



MicroRNAs in Tumor Cell Metabolism: Roles and Therapeutic Opportunities

Abraham Pedroza-Torres^{1††}, Sandra L. Romero-Córdoba^{2†}, Montserrat Justo-Garrido³, Iván Salido-Guadarrama⁴, Rubén Rodríguez-Bautista⁵, Sarita Montaña⁶, Rodolfo Muñiz-Mendoza⁷, Cristian Arriaga-Canon³, Verónica Frago-Ontiveros⁷, Rosa María Álvarez-Gómez⁷, Greco Hernández⁸ and Luis A. Herrera^{3*}

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*Correspondence:

Abraham Pedroza-Torres
abraneet@gmail.com
Luis A. Herrera
metil@hotmail.com

†These authors have contributed
equally to this work

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¹ Cátedra CONACyT-Clinica de Cáncer Hereditario, Instituto Nacional de Cancerología, Mexico City, Mexico, ² Departamento de Bioquímica, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, Mexico City, Mexico, ³ Unidad de Investigación Biomédica en Cáncer, Instituto Nacional de Cancerología - Instituto de Investigaciones Biomédicas - Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico, ⁴ Biología Computacional, Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”, Mexico City, Mexico, ⁵ Unidad de Oncología Torácica y Laboratorio de Medicina Personalizada, Instituto Nacional de Cancerología, Mexico City, Mexico, ⁶ Laboratorio de Bioinformática, Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Sinaloa (FCQB-UAS), Culiacán, Mexico, ⁷ Clínica de Cáncer Hereditario, Instituto Nacional de Cancerología, Mexico City, Mexico, ⁸ Laboratorio de Traducción y Cáncer, Unidad de Investigaciones Biomedicas en Cáncer, Instituto Nacional de Cancerología, Mexico City, Mexico

Dysregulated metabolism is a common feature of cancer cells and is considered a hallmark of cancer. Altered tumor-metabolism confers an adaptive advantage to cancer cells to fulfill the high energetic requirements for the maintenance of high proliferation rates, similarly, reprogramming metabolism confers the ability to grow at low oxygen concentrations and to use alternative carbon sources. These phenomena result from the dysregulated expression of diverse genes, including those encoding microRNAs (miRNAs) which are involved in several metabolic and tumorigenic pathways through its post-transcriptional-regulatory activity. Further, the identification of key actionable altered miRNA has allowed to propose novel targeted therapies to modulated tumor-metabolism. In this review, we discussed the different roles of miRNAs in cancer cell metabolism and novel miRNA-based strategies designed to target the metabolic machinery in human cancer.

Keywords: microRNAs, reprogramming metabolism, regulation, therapeutic targets, tumor cell metabolism

INTRODUCTION

Ever since their discovery in 1993 (1), microRNAs emerged as a new class of small RNAs with a critical role in the regulation of gene expression. MicroRNAs (miRNAs or miRs) are endogenous small non-coding RNAs from 18-25 nucleotides in length that regulate gene expression via base complementarity between the seed region of the microRNA and the 3'-untranslated region (UTR) of the target mRNA (1, 2). Depending on the degree of complementarity, miRNAs binding can induce mRNA degradation, translational repression, or both (3–5). For the considerable relevance of miRNAs in gene expression, these tiny RNA molecules have recently been called “master regulators of gene expression” (6).

The biogenesis of miRNAs has been extensively studied (7–9). For instance, genes encoding miRNAs show distinct genomic locations, such as intergenic, intronic, exonic, or mirtronic (a type

of miRNA that is located in the introns of the mRNAs). Genes encoding miRNAs are transcribed in the nucleus in the form of long primary transcripts (pri-miRNAs) typically, although not exclusively, by RNA Pol II (10). Afterward, pri-miRNAs are processed into a small stem-loop transcript of approximately 55–70 nucleotides by the RNA-binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) and Drosha (a ribonuclease III enzyme) (11, 12). This new structure, termed pre-miRNA, is recognized by Exportin 5 (Exp 5) and is exported from the nucleus to the cytoplasm (13). Once in the cytoplasm, pre-miRNA hairpins are cleaved by the Dicer RNase III enzyme and TRBP (TAR RNA-binding protein), resulting in a ~22 nucleotide mature miRNA-miRNA* duplex (14–16).

Finally, the mature miRNA is loaded onto Argonaute 2 protein (AGO2) and the RNA-induced silencing complex (RISC) to catalyze site-specific cleavage or translational repression of their mRNA targets (17, 18). The post-transcriptional regulation of gene expression by miRNAs is of paramount importance, thus, it is estimated that miRNAs could regulate nearly 60% of all human protein-coding genes (19). miRNAs are involved in several cellular processes, such as proliferation, development, differentiation, apoptosis, carcinogenesis, and energy metabolism (20–26).

During tumorigenesis, dysregulated metabolism represents an adaptive advantage of cancer cell that promote uncontrolled cell division, cell growth, and survival (27, 28). One of the best characterized metabolic disorders during cancer development is the Warburg effect, that increase glucose uptake and lactate production. During the Warburg effect, miRNAs activity contributes to keeping high levels of glycolysis. miRNAs also control other crucial steps of the energy metabolism, including glucose transport, glycolysis, tricarboxylic acid cycle, glutaminolysis, altered lipid metabolism, insulin production, cholesterol, and lipid homeostasis, as well as amino acid and nucleotide biogenesis (29–33).

In this review, we focus on the different roles of miRNAs in cancer metabolism and discuss novel miRNA-based strategies designed to target different processes in human cancer. We also explore the links between microbiota and miRNA networks and cancer, with a particular focus on genotoxicity and tumor-metabolism.

METABOLIC REPROGRAMMING IN CANCER CELLS

Upon cancer onset and progression, cells exhibit various growth, proliferation, and survival phenotypes. These cancer hallmarks are supported by a catabolic and anabolic metabolism reprogramming. Increasing evidence has shown that metabolic changes are the result of complex processes, and several cellular pathways are implicated (34–36). Recent findings have led to a significant shift in our understanding of altered metabolic states, which now are seen as a central transformative force in cancer development (37–39).

The Warburg effect is thought to be an early event in cancer that promotes rapid adaptation to higher bioenergetic demands,

such as, excessive proliferation and hypoxic microenvironments. Warburg effect is characterized by: (a) supports the demand for ATP synthesis and promotes its flux into biosynthetic pathways to achieve an uncontrolled proliferation; (b) maintains an acidic microenvironment via the accumulation of lactate; and (c) allows for ROS signaling homeostasis (40–43). Moreover, reprogramming energy metabolism promotes tumor cells to use alternative carbon sources such as glutamine, considered to be the second source of nutrients after glucose. Glutamine is the most abundant amino acid in cells, and its catabolism results in several amounts of cellular precursors, including glutamate, aspartate, pyruvate, lactate, alanine, and citrate (44–46).

For many years, the Warburg effect was considered as a synonym for metabolic reprogramming. However, it is clear that this phenotype alone cannot explain all the metabolic alterations that enhance the formation of primary tumors and their development throughout invasion and metastasis. Recent publications have also reported the metabolic interactions between tumors and the microenvironment involving cancer-associated fibroblasts, immune cells, and microbiota, which allows us to expand our understanding of the metabolic reprogramming and reveals the complex interaction networks required to establish the tumor phenotype (47–49). Most of the aforementioned metabolic features are a consequence of the deregulation of several cell pathways and often involve altered oncogenes, tumor suppressors, and miRNA.

miRNAs REGULATION OF METABOLIC PATHWAYS IN CANCER

In the last decade, a growing volume of evidence has revealed the role of miRNAs in the regulation of energy metabolism, directly, through the regulation of glucose transporters (GLUT family), enzymes (hexokinase 1/2, Aldolase A), and protein kinases (AMPK, PI3K), or indirectly, through inhibition of several transcriptional factors (p53, c-Myc) (50–52). In any case, the role of miRNAs in the regulation of energy metabolism has gained much interest by their nature to modulate cellular metabolism and the possibility to use miRNAs-targets genes circuits as cancer therapies. Therefore, we review the main pathways of energy metabolism, the genes involved in each metabolic signaling and their transcriptional landscapes articulated by the miRNAs in cancer programs.

miRNAs AND GLUCOSE TRANSPORTERS

Glucose represents the main source of cellular energy. In cancer, tumor cells increase their glucose consumption to maintain the high energy requirements. However, due to the hydrophilic composition of glucose, it is not able to cross the plasma membrane by its own. To overcome this situation, tumor cells induce the expression of several members of the glucose transporters family (GLUTs, also named SLC2A proteins). Glucose transporters are membrane-associated carrier proteins responsible for facilitating the transport of glucose across the plasma membrane. In the human genome, 14 GLUT proteins

have been found. Among different members of the GLUTs family, the expression of GLUT1, GLUT2, and GLUT3 has been reported to be upregulated in different types of tumors, whereas GLUT4 and GLUT5 are downregulated (53, 54). miRNAs control glucose uptake by regulating the GLUTs expression; for example, miR-144 and miR-132 are two miRNAs that have been associated with the regulation of GLUT1, one of the most broadly expressed isoforms in various cell types. Lui et al. reported that the downregulation of miR-144 induces an increase in glucose uptake in lung cancer (55). Moreover, Qu et al. demonstrated that the decrease in miR-132 expression altered glucose metabolism in prostate cancer (56). Additionally, miR-150 has been reported as a GLUT1 regulator in CD4+ cells (57). In renal cell carcinoma, miR-138, miR-150, miR-199a-3p, and miR-532-5p overexpression are associated with a decreased expression of GLUT 1, whereas miR-19a, miR-19b, miR-130b, and miR-301a decrease are directly associated with an over-expression of GLUT 1 (58).

