5p and miRNA-143 are known to repress glucose uptake and glycolysis by inhibiting the expression of GLUT3 and hexokinase 2 (HK2) and AKT signaling pathways, respectively.[39–41] Therefore, repression of these miRNAs would facilitate the entry of glucose into the cancer cells as reported in case of human bladder cancer T24 cells.[39]

Glucose metabolism, being the central energy resource of the cell, is quite complex. Following the uptake of glucose through GLUT receptors, a large number of enzymes take part in its catabolism to trioses and pyruvate and ultimately to
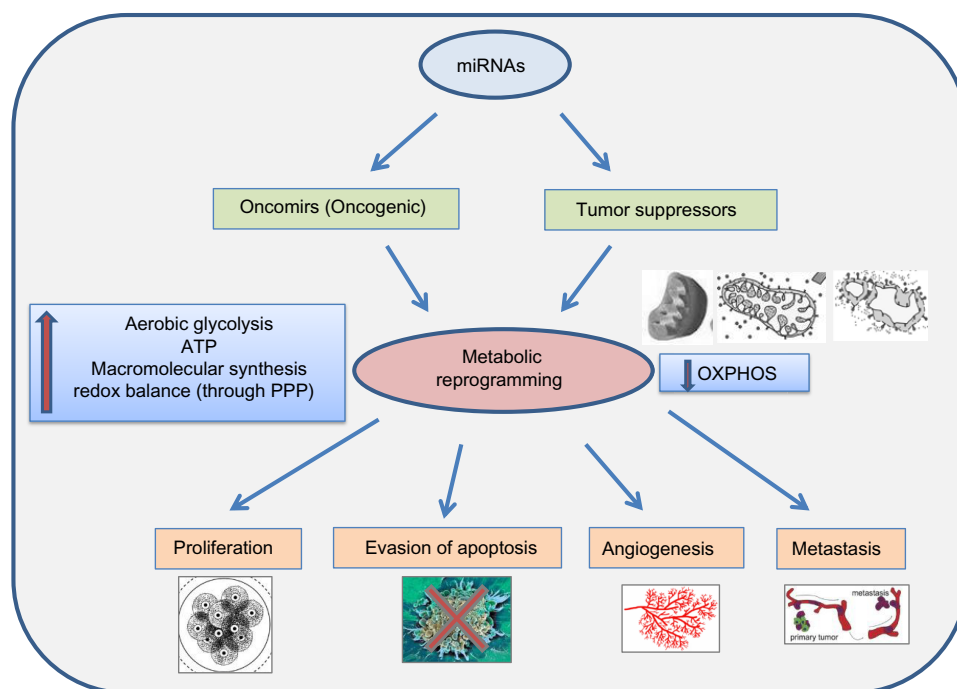

Figure 1. Schematic diagram/illustration showing the involvement of miRNAs in regulating the hallmarks of cancer through altered cell metabolism.
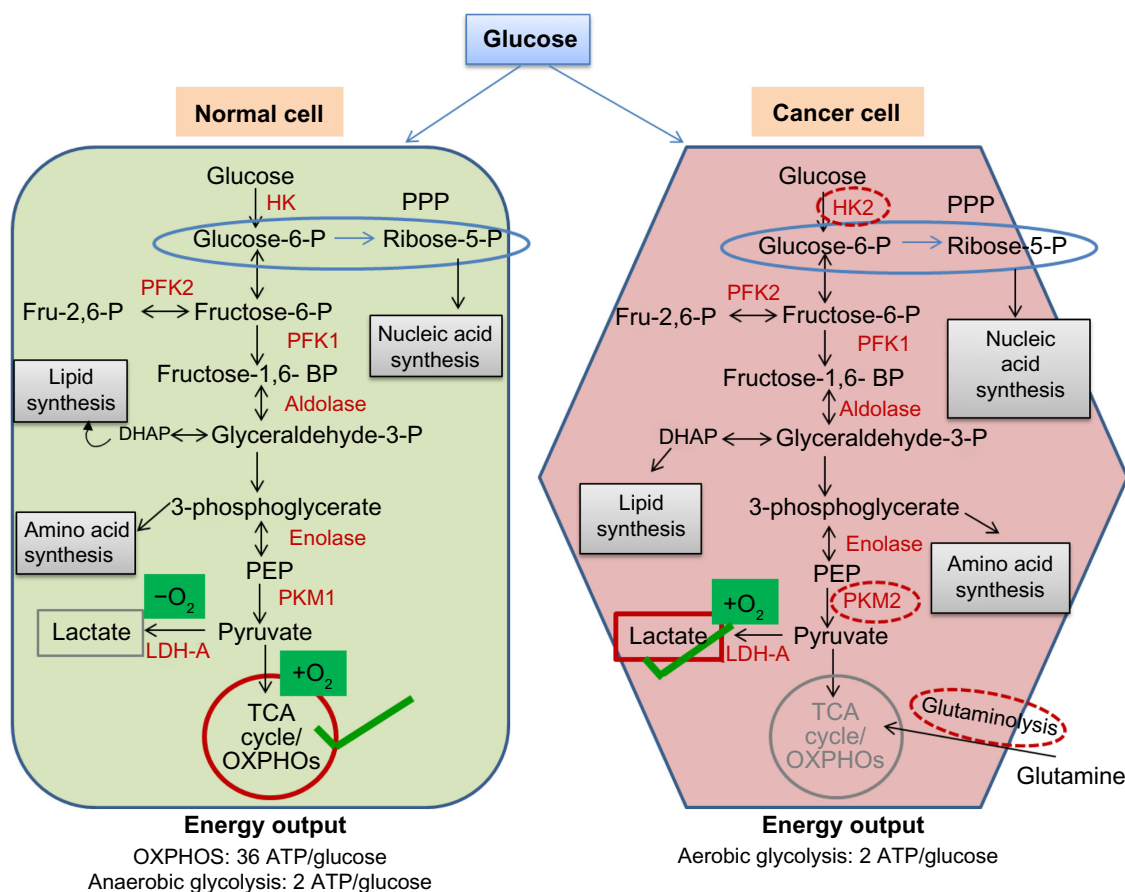
Figure 2. Warburg phenotype (enhanced aerobic glycolysis) in cancer cells showing alterations in enzymes and glutaminolysis.