GLUT3, another member of the glucose transport proteins family, is also regulated by miRNAs. Fei et al. demonstrated that miR-195-5p directly regulates the expression of GLUT3, and consequently decreases glucose uptake and inhibits cell growth in T24 bladder cancer cells (59). Similar results were reported by Dai DW in U251 and LN229 glioblastoma cells through the activity of miR-106a over GLUT3. Additionally, the authors indicated that miR-106a down-regulation is associated with glioblastoma patients survival (60).

Other examples of miRNAs that regulate glucose uptake are miR-233 and miR-133, which directly regulate the expression of GLUT4 (26, 61). Interestingly, miR-21 and miR-23a indirectly regulate the expression of GLUT4, as a result of their regulation over two GLUT4 translocators: PTEN and SMAD4 (62, 63). An exhaustive work published by Esteves et al., highlight the role of miR-21a-5p, miR-29a-3p, miR-29c-3p, miR-93-5p, miR-106b-5p, miR-133a-3p, miR-133b-3p, miR-222-3p, and miR-223-3p that directly or indirectly regulate the expression of GLUT4 (64). To our knowledge, there are no reports describing other members of the GLUT family regulated by miRNAs, although miRNA target prediction analysis identifies a set of miRNAs capable to silence them; however, further studies are needed to determine their contribution to aberrant tumor cell metabolism.

miRNAs IN GLYCOLYSIS

Unlike tumor cells, normal cells obtain energy in the form of ATP through the glucose-derived pyruvate by the mitochondrial oxidative phosphorylation. Conversely, regardless of oxygen conditions, tumor cells prefer anaerobic glycolysis, a less efficient process for obtaining ATP that produces large amounts of lactate. To compensate for this apparent decrease in energy flow, tumor cells increase glucose uptake and trigger alternative pathways to metabolize alternative carbon sources, such as glutamine, and some amino acids, such as arginine and glycine. This change in the energy metabolism confers several advantages to tumor cells, in addition it also provides necessary biomolecules for the high rates of cell division (65, 66).

During the first step of glycolysis, glucose is transformed into glucose-6 phosphate through the phosphorylation of the 6-hydroxyl group of glucose by the enzyme hexokinase (HK). The hexokinase family of enzymes comprises four isoforms (HK1–HK4) (67–69). Isoform 2 (HK2) has been reported to be upregulated in a wide variety of tumors (70–72).

One of the first works that demonstrated the regulation of miRNAs on the HK2 enzyme was published by Fang et al. Interestingly, they demonstrated that miR-125a and miR-143 regulate HK2, which modifies glucose metabolism and cell proliferation in lung cancer cells (73). This finding was confirmed by Peschiaroli et al. in head and neck squamous cell carcinoma (HNSCC)-derived cell lines (74), and by Gregersen et al. in colon cancer cells (75). Another miRNA, miR-199a-5p, regulates HK2 expression and has been reported to be under-expressed in liver cancer cells. Remarkably, overexpression of HIF1 α decreased miR-199a-5p expression, which promotes glycolysis and lactate production (30). In stomach cancer cells, miR-181b directly inhibits the expression of HK2 and causes a decrease in glucose uptake and lactate production (76). In addition, miR-155 has also been reported as a regulator of the expression of HK2. Jiang et al. demonstrated that miR-155 regulates the expression of HK2 by two different mechanisms. First, miR-155 promotes the indirect transcription of HK2 through the activation of STAT3, a transcriptional activator of HK2. Second, miR-155 regulates the expression of C/EBP β , a transcriptional activator of miR-143, whose overexpression is related to the inhibition of HK2 (77).

A couple of works showed that the enzyme responsible for catalyzing the second reaction of glycolysis, glucose-6-phosphate isomerase (GPI), is regulated by miR-200 in breast cancer cells (78) and by miR-302b and miR-17-5p in chicken primordial germ cells (79). Another glycolytic enzyme regulated by miRNAs is phosphofructokinase 1 (PFK1). PFK1 is the main regulatory enzyme for glycolysis; it catalyzes the phosphorylation reaction of fructose-6-phosphate to convert it into fructose-1,6-bisphosphate. In this sense, Yang et al. demonstrated that miR-135 targets PFK1, inhibits aerobic glycolysis, and suppresses tumor growth (31).

Similarly, Aldolase A, a glycolytic enzyme that catalyzes the conversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP), is targeted by several miRNAs. Among the miRNAs that have been reported to regulate Aldolase A expression are the following: miR-122 in liver cells (80), miR-15a and miR-16-1 in leukemia (81), and miR-31 and miR-200a in Y79 retinoblastoma cells (82).

The expression level of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) has been widely used for normalizing quantitative gene expression experiments. GAPDH catalyzes the sixth reaction of glycolysis, where a molecule of NADH is released. Like other enzymes in glycolysis, GAPDH is targeted by some miRNAs such as miR-644a (83) and miR-155 (84).

The last reaction of the glycolysis pathway is catalyzed by pyruvate kinase 2 (PKM2) enzyme. PKM2 dephosphorylates phosphoenolpyruvate to produce pyruvate regardless of oxygen concentration. PKM2 has been reported to be over-expressed in many tumors due to the dysregulation of various miRNAs that down-modulate it. Some of the miRNAs reported to directly

regulate the expression of PKM2 are miR-133a, miR-133b, miR-326, and miR-122 (85–87) whereas those that indirectly regulate it are miR-99a, miR-124, miR-137, and miR-340 (88, 89).

miRNAs INVOLVED IN LACTATE METABOLISM

In tumors, after the glycolysis phase, pyruvate is converted into lactate by the lactate dehydrogenase enzyme (LDH). Some works have reported increased levels of LDH and its correlation with tumor aggressiveness (90–92). Interestingly, LDH expression is also regulated by miRNAs. For instance, miR-375 regulates the subunit B of LDH (LDHB) in maxillary sinus and esophageal anaplasias (93). In addition, subunit A of LHA (LDHA) has been reported to be regulated by miR-34a, miR-34c, miR-369-3p, miR-374, miR4524a/b, miR-323a-3p, miR-200c, miR-30d-5p, and miR-30a-5p in breast cancer cells and osteosarcoma tissues, which induces a decrease in glycolysis, lactate production, ATP generation, and cell proliferation (94–99).

Lactate fluxes are mainly maintained by monocarboxylate transporter (MCTs). MCTs are membrane proteins acting as carriers for lactate, pyruvate, and ketone bodies. Up to now, four MCT isoforms (MCT1, MCT2, MCT2, and MCT4) have been described in humans, and each of them exhibits a distinct cellular distribution (100). In the same way as LDH enzymes, lactate carriers (MCT proteins) are regulated by diverse miRNAs. For example, MCT1 is targeted by miR-29a, miR-29b, miR-124, and miR-495 in pancreatic β cells (101, 102). Another MCT1-regulatory miRNA is miR-342-3p, which promotes alterations in lactate and glucose flows. In addition, miR-342-3p overexpression significantly decreased cell proliferation, viability, and migration in breast cancer cell lines (103). MCT4, another member of the family of lactate transporters, is regulated by miR-145, which causes the accumulation of lactate within tumor cells in hepatocellular carcinoma cells (HCC) (104).

miRNAs INVOLVED IN GLUTAMINE METABOLISM

Glutamine metabolism (glutaminolysis) represents the second source of nutrients in cancer cells. Actually, high rates of glutaminolysis are necessary for metabolic reprogramming as it provides substrates for increased lipogenesis and nucleic acid biosynthesis that are critical to preserve the high proliferation rates of tumor cells (105, 106). Glutaminolysis converts glutamine into TCA cycle metabolites through the activity of multiple enzymes. First, glutamine is transported into the cells by solute transporters SLC1A5 and SLC7A5. Once inside the cell, glutamine is converted into glutamate and later into alpha-ketoglutarate (α -KG) by glutaminase (GLS), glutamate dehydrogenase (GDH), and other enzymes, such as glutamate pyruvate transaminase (GPT) for alanine production and glutamate oxaloacetate transaminase (GOT) for aspartate production. In addition, glutaminolysis produces considerable amounts of succinate, fumarate, malate, NADH, and ATP molecules. The transport of glutamine into the cell is strictly

regulated by the membrane protein SLC1A5 (also called ASCT2 protein). SLC1A5 and other members of the ASC solute transporters family have been reported to be overexpressed in a wide variety of tumors. Dong J et al. showed that the exogenous expression of miR-137 and miR-122 markedly inhibited the SLC1A5 expression in a dose-dependent manner therefore altering tumor glutamine metabolism (107).