lactate. miRNA regulation of the glycolytic enzymes further increases this complexity. miR-26a inhibits the expression of pyruvate dehydrogenase protein X component (PDHX, a noncatalytic subunit of the PDH complex) by directly targeting the conserved miR-26a recognition motif of the 3′ UTR of PDHX mRNA, which efficiently decreases the process of pyruvate–acetyl-CoA conversion and thus blocks the key rate-limiting step of glycolysis to the citric acid cycle in glucose metabolism, thus impairing mitochondrial metabolism.[42] Pyruvate kinase regulates the final rate-limiting step of glycolysis, which catalyzes the transfer of a phosphate group from phosphoenolpyruvate to adenosine diphosphate, yielding one molecule of pyruvate and one molecule of adenosine triphosphate (ATP).[43] Four isoforms of pyruvate kinase (M1, M2, L, and R) exist in mammals and are expressed in different types of cells and tissues.[44] The pyruvate kinase M1 (PKM1) and M2 (PKM2) isoforms result from mutually exclusive alternative splicing of the PKM2 pre-mRNA, reflecting the inclusion of either exon 9 (PKM1) or exon 10 (PKM2), respectively.[45] While PKM2 is exclusively expressed in embryonic, proliferating, and cancer cells and promotes glycolysis even in an aerobic environment, PKM1 is expressed in normal differentiated tissues and promotes OXPHOS.[46,47] PKM (pyruvate kinase isozyme) alternative splicing proteins (PTB1/hnRNAPA1/hnRNAPA2), which control the inclusion of exon 9 (PKM1)

or exon 10 (PKM2), are targeted by miR-124, miR-137, and miR-340. High ratios of PKM1/PKM2 inhibit the glycolysis rate but elevate the glucose flux into OXPHOS. Thus, these miRNAs (miR-124, miR-137, and miR-340) impair cancer growth by counteracting the Warburg's effect by regulating alternative splicing of the PKM gene.[48] The expression of the splicing proteins is also under the tight control of the oncogene, c-myc.[49] Therefore, c-Myc could also regulate cancer growth directly through PKM alternative splicing proteins or indirectly through miR-124, miR-137, and miR-340. In the cancer cells, PKM2 not only supports cell growth via Warburg's effect as a metabolic enzyme but also promotes transactivation of HIF-1 target genes as a transcription coactivator.[50] PKM2 is also regulated by miR-326, which has tumor-suppressive properties and has been shown to regulate glucose metabolism in glioblastoma cells by targeting PKM2. Functional implications of targeting PKM2 by miR-326 include reduced growth and enhanced apoptosis, cellular invasion, metabolic activity, ATP and glutathione (GSH) levels, and AMPK in glioma and glioma stem cells.[51]

Role of miRNAs in the Suppression of Mitochondrial Function

It appears that tumor cells suppress the mitochondrial metabolism and enhance glycolysis to meet their energy requirements
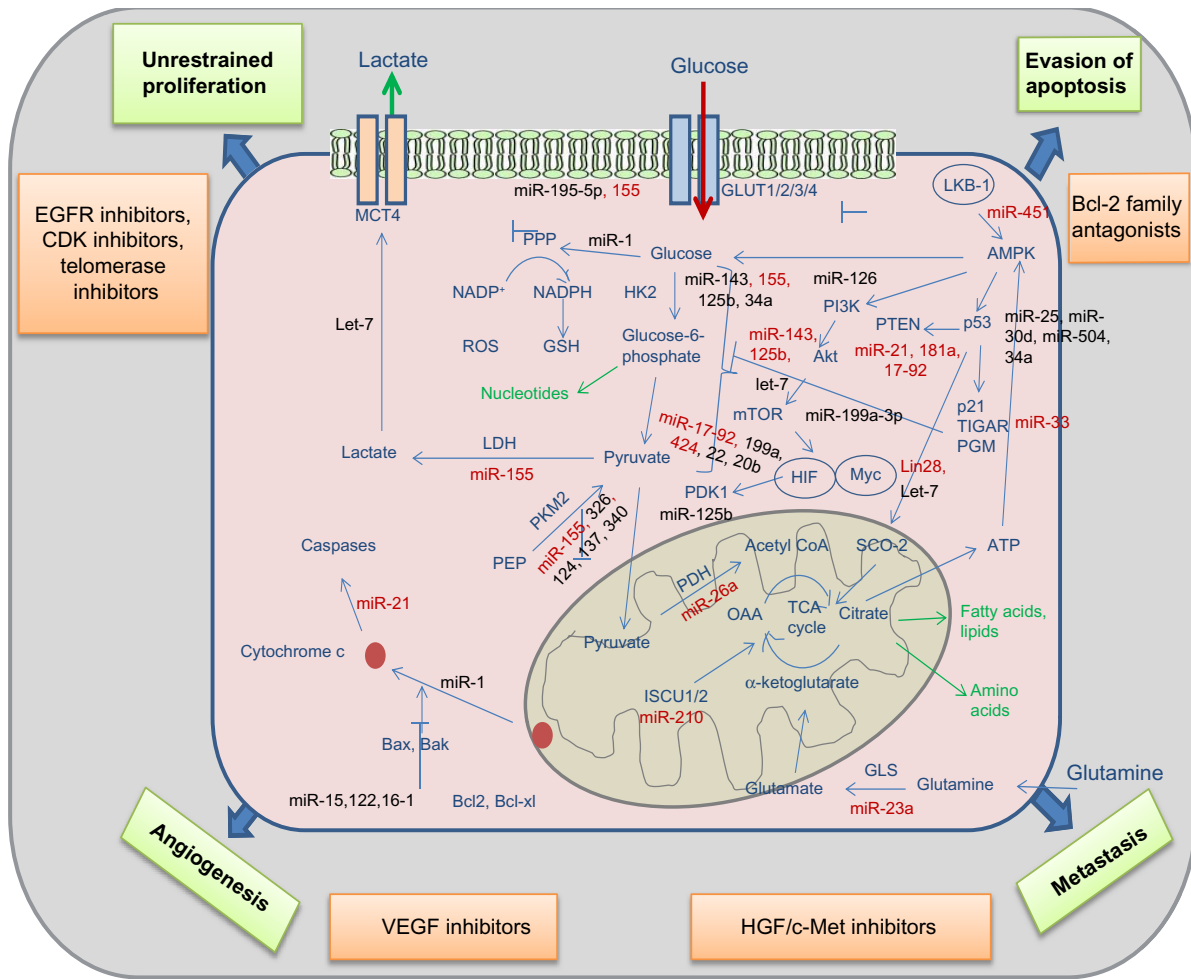
Figure 3. miRNAs regulate cell metabolism by targeting key metabolic enzymes and multiple oncogenic signaling pathways. miRNAs could regulate cell metabolism by modulating the expression of metabolic transporters (like GLUT), enzymes of the glycolytic/TCA cycle (HK2, aldolase, PDK1, etc.), key transcription factors involved in oncogenic transformation (p53, c-Myc, and HIF-1), or oncogenic signaling pathways (AKT/mTOR).
Abbreviations: MCT, monocarboxylate transporters; GLUT, glucose transporter; PPP, pentose phosphate pathway; LDH, lactate dehydrogenase; GSH, glutathione; NADP, nicotinamide adenine dinucleotide phosphate; HK2, hexokinase 2; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; LKB1, liver kinase B1; PGM, phosphoglycerate mutase; OAA, oxaloacetate; SCO2, synthesis of cytochrome *c* oxidase 2; ISCU1/2, iron–sulfur cluster assembly proteins; PKM2, pyruvate kinase M2 isoform; PEP, phosphoenolpyruvate; GLS, glutaminase; HIF, hypoxia-inducible factor; PI3K, phosphoinositide 3-kinase; TIGAR, TP53-induced glycolysis and apoptosis regulator; PTEN, phosphatase and tensin homolog; AMPK, adenosine monophosphate-activated protein kinase.