In a well-conducted work, Gao et al. demonstrated that the repression of miR-23a and miR-24b by the oncogenic transcription factor c-Myc resulted in a greater expression of GLS proteins and led to the upregulation of glutamine catabolism (108). Another miRNA reported to regulate GLS protein expression is miR-203, which additionally sensitizes malignant melanoma cells to temozolomide chemotherapy (109). Expression of glutamate cysteine ligase, the rate limiting enzyme of glutathione (GSH) synthesis, is attenuated by miR-18a in liver cancer (110) and by miRNA-153 in glioblastoma (111). Additionally, miR-450a limits the metastatic potential of ovarian cancer cells by targeting a set of mitochondrial mRNAs to reduce glycolysis and glutaminolysis (112).

miRNAs REGULATION OF OXPHOS

Oxidative phosphorylation (OXPHOS) is a metabolic pathway combining two cellular processes to generate energy in the form of ATP. First, in an oxidative stage, the electron donors such as NADH and FADH₂ are oxidized by the electron transport chain that turns the released energy into a proton gradient across the mitochondrial inner membrane. In the second stage, phosphorylation, ATP synthase uses the proton gradient to phosphorylate ADP to ATP. OXPHOS involves a system of protein complexes with oxidoreductase functions (complex I–IV) and ATP synthase (complex V). Even though OXPHOS is the most efficient way to produce cellular energy, tumor cells prefer to metabolize glucose via aerobic glycolysis. Several studies have recently indicated that, contrary to what is generally accepted, tumor cells could alternate between these two processes, OXPHOS and aerobic glycolysis, depending on the tumor microenvironment (113–115).

Interestingly, it has been proposed that several miRNAs regulate OXPHOS by inducing the inhibition of many components of the electron transport chain. For instance, miR-210 regulates the activity of the mitochondrial complex I (NADH: ubiquinone oxidoreductase) via the iron-sulfur cluster assembly enzyme (ISCU) by reducing the availability of iron and sulfur ions (116). Another study published by Muralimanoharan et al. revealed that miR-210 overexpression significantly reduces the complex III expression of the electron transport chain (ubiquinone:cytochrome c oxidoreductase) (117). Cytochrome c oxidase (complex IV), another enzyme of the electron transport chain, is also regulated by miRNAs. The following miRNAs have been reported to regulate cytochrome c oxidase: miR-181c (118), miR-338 (119), and miR-210 (117).

Finally, ATP synthase (complex V), a transmembrane enzyme that catalyzes ATP synthesis from an ADP molecule, is also regulated by miRNAs. Willers et al. reported that miR-127-5p

reduces the expression of the catalytic subunit of ATP synthase (β -F1 subunit) in BT-549 cells in breast cancer (120). Another miRNA, miR-141, reduces the activity of ATP synthase by reducing SLC25A3 proteins (121).

miRNAs REGULATION OF TRANSCRIPTION FACTORS AND SIGNALING PATHWAYS

miRNAs are also capable of modulating metabolic reprogramming through regulating various transcription factors relevant in metabolic pathways (122). The metabolic shift of tumor cells may be a potential strategy to evade programmed cell death and triggers cell survival and growth by activating oncogenes, such as RAS, MYC, and p53 (51, 123–126). Tumor metabolic reprogramming seems to be influenced by oncogenes and tumor suppressor networks. For example, phosphatidylinositol 3-kinase (PI3K), a lipid kinase that regulates the levels of phosphorylated phosphatidylinositol at the plasma membrane and enhances glucose uptake and glycolysis in cancer cell metabolism, is targeted by miR-320, miR-123a, miR-422, miR-506, and miR-136 (127). Catanzaro et al. showed evidence that downregulation of miR-139-5p in pediatric low-grade gliomas drives cell proliferation by regulating PI3K/AKT signaling (128). Furthermore, miR-33a/b, targets metabolic enzymes involved in fatty acid metabolism and the AMPK pathway, whereas miR-29b targets amino acid catabolism, which regulates cancer cell metabolism and biogenesis to support tumor growth and proliferation (61, 129–131). Like PI3K, AKT, and mTORC1, the MYC transcription factor has important metabolic roles beyond enhancing glycolysis. MYC promotes mitochondrial gene expression and mitochondrial biogenesis. MYC mainly depends on glutamine as a carbon source for mitochondrial metabolism (132). The oncogene MYC can bind to the promoter region of other oncogenes such as some miRNAs; for example, miR-9 is frequently upregulated in glioma specimens and cells, and it could significantly enhance proliferation, migration, and invasion of glioma cells (133).

On the other hand, miRNAs regulate important signaling pathways in mitochondria by triggering adaptive mechanisms to optimize the oxidative phosphorylation concerning the substrate supply and energy demands. For example, exogenous exosomes carrying miRNAs can induce metabolic reprogramming by restoring respiration in cancer cells and thus suppressing tumor growth. The exosomal-miRNAs involved in the modulation of cancer metabolism may be used for better diagnoses and therapies (134, 135).

Hypoxia-inducible factor 1 (HIF-1), another pathway related to tumor metabolism, is also regulated by miRNAs. HIF-1 activation can establish oncogenic signaling by promoting glycolysis of cancer cells; but also, an alternative mechanism over the glucose carbon mitochondrial metabolism confers HIF-1 a tumor suppressor role in some types of cancer (136, 137). In this way, miR-125-5p, miR-33-5p, and miR-190-5p are known to target the master regulator of oxygen deprivation response, HIF-1 (138). On the other hand, HIF-1 is a key

molecule in adapting cancer cells to the reduced oxygen availability in the microenvironment (139–141). HIF-1 induces metabolic reprogramming as it upregulates genes such as HK1, HK2, LDHA, PDK1, GLUT1, and GLUT3, which enhance lactate production through the glycolytic pathway (142, 143). HIF1 also influences the activity of the pentose phosphate pathway, nucleotide biogenesis, angiogenesis, and suppresses the mitochondrial function (144, 145).

Finally, the oncogene c-MYC regulates HIF1 expression regardless of oxygen levels, and both act in concert to “fine-tune” adaptive responses during tumor growth (146–149). Moreover, it has been reported that more than 50% of tumors have mutations in the tumor suppressor p53, which leads to metabolic changes and contributes to the Warburg effect through the upregulation of c-MYC, HIF-1, and a broad range of genes involved in other aspects of cancer biology, including tumor cell survival and proliferation, migration, drug resistance, and immune evasion (51, 150, 151). The advance in molecular biology techniques has allowed us to detect how a diversity of miRNAs regulate tumor metabolism, as we show in **Table 1** and **Figure 1**.

DRUGGABLE miRNA-METABOLIC NETWORKS WITH POTENTIAL VALUE FOR CANCER THERAPY

The unveiled connection between cancer profiles and metabolic reprogramming shed light on the reassessment of metabolism-targeting pharmacologic therapies as potential opportunities in cancer. Alterations in key miRNA regulatory networks contribute to the oncogenic transformation of cancer cells through genes involved in the metabolic switch (163). New insights into the altered tumor metabolism have provided novel therapeutic strategies that are being evaluated in preclinical models or clinical trials as effective therapies for many human cancers (164). Pharmacological targeting of altered miRNAs may have therapeutic effects by suppressing relevant cancer signaling pathways without affecting normal cells (165). Furthermore, pleuritic effects of metabolic drugs include miRNAs modulation that impairs signaling pathways and regulates cell energy production, which reveal miRNAs as potential drug targets.

Numerous studies now suggest that drug repurposing, which is the discovery of new therapeutic indications for known drugs, represents an attractive route in drug harnessing in cancer. Unlike the development of new molecules, drug repurposing identifies new uses for existing drugs that already have clinical and safety descriptions (166). Repurposing drugs with an oncological and non-oncological primary purpose, such as metabolic-based drugs, might be an attractive strategy to offer more effective treatment options to cancer patients and faster translate the research knowledge into the clinics (167). Interestingly, a growing body of evidence has shown that many of the antineoplastic effects and improved responses to these metabolic-based drugs may be mediated through induction of tumor suppressor miRNAs and suppression of oncogenic miRNAs.

TABLE 1 | Main miRNAs that regulate cellular metabolism in different types of cancer.

miRNA	Location	Cancer type	Target gene/pathway	References
miR-125a	19q13.41	Hepatocellular carcinoma	HK2	(152, 153)
miR-192/215-5p	11q13.1, 1q41	Colorectal cancer	ZEB1 and ZEB2, Type I collagens	(104)
miR-140-3p	16q22.1	Chronic myeloid leukemia	SIX	(154)
miR-140-3p	16q22.1	Spindle cell oncocyomas	TCA, carbohydrate, lipid metabolism	(155)
miR-940	16p13.3	Glioma	MTHFD2	(156)
miR-139-5p	11q13.4	Pediatric low-grade gliomas	PI3K/AKT signaling	(128)
miR-151a-5p	8q24.3	Malignant pleural mesothelioma	FASN, OXSM, ACACB	(157)
miR-361-5p	Xq21.2	Prostate cancer	Sp1/PKM2 axis	(158)
miR-7, let-7a, miR-34a and miR-143	9q21.32, 9q22.32, 1p36.22; 1p36.22, 5q3	Glioblastoma	Critical regulators of aerobic glycolysis	(159)
miR-125	19q13.41	Hepatocellular carcinoma	HK2	(160)
miR-122	18q21.31	Hepatocellular carcinoma	PKM2 and represses glycolytic metabolism	(161)
miR-126	9q34.3	Mesothelioma, hepatocellular, pancreatic and breast cancer	Insulin receptor substrate-1 (IRS1)	(134)
miR-195-5p	17p13.1	Bladder cancer	GLUT-3	(59)
miR-155	21q21.3	Breast cancer	miR-143	(77)
miR-378	5q32	Breast cancer	ERR γ and GABPA	(162)

In this section, we describe existing evidence of molecules with biochemical mechanisms impairing tumor metabolism. These molecules appear as the most promising repurposing and *de-novo* pharmacological interventions as shown by preclinical and clinical studies. Particular emphasis was put on chemoresistance, which is recognized as a critical cause of treatment failure. It is reported that dysregulations of miRNAs contribute to therapy resistance via drug efflux mechanisms, alterations in drug targets, energy metabolism, DNA repair pathways, evasion of apoptosis, cell cycle control, among others (6, 168, 169). We briefly described below some pharmacologic therapies employed in different metabolic-related diseases and how they could selectively target metabolic pathways in cancer cells and modulate miRNAs networks, we will also comment some of the most relevant evidence of each of the metabolic therapeutically intervention and its anti-carcinogenic properties via miRNA activity. A more extensive over-view of miRNA expression portraits modulated by pharmacological treatment, as well as cooperative or resistance phenotypes toward drug activity is listed in **Table 2** and **Figure 2**.