for supporting continuous growth. For example, miR-378* expression is regulated by Erb-B2 receptor tyrosine kinase 2 and induces a metabolic shift in breast cancer cells by inhibiting the expression of estrogen-related receptor-γ and GA-binding protein transcription factor, alpha subunit (60 kDa), two PGC-1b partners and important regulators of energy metabolism. This leads to a reduction in the tricarboxylic acid (TCA) cycle-related gene expression, such as fumarate hydratase, aconitase, succinate dehydrogenase, and oxygen consumption, decreasing the dependency on OXPHOS for fulfilling the energy requirement and increasing the lactate production, thus facilitating cell proliferation.[52] Since PGC-1b and PGC-1α [transcriptional coactivators of the key gluconeogenic enzyme, glucose-6-phosphatase, catalytic subunit (G6PC)] play a regulatory role in mitochondrial respiration and biogenesis,

miR-23a-mediated suppression of PGC-1α could also facilitate a metabolic switch from OXPHOS to anaerobic glycolysis to synthesize anabolic precursors to sustain proliferation of tumor cells.[53,54] interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling in tumor cells activates the expression of miR-23a, which directly targets G6PC and PGC-1α, leading to the accumulation of glucose-6-phosphate (G6P). Therefore, increased G6P levels may aid tumor cells in maintaining high rates of proliferation.[55] On the other hand, overexpression of miR-125b results in the repression of many transcripts encoding enzymes implicated in glucose, GSH, and lipid metabolism including phosphatidylcholine transfer protein, lipase A, lysosomal acid, cholesterol esterase, glutathione synthetase, acyl-CoA synthetase short-chain family member 1, HK2, stearoyl-CoA desaturase 1, AKT2, and pyruvate

Figure 4. Schematic diagram showing up- and downregulated miRNAs involved in metabolic modulation and tumor–stroma (microenvironment) interactions facilitating invasion, angiogenesis, and metastases.

dehydrogenase kinase 1 (PDK1).[56] Thus, by coordinated fine-tuning the expression of a large number of enzymes, miR-378*, miR-23a, and miR-125b act as rheostats to regulate the metabolic intensity in a given cell for the adaptation of cell metabolism to a transformed state.

Under hypoxic conditions, miR-210 represses ISCU1/2 (the iron–sulfur cluster assembly proteins) and thus decreases the activity of prototypical iron–sulfur proteins controlling mitochondrial metabolism, including complex I and aconitase.[57] It also represses COX10 (cytochrome *c* oxidase assembly protein), another important factor of the mitochondria electron transport chain and the TCA cycle.[58] miR-210 is significantly overexpressed in many cancers and represses

mitochondrial respiration, thereby indirectly facilitating aerobic glycolysis in cancer.[59]

Metabolic Reprograming and Uncontrolled Proliferation: miRNAs as the Connecting Link

Cancer cells must integrate multiple biosynthetic demands to drive indefinite proliferation. For this, neoplastic cells are highly dependent on the de novo synthesis of nucleotides to maintain sufficient pools to support DNA replication and the production of RNA for driving protein synthesis. The metabolic pathways supporting nucleotide production are dependent on metabolic intermediates provided by glycolysis and the TCA cycle.[60] The non-oxidative part of the pentose phosphate

pathway (PPP), controlled by thiamine (vitamin B1)-dependent transketolase (TKT) enzyme reactions, allows glucose conversion to ribose (the 5-carbon sugar moiety of nucleotides) for nucleic acid synthesis and oxygen-independent glucose degradation to lactate, which is of utmost importance for the proliferation process.[61,62] Earlier studies in pancreatic cancer cells have shown that pentose cycle contributes to >85% of de novo ribose synthesis in RNA with the majority derived from the non-oxidative (TKT-regulated) pathway.[63] The synthesis of purines and pyrimidines is also upregulated in cancer cells, and enzymes that catalyze these pathways, including thymidylate synthase (TS) and inosine synthetase 2, are subject to Myc-induced upregulation. Myc stimulates these genes involved in nucleotide metabolism and specifically interacts with the E2F family of transcription factors to drive proliferating cells into S phase for DNA replication.[64–66]

miR-1, which is a tumor-suppressive miRNA, has been found to be silenced by promoter methylation in primary human hepatocellular carcinoma (HCC).[67] It directly targets glucose flux through the PPP by inhibiting multiple enzymes within the PPP: glucose-6-phosphate dehydrogenase (G6PD), 6-phosphogluconate dehydrogenase (6PGD), and TKT. The shift in the primary glucose metabolism caused by reduced levels of miR-1 facilitates glycolysis, nucleotide synthesis through the production of ribose-5-phosphate, and regeneration of NADPH to counter oxidative stress through PPP, promoting tumor cell proliferation and inhibition of apoptosis.[68]

Of the numerous Akt target proteins reported to date, mTOR appears to be the most critical downstream effector of Akt-dependent cell proliferation and altered susceptibility to oncogenic transformation.[69] mTOR 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.[70] The activation of mTOR signaling leads to an increase in the protein synthesis of HIF-1α in response to growth factors and PI3K/Akt signaling, and thus, leads to enhanced expression of glycolytic enzymes, including lactate dehydrogenase isoform B (LDH-B), PKM2 and glucose transporter 1 (GLUT1).[71,72] While miR-126 impedes tumor cell growth by targeting the p85b subunit of PI3K, the translational repression of mTOR1 and c-met by miR-199a-3p has been reported in HCC.[73,74] As PI3K/Akt triggers downstream signals to mTOR for cellular growth and proliferation, the loss of miR-126 and miR-199a-3p could facilitate tumor growth.

Recently, the overexpression of miR-155 has been found to increase the rate of glucose consumption and lactate production through the regulation of numerous enzymes involved in glucose transport and anaerobic glycolysis, including HK2, GLUT1, phosphofructokinase 2, pyruvate dehydrogenase, PKM2, and lactate dehydrogenase isoform A (LDHA). miR-155 upregulates HK2 through the activation of STAT3 and suppression of miR-143, which can directly target HK2, leading to increased rates of glucose consumption through aerobic glycolysis and lactate production that are required to support the high rate of proliferation.[75] More recently, a novel role of miR-155 in cancer metabolism through the upregulation of thiamine has been reported in breast cancer cells. Thiamine (vitamin B1) is a crucial cofactor of various metabolic enzymes such as pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase, and TKT. Bioinformatics and metabolomic approaches have clearly established a positive correlation between miR-155 and thiamine level. miR-155 appears to be involved in thiamine homeostasis by regulating the expression of two thiamine transporter genes (SLC19A2, SLC25A19) and thiamine pyrophosphokinase-1 at both the RNA and protein level, thus implicating the role of this oncogenic miRNA in cancer cell metabolism, leading to higher rates of proliferation.[76]

Role of miRNAs in the Suppression of Apoptosis

Cancer cells show an increased resistance to the intrinsic apoptotic pathway through the inhibition of the release of cytochrome *c* from mitochondria by a mechanism dependent on glucose metabolism, which allows for their long-term survival.[77] The proapoptotic activity of cytochrome *c* is influenced by its redox state, and the increase in reactive oxygen species (ROS) following an apoptotic insult leads to the oxidation and activation of cytochrome *c*. However, in cancer cells, cytochrome *c* is reduced and held inactive by intracellular GSH, whose levels are maintained in cells by NADPH, generated as a result of glucose metabolism by PPP. In addition, the enhanced level and mitochondrial association of HK2 also impair the release of cytochrome *c* from mitochondria.[78] Thus, the reduced levels of miR-1 could also offer an adaptive advantage for cancer cell evasion of apoptosis and for long-term survival through derepression of the PPP and inactivation of cytochrome *c*.

Oncomir-1 or the miR-17-92 polycistron is a direct transcriptional target of myc protein, which consists of a cluster of six mature miRNAs – miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1.[79] The tumor suppressors, p21 and PTEN, and the proapoptotic protein Bim have emerged as important targets repressed by oncomir-1-derived miRNAs.[80] The miR-17-92 cluster modulates the tumor growth by inhibiting HIF-1α expression and E2F1, thereby influencing apoptosis-mediated cell death through the anti-oxidant response element (ARE) - p53 pathway.[81,82] Thus, miRNAs within the mir-17-92 cluster appear to function cooperatively as oncogenes, possibly by targeting cell cycle-regulating proteins and apoptotic factors that are activated in response to the overexpression of MYC, leading to continuous proliferation.

PI3K/Akt signaling activation leads to the translocation of HK2 to the mitochondrial membrane, facilitating its binding to the voltage-dependent anion channel, negatively modulating truncated BH3-interacting domain death agonist, and BCL2 antagonist of cell death to inhibit apoptosis.[83] Cells lacking the proapoptotic Bcl-2 family proteins, Bax and Bak, resist cell death for prolonged periods under conditions of nutrient starvation through the activation of autophagy and use of alternate fuels.[84] The BCL2 expression is inhibited at

the posttranscriptional level by miR-15 and miR-16-1, suggesting that the somatic deletion of miR-15 and miR-16-1 aids in the development of leukemias, lymphomas, and carcinomas by allowing tumors to sidestep apoptosis, pointing to their tumor-suppressive role.[85] Similarly, miR-122, a hepato-specific miRNA, is frequently downregulated in human HCC.[86] The decreased miR-122 expression helps the cells to evade cell death, a cardinal feature of cancer cells, by upregulating Bcl-w and increasing the Bcl-w/Bax ratio.[87] miR-125b is upregulated and stimulates androgen-independent growth in prostate cancer by targeting Bak1 (a member of the proapoptotic Bcl-1 family of proteins), thereby acting as an oncogene in the neoplastic progression of prostate epithelium.[88]

It appears that the stimulation of the PI3K/Akt pathway by miRNAs underlies the evasion of cell death in cancer cells. miR-21 has been found to be overexpressed in a wide variety of human cancers[30,89,90] and is known to stimulate proliferation, migration, and invasion by targeting the PTEN tumor suppressor gene, leading to the activation of PI3K/Akt pathway. It also suppresses the activation of caspases and caspase-activated DNase, leading to decreased apoptotic cell death, which suggests that aberrantly expressed miR-21 may contribute to the malignant phenotype by blocking the expression of critical apoptosis-related genes.[91,92]

The miR-17-92 cluster is markedly increased in lung cancer, especially in the most aggressive form, small-cell lung cancer, and is implicated in enhancing lung cancer cell growth by targeting two tumor suppressor genes, PTEN and RB2.[93,94] miR-19, a component of miR-17-92 cluster, activates the Akt/mTOR pathway, thereby functionally antagonizing PTEN to promote cell survival and metabolism. Further, PI3K/Akt signaling is known to strongly promote glucose metabolism and fatty acid synthesis by upregulating GLUT and glycolytic enzyme activity.[95]

Facilitation of Tumor Angiogenesis and Metastasis by miRNAs

During the course of cancer progression, there occurs an imbalance between angiogenic and proangiogenic factors resulting in an inclination toward proangiogenic stimuli for the growth of the tumor bulk and its metastatic spread. The altered angiogenic phenotype is mirrored by aberrant miRNA profile mediated by the metabolic reprograming. The involvement of miRNAs in the modulation of the angiogenic response to metabolic alterations associated with oncogenic process is discussed further in detail.

Deregulated expression of certain miRNAs, such as Let-7, miR-27, and miR-143, has been associated with the metabolic status in pathological conditions such as obesity and diabetes.[96,97] Interestingly, these miRNAs have also been found to be aberrantly expressed in the process of carcinogenesis, indicating a plausible link between obesity, diabetes, inflammation, and cancer.[98] Studies using calorie restriction and diet-induced obesity in colon carcinogenesis have shown

that these differential diets altered several biological pathways previously hypothesized to be involved in obesity and cancer, including inflammation, insulin growth factor (IGF)-1, adipokines, and miRNAs.[99] Certain miRNAs are known to depend on glucose dynamics for their function. For example, miR-451 in gliomas has been shown to adapt its expression and function differentially depending on the glucose availability allowing survival adaptation to locoregional metabolic stress by activating the liver kinase B1 (LKB1)/AMPK signaling pathway. Under sufficient glucose conditions, increased expression of miR-451 promotes cell growth, while it reduces proliferation and enhances migration and survival during low levels of glucose.[100–102] As the cancer progresses, Let-7 is downregulated leading to an increased expression and activity of metabolism-related factors, such as Ras, c-myc, and Lin-28, in cancer cells.[103,104] In breast cancer, let-7 inhibits Lin-28-mediated insulin/PI3K/mTOR signaling cascade, inhibiting cancer progression.[105] Initially, it was discovered that the oncomir, miR-378*, is linked to the metabolic switch in breast cancer cells, thereby shutting down the OXPHOS/TCA cycle and upregulating the glycolytic pathway further facilitating the cancer progression.[52] Later, miR-378* was also classified as proangiomir and shown to enhance angiogenesis via regulating the two transcription factors, SuFu and Fus-1,[106] thus, accentuating the growth, proliferation, and progression of cancer by dysregulating energy metabolism.