TARGETING GLUCOSE METABOLISM: METFORMIN

Metformin, a commonly prescribed drug for treating type 2 diabetes, inhibits the mitochondrial complex I that impairs

respiration, which results in a systemic impede of glucose uptake and neoglucogenesis (217–220) that reduces blood glycemia and insulinemia in hyperglycemic/diabetic patients. The tumor-suppressing effect of metformin has been reported in epidemiological studies describing a statistical association between metformin use and improved clinical outcomes in cancer (221–224). One striking example of this onco-suppressive feature is the cooperative effect of metformin and neoadjuvant chemotherapy to achieve complete tumor regression in some breast cancer patients (225). Although the precise anti-tumorigenic mechanism of action is not well-described, recent studies have shown that metformin can partially direct mitochondrial complex I inhibition, reduce NADH oxidation, and increase AMP/ATP ratio in tumors, with the consequent inhibition of mTOR signaling and decrease of fatty acid and cholesterol synthesis (218, 220, 226). Thus, metformin favors a catabolic process over an anabolic one in tumor cells. Overall, this metabolic pressure causes proliferation decline and triggers apoptosis in cancer cell lines [(227); **Table 2** and **Figure 2**].

A variety of evidence, both *in-vitro* and *in-vivo* along with epidemiological studies, supported the protective effect of metformin against cancer development (228–231). Even more, the role of metformin on cancer not only fall in limiting its incidence, but also as a novel therapeutically intervention as shown by the 335 registered clinical trials that have evaluated patients benefit of incorporate Metformin in their treatment. The

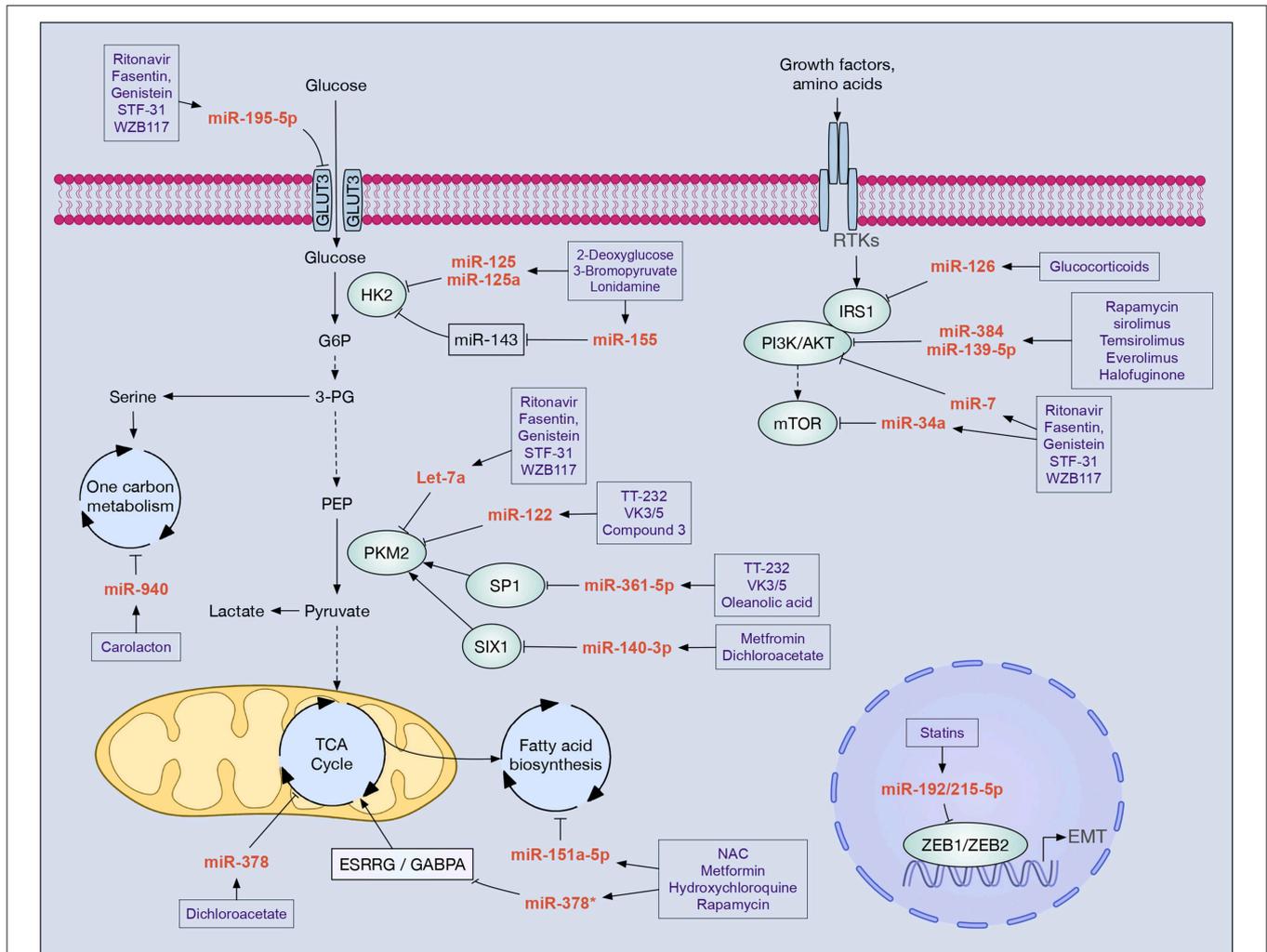


FIGURE 1 | Drugs with clinical potential in cancer that modulate miRNAs implicated in cell metabolism. In boxes are shown drugs that potentially modulate the main miRNAs involved in the metabolic reprogramming of tumor cells. Increased glycolysis flow, alteration of the PI3K/AKT/mTOR pathway, and epithelial-mesenchymal transition (EMT) are key processes that allow tumor cells to reprogram their metabolism in order to survive, proliferate, migrate, and evade new niches. Different miRNAs participate in these processes inhibiting the expression of enzymes (e.g., HK2, PKM2, IRS1, PI3K, AKT, mTOR), transcription factors (e.g., SP1, SIX1, ZEB1, ZEB2, GABPA), and cellular receptors (e.g., GLUT3, ESRRG).

underlying mechanism of the anticancer activity of Metformin can be partially explained through its ability to modulate miRNA expression, activity and biogenesis in a variety of tumor types (Table 2 and Figure 2). For instance, overexpression of the tumor suppressors let-7, miR-26, and miR-200 family members has been reported in the literature as a pleuritic effect of Metformin molecular activity in breast, colorectal, pancreatic, oral and renal cancer. Briefly, Metformin up-modulates let-7a, that epigenetically inhibits the oncomiR miRNA-181a, which actively participated in the epithelial-to-mesenchymal transition, thus, abrogating this aggressive phenotype in BRCA (170). In CRC, the metabolic drug overexpress let-7, miR-200b/c, and miR-26a that limit the stem-like phenotype, which has been linked to poor clinical outcomes (171). Consistently, in pancreatic tumors Metformin induces the expression of miR-26a and let-7c miRNAs reducing cell proliferation, invasion, and migration. Particularly,

miR-26a down-regulates the oncogene HMGA1 contributing to the observed phenotype (172). Studies in oral cancer cell models reveal that Metformin significantly increases miR-26a levels which directly decreases Mcl-1 expression that enhances apoptotic rates and reduces tumor-cell viability (173). Finally, in renal carcinoma Metformin treatment limits cell proliferation by miR-26a up-modulation that in turn down-regulates Bcl-2, cyclin D1 and upregulates the tumor suppressor PTEN, which all together influence cell cycle and cell death (174).

TARGETING AEROBIC GLYCOLYSIS: PDK INHIBITORS

Dichloroacetate (DCA, PDK inhibitor) is a small molecule that inhibits the pyruvate dehydrogenase kinase (PDK) and

TABLE 2 | miRNAs target by metabolic-drugs or miRNAs related to therapy resistance.