The oncogenic miRNA, miR-21, is known to induce tumor-associated neovascularization by directly targeting PTEN and activating PI3K/Akt as well as ERK1/2 signaling pathways, which increases HIF-1α and vascular endothelial growth factor (VEGF) expression.[91,107] In patients with diabetes-associated vascular disease, increased miR-21 levels/expression has been found in response to high systemic glucose, protecting endothelial cells (ECs) against high glucose-induced apoptosis.[108] Interestingly, miR-221/222 gene cluster, which is an activator of PI3K/Akt, has been found to inhibit the process of angiogenesis.[109,110] This cluster plays an important role in maintaining the EC differentiation and integrity in quiescent form. However, it inhibits proangiogenic activity, proliferation, and migration of ECs possibly by repressing ETS-1 signaling upon forming a complex of protooncogene ETS-1 and miR-222 (ETS-1/miR-222).[111,112] Similarly, miR-126 is also known to maintain vascular integrity and reported to inhibit tumor angiogenesis through the regulation of VEGF-A signaling.[113] Both glucose levels and hypoxia in the tumor microenvironment are reported to downregulate miR-126. Suppression of miR-126 upregulates the proangiogenic factors and causes invasive growth in cervical cancer.[114] The proangiogenic activation by suppression of miR-126 has also been associated with an increase in mitogen-activated protein kinase (MAPK) and PI3K signaling in response to proangiogenic factors.[115,116]

miR-18a and miR-19a/b, from miR-17-92 cluster, have been shown to regulate proangiogenic effect under the influence

of activated MYC through thrombospondin-1 targeting and hence tumor growth as shown in murine colon carcinoma.[117] MYC is also known to induce another very important oncogenic miRNA, miR-9, that is outside the miR-17-92 cluster and has been implicated in tumor cell invasiveness and metastasis.[118,119] In a breast cancer xenograft model, miR-9 has been shown to promote tumorigenesis by enhanced tumor cell invasion and metastasis. This has been attributed to the downregulation of E-cadherin, thereby inducing β-catenin activation leading to increased VEGF levels.[118,119]

miR-155 is a prominent oncomir that plays an important role in the metabolically driven oncogenic process in cancers of the breast, lung, stomach, and lymphatic system.[120] miR-155 expression in cancer cells regulates the multiple aspects of tumorigenesis, including transforming growth factor-mediated epithelial–mesenchymal transition (EMT), along with the migration and invasion by Ras homolog gene family, member A.[120] As discussed earlier, miR-155 in breast cancer cells is reported to induce aerobic glycolysis via HK2 upregulation through irreversible repression of mir-143, which is a negative regulator of HK2.[75] Most recently, rosmarinic acid has been shown to possess anti-Warburg's effect induced by the downregulation of miR-155 and inhibition of inflammatory IL-6/STAT3 pathway, thus inhibiting the gastric cancer (*in vitro* and *in vivo*) and suggesting an important link between the Warburg's effect, inflammation, and tumorigenesis[121] Besides cancer cells, the overexpression of miR-155 observed in the activated macrophages and recruited proangiogenic neutrophils suggests its involvement in the protumorigenic and proangiogenic state early during the carcinogenic process.[122,123] Cytokines released during the inflammation has been shown to upregulate the glycolysis by miR-155/miR-143 cascade in breast cancer cells.[124] Inflammation-induced increase in miR-155 levels represses miR-143, which is a negative regulator of HK2, by targeting its transcriptional activator CCAAT/enhancer binding protein beta (C/EBPβ)and also enhances the transcription of HK2 by targeting suppressor of cytokine signaling 1 (SOCS1), a repressor of Janus kinase/STAT signaling, thereby activating protumorigenic inflammatory STAT3.[75,124] Thus, the miR-155-SOCS1-STAT3-HK2 and miR-155-C/EBPβ-miR-143-HK2 cascades display a direct link between miRNA regulation of inflammation-mediated upregulated glycolysis and cancer. Recent observations on a differential effect of miRNA deregulation on the growth of normal and tumor cells[35] suggest that miRNAs may be better targets for developing anticancer therapeutics.[125] However, similarities in the programming of metabolism in cancer cells and the activated immune cells[126] may pose not only problems of differential response but also efficacy at the systemic level as immune modulation contributes to the local tumor control.[127,128]

During cancer progression, the limitation of nutrients in the micro milieu of the tumor gives rise to the upregulation of glucose metabolism for catering the energy requirements related to the tumor cell survival and metastasis to other sites involving processes such as invasion, migration, and EMT.[129] Emerging evidences suggest that miRNAs can also act at distant sites upon transport through the bloodstream in the form of mature or pre-miRNA packaged into vesicles (exosomes), thereby regulating the expression or activity of target protein. miRNA, miR-122, has been recently shown to reprogram the glucose metabolism by inhibiting pyruvate kinase in nontumor cells of the distant premetastatic environment.[129] This host–tumor crosstalk causes increased glucose availability to the tumor cells in the premetastatic niche, favoring metastasis in patients with breast cancer.[130] In addition to tumor cells, the activated tumor-associated stromal cells and ECs are known to rely on glycolysis during disease progression.[131] The suppression of glucose metabolism in tumor stroma by secreted miR-122 is a sustenance mechanism during local nutrient limitation and dissemination to a secondary site for its establishment and further growth.

It has been recently reported that miR-7 plays a tumor suppressor role by downregulating the metabolic IGF-1R/Akt and PI3K/Akt/mTOR signaling pathway, and its over expression reverses the invasion, extrahepatic migration, and metastasis of HCC as a consequence of suppressed glucose metabolism.[132,133] Similarly, the downregulation of miR-1291 has been shown to enhance proliferation, migration, and invasion of renal carcinoma cells through targeting of SLC2A1/GLUT-1.[134] There exists an inverse relationship between miR-1291 and GLUT-1, where the upregulation of SLC2A1/GLUT1 facilitating the GLUT is associated with poor prognosis in a variety of cancers,[135,136] while a positive correlation of lymph node metastasis with enhanced SLC2A1/GLUT has been shown in head and neck carcinomas.[137] Nuclear factor erythroid-2-related factor 2 (leucine zipper family transcription factor) has been shown to promote neoplasia via epigenetic regulation of miR-1 and miR-206,[138] which leads to metabolic reprograming through the activation of the PPP. This altered metabolism is accompanied by miR-1 tumor suppressor activity, which is corroborated by the miR-1-mediated alteration in the cellular organization of F-actin, thus inhibiting the invasion and filipodia formation by tumor cells.[139] These studies provide a direct evidence of functional outcome of miRNA regulation mediated by oncogenic–metabolic interplay.