Drug	Druggable miRNA/Therapy-resistance miRNA*	Cancer	References
Targeting glucose metabolism			
Metformin	↑let-7a, let-7b, miR-26a, 101, 192, 200b and 200c. Over-expression of miR-26a decrease cancer stem-cells markers, an enhanced apoptosis rate. Let-7b re-expression blocks stem cells features	PC BRCA Oral Renal	(170–174)
	↑miR-34a in obese mice reducing its putative targets (Notch, Slug, Snail)	PC	(175)
	↑miR-34a which in turn restrict Sirt1/Pgc1 α /Nrf2 signaling pathway and decrease proliferation rates		(176, 177)
	↓miR-27a which AMPK α and ↑miR-193 family that increased AMPK α and decrease FASN levels, resulting in limiting mammospheres phenotype	BRCA	(178, 179)
	Combined treatment of metformin + FuOx ↓miR-21 and ↑miR-145, that suppress β -catenin and c-Myc signaling expression colon cancer cells	CRC	(180)
	↑miR-141, 200a, 205 and 429 inhibiting EMT, thus, modulating metastatic traits	GC	(181)
	↑mir-124, 182, 27b, let7b and ↓miR-221 and 181a; inhibiting cell proliferation	CLC	(182)
	↑miR-192-5p, 584-3p, and 1246; suppressing cell motility and cell cycle	M	(183)
	↑DROSHA, modulate the miRNA biogenesis, to affect these miRNAs expression	CLC	(182)
	↓miR-222 resulting in enhance abundance of p27, p57, and PTEN ↓miR-222 resulting in enhance abundance of p27, p57, and PTEN	Lung	(184)
	↑DICER expression and miR-33a that targets c-MYC	BRCA	(185)
	↓miR-146a, 100, 425, 193a-3p and 106b involved in cell migration, invasion and proliferation	PCA	(186)
	↑miR-192-5p, miR-584-3p, and miR-1246 enhance EFEMP1 and SCAMP3 downmodulation favoring the suppression of cancer cell motility and growth through G2/M cell cycle arrest and cell apoptosis	M	(183)
	RS: ↑miR-21	CRC	(187)
	↓miR-21 and ↑miR-145 over combined treatment with 5-fluorouracil and oxaliplatin, that suppress β -catenin and c-Myc expression, and consequently reduce cell growth and sphere formation	BRCA	(180)
	↓miR-21-5p in cell lines model, xenograft murine model and in tissue from human patients. Since also the pre-miRNA sequence is down-modulated the modulation seems to be at the transcriptional level. Functional reduction of miR-21-5p allow the expression of upstream activators of the AMPK, CAB39L and SESN1		(188)
	Dichloroacetate (DCA)	Promising therapeutic agents to ↓miR-210	Cancer
↑miR-375 resulting in anti-proliferating effects		PCA	(190)
CPI-613	May improve miR-497-5p, -449a, -25-3p, -6838-5p, -520d-3p that down-modulates the expression of Cyclin D3, E1, E2, F, A2, B1 and CDK2 genes of BxPC-3	Cancer	(189)
Targeting FA metabolism			
Statins	Lovastatin upregulated miR-33b expression, reduced cell proliferation and impaired c-Myc expression	MB	(191)
	Simvastatin: inhibits the growth of human CRPC cells by suppressing NF- κ B and LIN28B and ↑let-7 miRNA family	PCA	(192)
	Simvastatin: ↓miR-34a, which regulates the NAD $^{+}$ -dependent histone deacetylase SIRT1. ↑miR-612, which is known to reduce stemness	BRCA, PCA, OsC	(193)
	Simvastatin is an activator of miR-192 which subsequently led to suppressed proliferation, migration and invasion	CRC	(194)
	Atorvastatin: ↑miR-182 that targets the anti-apoptotic Bcl-2 and p21	PCA	(195)
	↑miR-140-5p activating the transcription factor NRF1 that reduced cell proliferation and induced apoptosis	BRCA	(196)
	Fluvastatin: ↓miR-140-3p-1 and its downstream pathway such as cell growth	BRCA	(197)
	Statin: ↑miR-33a promoting a proliferation inhibitory effect	PCA	(198)
	lovastatin: ↓miR-133a promoting GCH1 important for endothelial nitric oxide synthase	Cancer	(199)
	Rapamycin	Rapamycin-dependent miRNA: ↑miR-29b, 21, 24, 221, 106a, and 199a	Renal
	↑let-7, miR-125a, -125b, -21, and -26a. Rapamycin is mediated by let-7 family with anti-proliferative effects	Renal	(201)
	*RS: miR-21 supports mitochondrial function and adaptation to rapamycin	Renal	(200)
	Long-term rapamycin treatment RS: ↑MYC that results in ↑miR-17–92	Brain	(201)

(Continued)

TABLE 2 | Continued

Drug	Druggable miRNA/Therapy-resistance miRNA*	Cancer	References
Aspirin and non-steroidal anti-inflammatory agents	↑miR-98 that targets WNT1, suppressing cell proliferation	Lung	(202)
	Sulindac drug: ↓miR-9, -10b, -17, and -21 by suppressing NF-κB-mediated transcription of miRNAs	BRCA CRC	(203)
	↓miR-21 decreasing cell proliferation and invasion upon inactivation of β-catenin/TCF4 signaling	CRC	(204)
	↑let-7 by decreasing the miRNA-sponge H19, resulting in the down-modulation Hypoxia-inducible factor 1α reducing I PDK1, attenuating glycolysis	BRCA	(195)
	Celecoxib: ↑miR-29c suppress the oncogen MCL-1 reducing apoptosis	GC	(205)
TVB-2640	miR-15 and miR-16-6: Inhibition of FASN: Agonist effect	BRCA	(206)
Targeting lactate metabolism: LDHA inhibitors			
AZD3965	miR-342-3p: Inhibition of the monocarboxylate transporter MCT1: Agonist effect	BRCA	(103)
Antimetabolite chemotherapeutic agents			
Methotrexate (MTX)	*RS: ↑miR-24 SNP results		(207)
	*RS: ↑miR-140	OsC, CRC	(208)
	*RS: ↑miR-215 modulated DTL, a cell cycle-regulated gene	OsC, CRC	(209)
Capecitabine	↑miR-125b-5p ↑miR-137	Cancer	(189)
5-Fluorouracil	↓Relevant oncogenes such as miR-210	HCC CRC OsC	(208, 210, 211)
	↑Relevant tumor suppressor miRNAs: let-7 family, miR-15b, -16, -23a, -23b, and -200c	BRCA	(189)
	*ES: ↑miR122 through the inhibition of M2 splice isoform of pyruvate kinase (PKM2) <i>in vitro</i> and <i>in vivo</i>	CRC	(212)
	*RS: ↑miR-21 and -221	BRCA	(213)
	*RS: ↑miR-21, -34, -140	HCC CRC OsC	(212)
Gemcitabine	May impact the expression of 56 relevant miRNAs such as miR-200, -205, -27a, -27b, and let 7 family	Cancer	(214, 215)
	*ES: ↑microRNA-218 by inhibiting the secretion of HMGB1 by PANC-1 cells and the PI3K/Akt pathway	PC	(212)
	*RS: ↑miR-21, -34, -140	PC	(214, 215)
Targeting glutamine metabolism			
Pegylated arginine deiminase (ADI-PEG)	Bioengineered pre-miR-1291 processed to high levels of mature miR-1291. *ER: ↑miR-1291 increases sensitivity to ADI-PEG (through modulation of ASS1 and GLUT1)	PC	(216)

*Therapy-resistance miRNA. ↑, over-expression; ↓, down-regulation. Therapy-resistance miRNA: RS, reduce sensitivity; ES, enhanced sensitivity. Cancer: BRCA, breast cancer; CRC, colorectal cancer; PCA, prostate cancer; PC, pancreatic cancer; HCC hepatocarcinoma; CLC, cholangiocarcinoma; MB, medulloblastoma; OsC, osteosarcoma; GC, Gastric; M, Melanoma.

regulates mitochondrial pyruvate dehydrogenase complex that catalyzes the irreversible decarboxylation of pyruvate into acetyl-CoA (232). PDK is overexpressed in several tumors and favors pyruvate conversion into lactate (233). Inhibition of PDK by DCA in cancer cells prompts glucose oxidation, reverses mitochondrial apoptosis, and suppresses tumor growth (234). CPI-613 is a novel anticancer agent (lipoic acid analog) that inhibits PDK through targeting lipoyl-binding pockets and selectively target the altered mitochondrial energy metabolism in tumor cells and produces changes in mitochondrial and redox status, which leads to tumor cells death (232, 235, 236). One of the main clinical challenges in colorectal cancer management is the development of chemoresistance. Interestingly, DCA treatment improve chemosensitivity to 5-fluorouracil. The evidence pointed out that the DCA over-express miR-149-3p which consequently enhanced 5-FU-induced apoptosis. Importantly,

miR-149-3p is a post-transcriptional regulator of PDK2 transcript. Thus, DCA treatment overcome chemoresistant phenotype by modulating miR-149-3p/PDK2 axis (237).

TARGETING FA METABOLISM

Several pieces of evidence propose that targeting *de novo* fatty acid synthesis might be effective in the treatment of some cancers. For example, statins, cholesterol-lowering drugs, have been recently related to antitumor, cytostatic, and cytotoxic activity in diverse clinical trials of advanced malignancies (238); however, the studies are still inconclusive. Epidemiological studies have shown that statins lower the risk of presenting lung, breast, bowel, and prostate cancer (239, 240). Furthermore, different preclinical *in-vitro* studies show that statins may produce a variety of antineoplastic responses in cancer cells, including a cytostatic

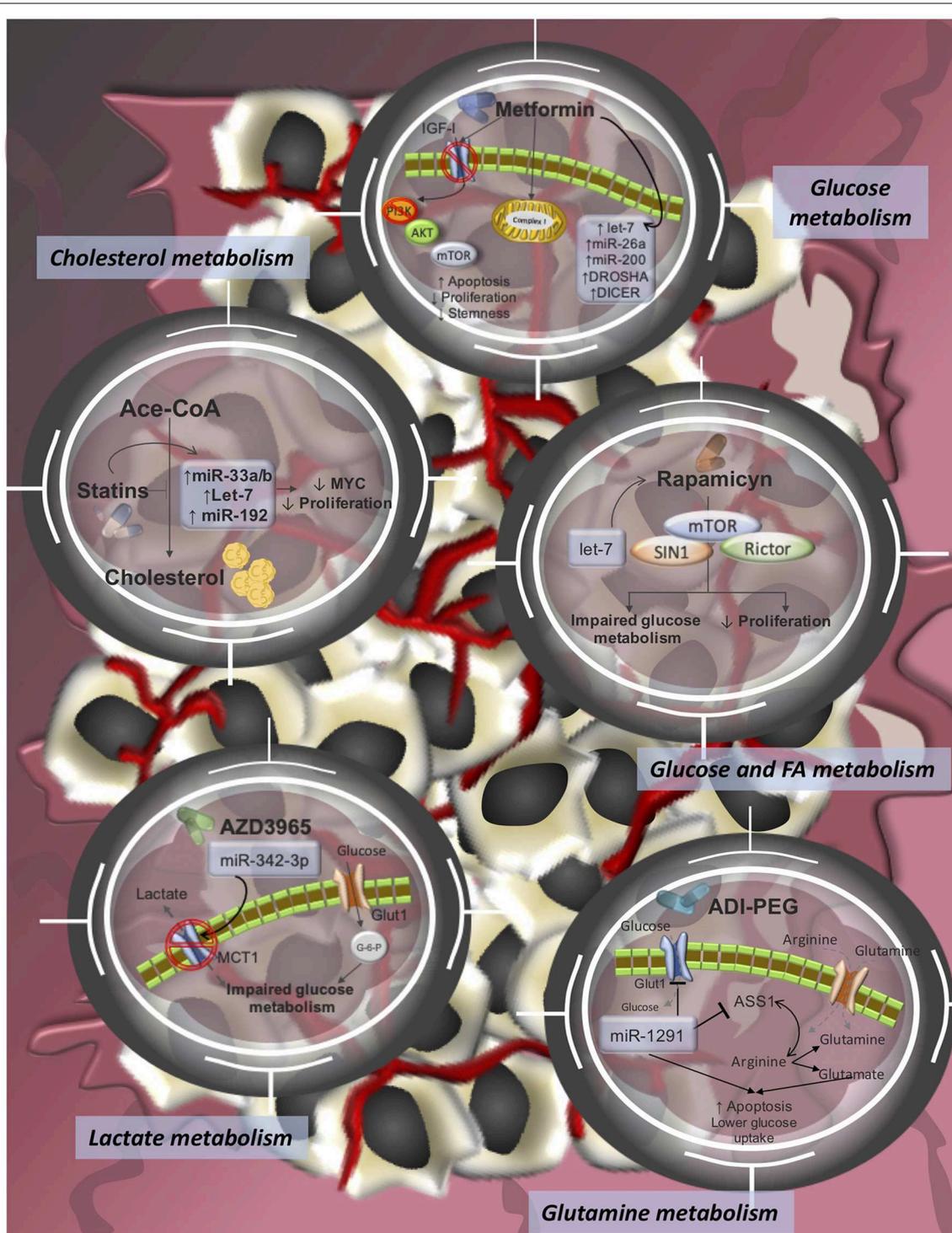


FIGURE 2 | Pharmacological-targeting of tumor metabolism and miRNA-modulating networks of drugs tested in clinical trials or already approved FDA drugs for cancer treatments. It is reported that dysregulations of miRNAs contribute to therapy resistance via drug efflux mechanisms, alterations in drug targets, energy metabolism, Glutamine metabolism, lactate metabolism, cholesterol metabolism, among others.

effect (cell cycle G1/S phase arrest), pro-apoptotic activity by downmodulating BCL-2 (241, 242), anti-metastatic properties through NF- κ B and matrix metalloproteinase inactivation (243,

244) and anti-angiogenic properties. Different studies have provided novel evidence of the pleiotropic effects of statins independent to its cholesterol signaling modulation in cancer.

For instance, *in-vitro* assays have shown that more than 400 miRNAs are altered by statins interventions. Including, some well-known tumor suppressor miRNAs such as miR-612, which is up-modulated after statins treatment promoting cancer cell differentiation and enhancing cancer cells response to chemotherapy (193). In another study, miR33a (198), and miR-33b (191) resulted up-modulated and participates in the anti-oncogenic properties of statins by promoting proliferation inhibitory effects and down-regulating the oncogene *c-Myc*. Another statin-regulated miRNA is miR-182, which down-regulates the antiapoptotic *Bcl-2* transcript and consequently favors cell apoptosis (195). In a more complex regulatory circuit, simvastatin reduces NF- κ B and LIN28B expression and subsequently increased let-7 levels, that in summary significantly inhibited cell viability and clonal proliferation [(192); **Table 2** and **Figure 2**].

In a different fashion, rapalogs that inhibit mTOR (e.g., rapamycin and its derivatives, everolimus, and temsirolimus) exhibit anti-tumor effects by targeting PI3K/Akt/mTOR axis and cell proliferation. A wide spectrum of tumors is being evaluated in monotherapy or in combination. Temsirolimus and everolimus have been recently approved for the treatment of patients with advanced renal cell carcinoma (245, 246). Since mTOR is also involved in glucose metabolism by stimulating GLUT1, it is reasonable to propose a combinatory therapy with metformin to synergistically kill tumor cells [(247); **Table 2**]. Once again, let-7 family is one of the most reported miRNAs related with Rapamycin mechanism, playing a dual role. In one hand, in short-term treatments the inhibitory effect of rapamycin over cancer cells is mediated by increased expression of let-7 members that regulates *c-MYC* post-transcriptionally regulates *c-MYC*. On the other hand, re-expression of let-7 restore rapamycin sensitivity in resistant tumor cells (201). Long-term rapamycin treatment up-modulates miR-17-92 cluster that is related to rapamycin resistance, probably by its positive regulation over *c-Myc* (201). From a combinatory point of view rapamycin and metformin are able to synergize their activities against cancer cells, since this last one inhibits miR-21-5p which induces signaling of mTOR, a rapamycin-target (188).

Finally, TVB- 2640 compound is one of the first bioavailable fatty acid synthase (FASN) inhibitor to enter clinical trials for breast, colon, and astrocytic tumors, in combination with chemotherapy with the aim of enhancing clinical responses and prolonging stable disease times (NIH). Its antineoplastic activity leads to reduced cell signaling, induces tumor cell apoptosis, and inhibits cell proliferation in tumor cells by restricting lipid signaling, mainly fatty acid production, which is necessary to satisfy tumors metabolic needs [(248–250); **Table 2** and **Figure 2**].

ASPIRIN: ANTI-INFLAMMATORY AND METABOLIC DRUG IN CANCER CELLS

Aspirin, a non-steroidal anti-inflammatory drug (NSAIDs), has shown metabolic and antitumor properties (251). Aspirin may impair tumor cell migration and metastasis through preventing

platelet clot formation (252). Aspirin also activates AMPK and inhibits mTOR and FA synthesis in cancer cell lines (253). Recently, aspirin has been demonstrated to have effective anti-tumor effects against RAS/RAF-mutant cells in colorectal cancer by simultaneously affecting BRAF/CRAF dimerization and hyper-activating the AMPK and ERK pathway [(254); **Table 2** and **Figure 2**]. Besides the well-described cardioprotective effects of NSAIDs, there are substantial preclinical, clinical, and observational data that supports its activity in preventing cancer, with strong evidence in colorectal (255), lung (256), and ovarian cancer (257, 258). In preclinical studies NSAIDs administration confer a chemopreventive effect in different cancer cell models and *in-vivo* assays, probably via miRNA modulation. Recently, a novel mechanism of action of aspirin has been reported, in which the drug induces the expression of well-known tumor suppressors miRNAs, such as miR-98 that in turn suppress WNT1 and consequently limits cell proliferation in lung cancer (202). Moreover, NSAIDs favor let-7 expression by decreasing the abundance of one of its ncRNA-sponge, attenuating in this way glycolysis in breast cancer [(195); **Table 2**]. Anti-inflammatory drugs are also able to abrogate the oncogene miR-21, that results in low cell proliferation and invasion rates in BRCA and CRC (203, 204).

TARGETING LACTATE METABOLISM: LDHA INHIBITORS

Several clinical trials evaluating LDHA inhibitors in different solid cancers are currently underway. One mechanism of action of LDHA inhibitors is to limit lactate export from cancer cells into the extracellular space. Accumulating intracellular lactate moves LDHA catalyzed-reaction to produce pyruvate, which prevents NAD⁺ regeneration and affects the energy source that established a fine competition between cancer cells that resulted in cell death. AZD3965, a drug affecting lactate metabolism, inhibits lactate transporter MCT1, which is overexpressed in several tumors and is associated with poor outcomes (259–262). MCT1 inhibitors probably synergize with the exogenous restoration of miR-342-3p that should provide a more effective inhibition of lactate transportation, which result in loss of cancer cell metabolism homeostasis [(103); **Table 2** and **Figure 2**].