Besides targeting the major rate-limiting steps in glycolysis, miRNAs are also involved in the regulation of some important intermediate steps of glycolysis, affecting tumor angiogenesis and metastases. For example, Aldo A, which catalyzes fructose 1,6-bisphosphate into glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, is suppressed by miR-15a/16-1 cluster.[85] Similarly, phosphoglucose isomerase, which plays an important role in invasion as well as metastasis, has been shown to be under the control of miR-200 family (miR-200a, miR-200b, and miR-200c).[140–142] The miR-200 family inhibits metastatic potential and angiogenesis by maintaining epithelial

characteristics, thereby impairing EMT and targeting IL-8 and chemokine (C-X-C motif) ligand 1 (CXCL1) secreted by tumor and the associated endothelium.[141,143] As discussed earlier, miR-17-92 oncomir cluster regulates either positively or negatively numerous pathways/processes, resulting in increased invasion, metastasis, and angiogenesis involving the induction of PI3K/Akt-mTOR pathway associated with abnormal glucose metabolism.[95,144]

Altered miRNA expression profiles have been observed in hypoxic conditions of tumor microenvironment. Increased HIF levels results in the modulation of glucose uptake, glucose metabolism, and OXPHOS, thereby promoting invasion, metastasis, and angiogenesis.[144–146] An increased level of HIF-dependent hypoxamir, miR-210, has been found to participate in the upregulation of glycolysis by inhibiting mitochondrial respiration (OXPHOS). miR-210, also known as proangiomir, induces the expression of glucose transporter, Glut-1, followed by the upregulation of VEGF and platelet-derived growth factor, creating a proangiogenic microenvironment.[147] The angiogenic regulation by hypoxia is an important component of adaptive mechanisms, which bridges the metabolic demand with the vascular network oxygen supply. Recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis has been shown to be under the regulation of HIF-1α.[148] The overexpression of miR-210 in ECs (*in-vitro*) stimulates angiogenesis with increased migration potential and its downregulation reduced hypoxia-induced capillary formation.[149] Receptor tyrosine kinase, Ephrin-A3, that is associated with vascular remodeling is identified as another important miR-210 target.[150] Interactions between miRNAs and HIF add another molecular-level complexity in hypoxia-driven-altered glucose metabolism supporting invasion, angiogenesis, and metastasis in various tumor types such as lung, breast, and gliomas.

Several studies have established an association between p53 mutations and the star hallmark of cancer, that is, metabolic reprograming (Warburg's effect) in a majority of cancer types.[151] Recently, miR-34a, a direct transcriptional target of p53, has been shown to function as a tumor suppressor inhibiting metastasis and angiogenesis indirectly by repressing glycolysis via the inhibition of glycolytic enzymes such as HK1, HK2, glucose-6-phosphate isomerase (G6PI), and PDK1 and also by directly targeting CD44 in bladder cancer.[152] Various isoforms of CD44 gene have been attributed to EMT, angiogenesis, invasion, metastasis, invasion, migration, and metabolism correlated with increased Akt activity.[153–155] Further, overexpression of miR-34a was shown to downregulate matrix metalloproteinase (MMP)-1 and MMP-9 expression, strongly inhibiting migration and invasion as shown in colon cancer cells,[156] while p53 mutation or loss of miR-34a function has been shown to facilitate invasive and migratory phenotype through upregulated glycolysis.

A symbiotic relationship between cancer cells and cancer-associated fibrobalsts as well as ECs involving peroxide generated by tumor cells and lactate by stromal cells has been recently shown to facilitate tumor growth and metastasis.[157,158] It appears that miRNAs facilitate the bidirectional communication between cancer cells and the stroma through microvesicles, thereby promoting angiogenesis and tumor growth (Fig. 4). Tumor suppressor miRNA, miR-320, influences glycolysis via downregulation of the PI3K/Akt pathway.[159] miR-320 is a crucial player of the tumor-suppressive PTEN-controlled axis in stromal fibroblasts and is considered as metabolic stress/status responsive miRNA.[160] The attainment of the protumorigenic microenvironment with increased migration, invasion, and neovascularization upon loss of PTEN and miR-320 is shown to be linked with unique tumor-promoting secretory factors called *secretomes*.[160,161] *In vitro* studies in human umbilical vein endothelial cells have shown a significant decrease in the expression of miR-320 under high glucose conditions (similar to diabetes), while upregulating the expression of ET-1, VEGF, and FN through its direct influence on ERK1/2 MAPK.[162] Similarly, suppression of miR-320a has been found to enhance the levels of PFKm (muscle type), the rate-limiting enzyme of glycolysis, in the lung adenocarcinoma tissue and muscle, suggesting a distinct link between miR-320-mediated glucose regulation and malignant phenotype.[163,164] Further, miR-26a is also a direct regulator of PTEN, as seen in human as well as in rodent model gliomas and lung where PTEN loss has been associated with deregulated Akt activity and miR-26a expression with metastatic and angiogenic potential.[165–167]

Role of miRNAs in the Regulation of Oncogenic Signaling Pathways Closely Linked to Metabolic Reprograming

The process of carcinogenesis is marked by progressive changes in intra- and intercellular signaling pathways that are closely associated with oncogenic transformation and/or metabolic reprograming. Significant advances that have been made in unraveling the role of miRNAs involved in the alterations of certain key signaling pathways will be discussed here.

PI3K/Akt/mTOR pathway. The serine/threonine kinase Akt – also known as protein kinase B – is the most frequently activated protein kinases in human cancers. The predominant mechanisms by which Akt is activated in human cancer are through mutational inactivation of PTEN by NADPH through a redox modification mechanism and mutational activation of the catalytic subunit of PI3K.[168,169] Akt hyperactivation is closely associated with cellular processes that contribute to the classical Warburg's effect in cancer cells and can contribute in the process of carcinogenesis by inhibiting apoptosis, increasing cell proliferation, and/or by accelerating oncogenic mutation rates.[170]

The expression of miR-181a is found to be enhanced in colon cancer cells, which induce a metabolic shift by inhibiting the expression of PTEN, leading to an increase in phosphorylated Akt. The increase in lactate production induced

by miR-181a as a result of upregulated glycolysis in response to activated PI3K/Akt signaling supports the rapid growth of cancer cells and suppresses apoptosis. Cyclin D1, a cell cycle checkpoint protein, is also upregulated in miR-181a-overexpressing cells, further supporting the regulation of cell growth by miR-181a.[171]