ANTI-TUMORAL THERAPY WITH ANTIMETABOLITE CHEMOTHERAPEUTIC AGENTS

Antimetabolites as chemotherapeutic agents (e.g., methotrexate, capecitabine, 5-fluorouracil, and gemcitabine) are small molecules that resemble nucleotide metabolites; they inhibit the activity of enzymes involved in nucleotide synthesis by preventing cell division and triggering cell death. They are widely used in clinics to treat cancer since neoplastic cells have an increased metabolic demand that requires a huge nucleotide biosynthesis and DNA replication (263). More in detail, methotrexate is a folate analog that inhibits carbon transfer reactions required for *de novo* nucleotide synthesis.

Fluorouracil (5-FU) is a synthetic analog of uracil that inhibits thymidylate synthase by limiting the availability of thymidine nucleotides for DNA synthesis (264) and has been reported that enhances the expression of relevant tumor suppressors such as let-7 family, miR-15b, -16, -23a, -23b, and -200c, some of them well-describe metabolic modulators (189). Moreover, 5-FU represses miR-210 (208, 210, 211), that down-modulates GPD1L, a negative regulator of HIF, restricting HIF-1 α stability [(265, 266); **Table 2**]. Similarly, capecitabine is widely used in chemotherapies for gastrointestinal cancers. It halts tumor cells by inhibiting DNA and RNA synthesis and limiting the precursor of thymidine triphosphate (267, 268). Gemcitabine, another nucleoside analog, is intercalated into the DNA molecule and blocks DNA polymerases (269). Notably, the literature reports its effect over several miRNAs such as miR-200, -205, -27a, -27b, and let 7 family [(215, 269); **Table 2**]. All these agents can achieve important clinical responses and lead to complete remission in many cases.

In recent years, there has been substantial attention to the role of miRNAs in regulating metabolic reprogramming. Researchers have tried to reveal the mechanisms that regulate metabolic alterations in tumor cells and identify the interactions (miRNA-mRNA, miRNA-transcription factor, and miRNA-metabolic pathway) that are susceptible of being therapeutically actionable. Although studies are still incipient, robust data have been generated, describing how miRNAs directly or indirectly regulate the dysregulated metabolism of tumor cells. Based on the evidence described in this work, it is appropriate to hypothesize that there are miRNA interactions susceptible of being modulated by therapeutic interventions to reverse the metabolic alterations that allow tumor cells to uncontrollably proliferate. In addition, it is necessary to emphasize the usefulness of miRNAs-based gene therapies to enhance the regulatory activity of those identified miRNAs. However, more studies need to be conducted in a broader spectrum of components of the energetic metabolism of tumor cells, such as enzymes, transcription factors, positive regulators, and enhancers to provide more evidence on the impact of regulation mediated by miRNAs and their signaling networks on oncogenic processes.

NEW DRUGGABLE TARGETS WITH HUGE IMPACT IN CANCER METABOLISM: THE EMERGENCE OF miRNA-BASED THERAPIES

In the last section we discussed how metabolic-target drugs and chemotherapy can modulate miRNA signaling programs as a beneficial pleiotropic effect. But it is also necessary to emphasize the usefulness of miRNAs-based therapies to improve or moderate their regulatory activity. Recent advances have permitted to study the effects of directly manipulating cellular miRNA levels by suppressing the expression of oncomiRs, that somehow enhance cancer metabolism, and which are frequently overexpressed in human cancers. Or on the contrary, by reestablishing the expression of tumor suppressor miRNAs that in many cases collaborate to restrict cancer energetics programs (270). Evidences obtained from these studies have prompted

the designing and refinement of dedicated technology aimed at, either, inhibiting miRNAs (i.e., antisense oligonucleotides, locked nucleic acid, antagomiRs, miRNA sponges, and small molecule inhibitors that inactivate mature miRNA sequence in the RISC complex) (271–273) or restoring their levels by mimic sequences that can be recognized by Dicer and Ago2 proteins to be functional. Notable, miRNA delivery systems have been improved during the last years, resulting in robust and more specific devices such as liposomes, adenovirus, adeno-associated virus, EDV nanocell, and nano-particles accompanied with conjugate antibodies (274–276).

Below we briefly describe some examples of clinical trials that have been evaluated the therapeutic impact of targeting miRNAs involved in the regulation of emerging hallmarks of cancer like tumor metabolism, already described in previous sections. For instance, MRX34 was the first miRNA-based therapy undergoing in a clinical trial for cancer treatment, its aim was to re-express miR-34, that regulates LDHA, by introducing a mimic sequence through the lipid carrier NOV40 to treat patients with lymphoma, melanoma, multiple myeloma, liver, small cell lung, and renal carcinoma. Unfortunately, although promising results were observed, the trial was terminated due to severe immune-related reactions developed by some patients (277).

The first completed phase 1 trial evaluated the TargomiR technology, intended for delivering miRNA mimic sequences in vehicles containing bacterially derived minicells and a targeting moiety antibody against EGFR to treat non-small cell lung cancer. A similar example is the MesomiR-1 drug, which reintroduces miR-16, a miRNA that regulates Aldolase A in glycolysis process (278, 279). Another, drug delivery system being evaluated in stage 1 clinical trial is the locked oligonucleotide acid-modified inhibitor for miR-155 (MRG-106), as part of the clinical intervention for cutaneous T-cell lymphoma patients (280, 281). This therapeutic intervention re-expresses miR-155 targets such as miR-143, that negatively regulates HK2 and consequently limits the active glycolytic phenotype (77). Other examples include the new miRNA delivery system from Regulus company named RGLS5579, an anti-miRNA against miR-10b, for patients diagnosed with glioblastoma multiforme (282). Interestingly, under hypoxic conditions, HIF1 upregulates the transcription factor TWIST that results in the induction of the oncomiR miR-10b (283).

A further candidate of miRNA-based therapeutic currently under evaluation by Regulus and Sanofi companies, although not for cancer patient's treatment, is RG-012 which silences miR-21 in patients with Alport syndrome (284). Along the text we widely discussed miR-21 activity as a promoter of the tumoral-metabolism and its role in resistance against metabolic-based drugs. Miragen, another company, maintains also an active phase 1 study for miR-29 mimic (MRG-201) to treat keloid, fibrosis and scar tissue formation (ClinicalTrials: NCT03601052). Importantly, miR-29 is frequently lost in cancer and has been reported to negatively regulates MCT1, a lactate transporter (101, 102).

Lastly, combinatorial therapy strategies have provided successful results to treat cancer since this approach can target several tumor cell survival pathways and establish molecular landscapes to overcome resistance, offering a holistic way

to reduce tumor development and evolution (285). Taking advantage of the technological advances, chemotherapeutic agents can be coordinately administrated with miRNA-based therapeutics to provide synergistic effects and enhance patient response. Since, these examples represent the first generation of miRNA-based therapeutics, there are some challenges and limitations. As an illustration, preclinical experiments in *in-vivo* models have shown low RNA stability, numerous mRNAs targets can be regulated by a single miRNA and different biological effects can be achieved by a miRNA in different tissues (286). Thus, it is important to guarantee tumor-specific delivery and local retention of miRNAs, for example by nanoparticle which facilitates target-specific shipment of miRNAs (286, 287).

PERSPECTIVES: HOW TO TAKE ADVANTAGE OF THE LOCAL AND SYSTEMIC METABOLIC CONTEXT AND ITS CONNECTION TO microRNA REGULATORY CIRCUITS IN CANCER?

In addition to tumoral-intracellular metabolic reprogramming, tumor cells encounter a variety of systemic factors that can influence tumorigenesis and cell metabolism (27, 34, 38, 41, 164, 288). For instance, obesity is a metabolic disorder that promote tumor growth and a connection between obesity and certain cancers, including colorectal, renal, breast cancer, esophageal, adenocarcinoma, thyroid, endometrial, prostate, and leukemia, have been reported in numerous cohort studies (289–292). In recent years, there has been substantial attention to miRNA roles in obesity-linked cancer (293). miRNA regulation programs can modulate adipogenic differentiation by controlling signaling pathways related to its biogenesis, additionally, several miRNAs associated with obesity also have well-described roles in carcinogenesis, thus, their deregulated expression portrait may act as a functional link between obesity and cancer (294–296).

Furthermore, over the last decade, a huge advent of next-generation sequencing occurred, allowing to deeply characterize the diversity of microorganisms that colonize human epitheliums, known as microbiota. Human microbiome

produces small molecules and metabolites through a complex community network with relevant biological effects both at local and systemic levels and its dysregulation contributes to cancer establishment, progression and therapy response (297–300). Carcinogenesis is a complex process on which exogenous, as well as, endogenous factors could impact in different ways on malignant transformation. Among endogenous factors, metabolites generated as byproducts of metabolic activity can either act as carcinogen compounds (i.e., nitrosamines, conversion of alcohol to acetaldehyde, and tumor-promoting secondary bile acids) or as anticarcinogens (i.e., activation of dietary phytochemicals and inactivation of hormones that stimulate tumor cells growth). Even more, metabolism of different substances within the body can be affected by different health conditions like diabetes or obesity, which is characterized by chronic inflammation. In this context, bacterial metagenome has revealed to be an important player in fine-tuning tumor metabolic function, as is enriched in genes that participates in nutrients, bile acid and xenobiotic metabolism, as well as biosynthesis of vitamins and isoprenoids, therefore has become an emergent factor that affects tumor development (301–303). Based on these novel data, the gut microbiome is increasingly being recognized as a dynamic ecosystem influenced by environmental conditions such as diet and drug therapy with relevant effects on tumoral biology and metabolism (304, 305). As an open system, gut microbes elicit their effects on cancer cells via their capacity to induce pro-inflammatory responses (306–308) or more indirectly by the production of secondary metabolites (309–311). Recent evidence showed that short chain fatty acids (SCFAs), hydrogen sulfide (H₂S), bile acids, and some other metabolites are produced by gut microbiota and impact the genome and epigenome of cancer cells, including miRNAs. Thus, the gut microbiome is an important regulator of host transcriptional dynamics in part through the establishment of inter-communications via miRNA signaling (312).