AMPK signaling. In untransformed cells, the 5′-AMPK pathway is the major cellular sensor of energy availability. AMPK is activated by metabolic stress to promote energy conservation and glucose uptake, allowing cells to survive periods of low energy (ATP) availability.[172] LKB1 (also known as serine/threonine kinase 11), a known tumor suppressor, is the key upstream activator of AMPK.[173] miR-451 regulates AMPK signaling in response to glucose levels in glioma cells by targeting the binding partner of LKB1, CAB39 (MO25a), thereby regulating cell survival, motility, and proliferation. Under conditions of sufficient nutrients (glucose), elevated miR-451 levels reduce the activation of LKB1/AMPK pathway, facilitating cell proliferation by allowing unrestrained mTOR activity and inhibition of apoptosis, promoting survival and motility in response to metabolic stress in glioma cells.[100] Accordingly, decreased miR-451 levels correlate with poor prognosis in gastric and colorectal cancers, perhaps by reduced ability to target macrophage migration inhibitory factor, which is a known activator of AMPK signaling.[174,175] Thus, the major function of miR-451 appears to be the suppression of AMPK.

miR-33a and miR-33b have also been shown to control the expression of AMP-activated kinase 1 (Ampkα1) and sirtuin 6 (Sirt6), which are involved in the regulation of lipid and glucose metabolism. Inhibition of AMPKα1 by miR-33 may increase the activity of the key regulated lipogenic enzymes 3-hydroxy-3-methylglutaryl-CoA reductase and acetyl-CoA carboxylase to boost the intracellular levels of cholesterol and fatty acids to sustain proliferation of tumor cells. In addition, insulin receptor substrate 2 (Irs2), an adaptor protein that controls insulin signaling in the liver, has also been shown to be a miR-33 target, thereby affecting the signaling of a complex downstream network of proteins, including Akt phosphorylation and forkhead box O1 cytoplasmic localization.[176]

Regulation of HIF signaling. The responses of tumor cells to hypoxia are at least partially orchestrated by activation of the HIFs. HIF-1, a transcription factor composed of HIF-1α and HIF-1β subunits, is stabilized and activated in response to low oxygen tension and plays critical roles in the adaptation of tumor cells to a hypoxic microenvironment.[177] It activates the transcription of genes, such as GLUT-1 (glucose uptake) and LDHA (lactate production), that are involved in crucial aspects of cancer biology, including glucose metabolism, cell survival, angiogenesis, and invasion and decreases reliance on mitochondrial OXPHOS.[178]

HIF-1α induces cell cycle arrest by activating p21 or p27 and apoptosis through stabilization of p53.[179] Induction of miR-17-92 through transcriptional activation by c-myc downregulates HIF-1α, leading to evasion of apoptosis and unrestrained growth.[144] HIF-1α level is also regulated by miR-199a, which directly targets HIF-1α[145] and several other miRNAs, whose levels are altered in multiple cancers, namely, miR-20a, miR-20b, miR-21, miR101, miR-106a, miR-106b, miR150, and miR-200b, which are predicated to target Von Hippel–Lindau factor, an E3 ubiquitin ligase that marks HIF-1α for degradation under normoxic conditions.[180] miR-424, a hypoxia-inducible miRNA, targets cullin 1 (CUL2), a scaffolding protein critical to the assembly of the ubiquitin ligase system, and hence, stabilizes HIF-1α.[181] miR-22 and miR-20b also act as tumor suppressors by inhibiting hypoxia signaling and suppressing HIF-1α translation. Since c-myc has been shown to limit miR-22 expression, tumors overexpressing c-myc might be expected to have lower levels of miR-22, higher levels of HIF-1α, and VEGF. Therefore, miR-22 may also play a significant role in the regulation of tumor angiogenesis and cell survival.[182]

Regulation of c-myc. The MYC oncogene is a key transforming oncogenic agent and frequently dysregulated in a wide variety of human tumors.[183] In normal cells, myc protein levels are transiently elevated during cell growth but decline to low levels as cells exit the cell cycle.[184] Dysregulated MYC induces immortalization, genomic instability, independence of growth factors, and escape from immune surveillance leading to a cancerous state.[185] With E2F1, c-Myc induces genes involved in nucleotide metabolism and DNA replication, and miRNAs that homeostatically attenuate E2F1 expression for safe passage of cells through S phase, whereas in association with HIF-1α, it programs the adaptive response of cells to hypoxic conditions.[65,186] MYC directly regulates the expression of genes that encode the enzymes in the nucleotide biosynthetic pathways and in the feeder pathways for the production of the precursors of all nucleotides including the amino acids aspartate, glutamine, serine, glycine, and CO_2, as well as coordinates RNA and protein biosynthesis.[187–189] It has been shown that the inhibition of C-MYC results in the repression of several enzymes rate-limiting for nucleotide metabolism including TS, inosine monophosphate dehydrogenase 2, and phosphoribosyl pyrophosphate synthetase 2 (PRPS2). It also leads to the depletion of intracellular deoxyribonucleoside triphosphates, and subsequently, suppression of proliferation.[64] PRPS2 couples protein and nucleotide biosynthesis through a specialized cis-regulatory element within the PRPS2 5′ UTR, called the pyrimidine-rich translational element (PRTE), which is controlled by the oncogene and translation initiation factor eIF4E downstream of Myc activation. Thus, PRTE enables translational regulation by Myc to directly increase nucleotide biosynthesis proportionately to the increased protein synthesis rates of cancer cells.[190]

In addition to glycolysis, c-myc stimulates glutamine catabolism to fuel growth and proliferation of cancer cells.[82] Glutamine serves as a nitrogen source for multiple steps of both purine and pyrimidine synthesis. Also, glutaminolysis is the major mechanism for TCA anapleurosis to replenish TCA intermediates

diverted for nucleotide synthesis.[191] miR-23 targets glutaminase (GLS) mRNA and inhibits the expression of GLS protein, inducing mitochondrial dysfunction leading to cell death. c-myc transcriptionally represses miR-23a and miR-23b, which target GLS mRNA, resulting in a greater expression of GLS protein.[192] Tumor cells grown in glutamine have been shown to have increased nuclear factor-kappa B p65 subunit translocation to the nucleus where it controls glutamine metabolism by downregulating miR-23a levels by binding to its promoter.[193] Therefore, p65 activation decreases miR-23a expression, facilitating glutamine consumption and faster proliferation, allowing cancer cells to use this alternative source of carbon and favoring their adaptation to the altered metabolic environment.

After conversion of glutamine to glutamate, glutamate can also be converted to proline through Δ1-pyrroline-5-carboxylate (P5C) and vice versa. Proline oxidase, also known as proline dehydrogenase (POX/PRODH), the first enzyme in proline catabolism, is directly induced by p53 and is a mitochondrial tumor suppressor that inhibits proliferation by causing cell cycle arrest at the G2-M checkpoint and inducing apoptosis.[194] myc regulates proline metabolism by suppressing POX/PRODH expression primarily by upregulating miR-23b* and increasing the enzymes of proline biosynthesis from glutamine, including P5C synthase and P5C reductase 1. Suppression of myc leads to an increase in POX/PRODH ratio inducing ROS generation and apoptosis, leading to decreased cell proliferation and growth.[195] Besides miR-23a, IL-6/STAT3 signaling also upregulates the expression of c-myc, which in turn can repress miR-23a expression.[196] Thus, myc-induced suppression of POX/PRODH contributes to myc-mediated changes in cell behavior including proliferation and metabolic reprograming that, in turn, contributes further in tumor progression.

C-myc also supports the tumor growth by c-myc-mediated transactivation of the RNA-binding proteins Lin-28a/b, which repress the let-7 miRNA family members.[197] The let-7 miRNA family members act as tumor suppressors by negatively regulating the translation of oncogenes (V-Ki-ras2 Kirsten rat sarcoma (KRAS), Neuroblastoma rat sarcoma (NRAS), V-Myc Avian Myelocytomatosis (MYC), and High-mobility group AT-hook 2 (HMGA2) and cell cycle regulators and are either suppressed or deleted in various human cancers.[198] For example, let-7 has been shown to function as a tumor suppressor in lung cells, directly controlling cellular proliferation by negatively regulating the human RAS genes, as well as a few key cell cycle proto-oncogenes, such as CDC25a, CDK6, and cyclin D, thus reducing flux through the pathways promoting G1 to S transition.[199,200]

The RNA-binding proteins, Lin28a and Lin28b (collectively referred to as Lin28a/b), are highly expressed during normal embryogenesis and upregulated in some cancers to potently and selectively block the maturation of let-7.[201,202] By repressing the biogenesis of let-7 miRNAs and in some cases through direct mRNA binding and enhanced translation, Lin28a/b regulates an array of targets involved in cell proliferation and differentiation.[203] Interestingly, the let-7/Lin 28 axis regulates glucose metabolism as well in cancer cells. Overexpression of let-7 or loss of Lin28a results in insulin resistance and impaired glucose tolerance that occurs, in part, through the let-7-mediated repression of multiple components of the insulin/PI3K/mTOR pathway, including IGF-1R, INSR, and IRS2.[105] PI3K/Akt signaling is known to promote GLUT4 translocation to upregulate glucose uptake, while mTOR signaling can promote glucose uptake and glycolysis by modulating gene expression independently of GLUT4 translocation.[204]

The altered metabolism of anaerobic glycolysis 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. The lactate generated in the cytosol is secreted outside the cells by the monocarboxylate transporters, whose membrane levels are regulated by CD147, a broadly expressed plasma membrane glycoprotein. Since the expression of CD147 is also regulated by let-7b, repression of glucose metabolism by let-7 in cancer cells is compensated by the upregulation of Lin28a/b, which promotes tumor growth, migration, and tumor metastasis.[205]

p53 signaling. The role of p53 as a central component of the stress response machinery is well established. Since any stress signal, whether extrinsic or intrinsic to the cell, can activate p53, the responses to metabolic stress resulting from limited nutrient, energy, or O_2 availability in cancer cells also involve p53. p53 inhibits glycolysis by transcriptionally repressing GLUT1 and GLUT4 and enhances mitochondrial respiration by inducing synthesis of cytochrome *c* oxidase 2 (SCO2) and glutaminase 2 (GLS2). In tumors where p53 is highly mutated and SCO2 is low, glycolysis appears to be the safest option to meet the high-energy demand of proliferating cells. p53 enhances the expression of TP53-induced glycolysis and apoptosis regulator, while inhibiting the expression of phosphoglycerate mutase, resulting in the inhibition of glycolysis.[206] p53 regulates and itself is regulated by various miRNAs. It activates the transcription of miR-34a and miR-194/miR-215 cluster, which functions as effectors in the p53 signaling pathway by inducing cell cycle arrest and apoptosis.[207] miR-34a indirectly activates p53 by downregulating SIRT1, which negatively regulates p53 through deacetylation, leading to induction of p21 and PUMA and ultimately apoptosis.[208] As SIRT1 activity is NAD dependent, the metabolic state of the cell may also influence the effectiveness of this regulation. miR-34a also inhibits cellular glycolysis by directly targeting hexokinase 1 (HK1), HK2, and G6PI. Loss of miR-34 through genetic or epigenetic mechanisms interrupts this feedback resulting in lower p53 activity and thereby provides a selective advantage for cancer cells by increasing glycolysis.[151] p53 also suppresses the transcription of some tumorigenic miRNAs such as miR-17-92 family.[209] Activation of miRNAs, miR-16-1, miR-143, and miR-145, by p53 through enhanced posttranscriptional processing further controls the cellular division through cell cycle arrest by

targeting KRAS and CDK6.[210] miR-25, miR-30d, miR-504, and miR-125b directly target p53 3′-UTR and hence impair p53 response and promote tumorigenicity through direct reduction in p53 protein levels.[211] miR-372 and miR-373 are two other oncogenic miRNAs that promote cell proliferation and tumor development by neutralizing p53-mediated CDK inhibition, possibly through direct inhibition of expression of the tumor suppressor gene LATS2 (large tumor suppressor kinase 2).[212] Since p53 is mutated/negatively regulated by miRNAs in most of the cancers, the tumor-suppressive function of p53 of inhibiting glycolysis is compromised to support the high rates of proliferation of cancer cells.

Summary and Conclusions

Although metabolic reprograming in the form of Warburg phenotype, regarded as one of the most important hallmarks of cancer, is known for nearly a century, translation of this knowledge into the development of therapeutics unfortunately has been not encouraging so far. While the initial excitement of using the glycolytic inhibitor 2-DG as a therapeutic[213] was soon aborted due to undesirable toxicity in the form of diaphoresis and disturbances in the central nervous system, the[214] deployment of this analog as an adjuvant in the radio- and chemotherapy has only made a modest progress despite excellent tolerance and minimal toxicity.[11,215–220] With increasing knowledge about the miRNA-mediated regulation of the interplay between the metabolic reprograming and the malignant phenotype, including resistance to therapies, hopefully, we will identify critical miRNA targets or events regulated by them that will pave way for the development of novel therapeutics with high-target specificity and minimum nontarget (normal tissue/cells) effects. Looking at the rate of advances made and the nature of insights obtained in the last couple of years, it appears that the translation of knowledge from research in the areas of metabolism, miRNA, and therapeutic response is round the corner.

Author Contributions

Prepared the preliminary draft of the manuscript: AA, SS. Contributed to the writing of the manuscript: SP. Jointly developed the structure and arguments for the paper: AA, SS, BSD, ANB. Made critical revisions and approved the final version of the manuscript: BSD, ANB, RS. All authors reviewed and approved the final manuscript.

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