Host microbiome has pointed out as a potential modulator of cancer metabolism and could be a future target for precision medicine. While there is less evidence of how microbiota affects most of the miRNA landscapes in human tumors, there are growing data that explain how the microbiota confers some

TABLE 3 | miRNA portrait and gut microbiota in cancer.

miRNA	Activity	Cancer	References
miR-182, miR-503, and mir-17~92 cluster	Differentially expression of these oncogenic miRNAs was correlated with the relative abundances of: <i>Firmicutes</i> , <i>Bacteroidetes</i> , and <i>Proteobacteria</i> . Possible role of these miRNAs in driven glycan production in tumor location through the recruitment of pathogenic microbial taxa and thus impact tumor development	CCR	(319)
Upregulation of miR-21	<i>Fusobacterium nucleatum</i> induces CRC cell proliferation by up-modulating the oncogenic miR-21 via TLR4 signaling	CRC	(320)
Upregulation of miR-20a-5p	The colibactin genotoxin produced by <i>Escherichia coli</i> promotes cellular senescence by the upregulation of miR-20a-5p, which in turn downregulates SENP1, resulting in the proliferation of uninfected cells and, subsequently, tumor growth. The over-expression of miR-20a-5p also alters p53 SUMOylation, which has been shown to promote tumor growth and metastasis	CRC	(321–323)

effect on cancer pathways in colorectal cancer (CRC). Under physiological conditions, the microbiota promotes a metabolic niche that produces a huge amount of the energy required

by the intestinal epithelial cells (313) through the production of butyrate, a SCFAs, as a result of complex carbohydrates fermentation. CRC cells preferentially use glucose over butyrate

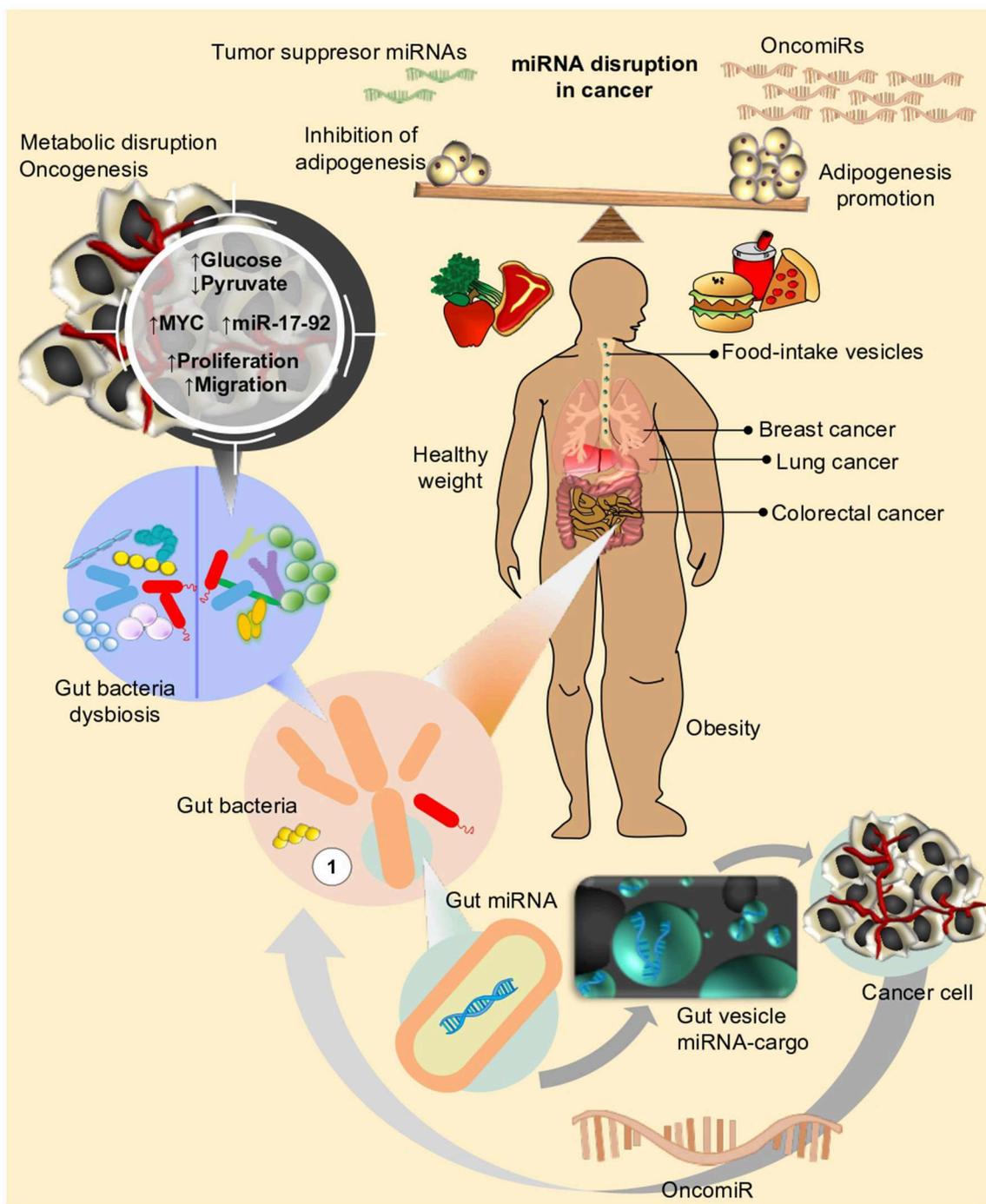


FIGURE 3 | Life style and diet has an impact on different metabolic mechanisms in human cells. Disruption of metabolic fluxes, might particularly affect expression of genes and miRNAs related to control of cell proliferation, cell cycle, and adhesion, eventually leading or favoring neoplastic processes to take place in different organs (i.e., Breast, Prostate, Lung, Colon, etc.). Microbiota, on the other side, the new star player in the complex interaction between environment and human organism, can also influence the effect of nutrients or drug intake within host. In an unhealthy weight scenario (i.e., obesity), disequilibrium in adipogenesis leads to chronic inflammation and triggering of signals for over-expression of oncomiRs. Under this condition, dysbiosis (e.g., loss of balance in gut bacteria composition) could further concur to sustain or even enhance the metabolic perturbations favoring neoplastic transformations.

as the major source of energy, resulting in a gut microbiome related dysbiosis (314). In the tumoral context, low butyrate concentrations enhance MYC expression, which in turn up-modulates the levels of the oncogenic miR-17-92 cluster (315). The overexpression of miR-17-92a cluster has been shown to enhance cell proliferation, metastasis, and angiogenesis (316–318). This data demonstrates an antitumor mechanism of butyrate over the MYC /miR-17-92a axis in CRC cells. As exemplified, miRNAs activity is a relevant feature in mediating metabolic changes and modulating the interaction of host transcriptional portrait and microbiota. Some other evidences are described in **Table 3**. Results from numerous studies now suggest an additionally level in the complex interplay between miRNAs and gut microbiome, including data describing the influence of miRNAs in controlling gut composition and growth rates by improving selectively pressure on the surrounding microenvironment (**Table 3**).

Furthermore, results from numerous studies suggest that intestinal miRNAs come from two main sources: host and food (55, 324). The intestinal epithelial cells are the main contributors of host-derived miRNAs, but miRNAs contained in food can as well be absorbed by the host and regulate gene expression in a cross-species regulation manner (325, 326). Recently it has been showed that Ginger derived exosome-like vesicles, containing RNA, are taken up by the gut microbiota and can alter microbiome composition and host physiology. Briefly, the exosomal particles are preferentially engulfed by *Lactobacillus rhamnosus* and the exosomal microRNAs-cargo target various genes in the bacteria, such as Ginger miR7267-3p that mediate the production of IL-22, favoring an improvement in the colitis via IL-22-dependent mechanisms (324). These findings reveal how plant products and their effects on the microbiome may be exploited to specially target host processes to modify tumor growth through specific diet interventions (**Figure 3**).

Although studies are still incipient, robust data have been generated, describing how microRNAs serve as important

communication factors between the gut microbiome and the host. On the basis of these evidences, it's appropriate to hypothesize there is an open bi-directional communication between host cells and microbes, potentially mediated through miRNA activity. However, more studies are required to be conducted in a broader spectra of cancers, to provide more evidence on the impact of gut microbiota and their miRNAs signaling networks on oncogenic and metabolic processes (300), which finally will allow us take advantage of these changes and devise new strategies to translate the modulation of metabolic alterations into patient management.

AUTHOR CONTRIBUTIONS

AP-T, GH, SR-C, MJ-G, IS-G, RR-B, and SM conceived, designed, and wrote most of the manuscript. RM-M, CA-C, VF-O, RÁ-G, and LH contributed to the writing as well as gathered information for the manuscript. SR-C, MJ-G, IS-G, and RR-B assembled figures and tables.

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