MicroRNAs and their role in breast cancer metabolism (Review)

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Abstract. Breast cancer (BC) continues to be the leading cause of cancer-related mortality among women, placing a substantial disease burden on the global female population. MicroRNAs (miRNAs) are members of a large class of non-coding RNAs capable of regulating gene expression at the post-transcriptional level. With cases of early-onset BC on the rise, miRNAs are promising biomarkers and therapeutic targets for early BC detection and treatment. Dysregulated miRNA expression is known to be closely linked to BC development and metastasis in cancer cells via metabolic reprogramming. Normal cellular metabolism is tightly regulated by various complex signaling pathways. Therefore, dysregulation of metabolism due to metabolic reprogramming is considered a hallmark of cancer. The present review delves into the crucial roles that miRNAs serve in disordered cellular metabolism of BC by targeting gene transcripts, key metabolic enzymes and transporter proteins responsible for regulating major cellular metabolism pathways. The future outlook and clinical implications of miRNAs as potential diagnostic, prognostic and therapeutic markers in BC metabolism are also discussed.

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1. Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy affecting women, as well as the leading cause of cancer-related mortality among women worldwide (1). According to GLOBOCAN 2020 statistics, the number of new female BC cases globally was estimated to be 2.3 million (11.7% of all newly diagnosed cancer cases reported), along with 685,000 (6.9% of all cancer mortality cases reported) mortality cases in 2020 (2). Researchers from the International Agency for Research on Cancer predicted an increase in the future burden of female BC, and the numbers are estimated to increase to 3 million new cases and 1 million deaths in 2040 (3). In Malaysia, female BC is highly prevalent among women of all ethnic groups, with 1 in every 19 women at risk of developing BC (4). Family history, dietary factors, lifestyle, sex, old age, hormonal factors and reproductive factors are among the multitude of risk factors that might predispose an individual to an increased risk of BC (5).

BC can be broadly categorized into two histopathological subtypes: Non-invasive BC and invasive BC (6). In non-invasive BC, cells are confined to the milk ducts and do not invade fatty and connective tissues of the breast. Ductal carcinoma *in situ* and lobular carcinoma *in situ* are the two types of non-invasive BC (7,8). In invasive BC, the cells break through the duct and lobular wall, invading the tissues of the breast. Examples of invasive BC include infiltrating lobular carcinoma and infiltrating ductal carcinoma (IDC) (9). In addition, there are a few types of less commonly occurring BC, including medullary carcinoma, mucinous carcinoma and Paget's disease of the nipple, which have been clinically observed and diagnosed (10). In addition, BC subtypes can also be characterized according to their distinct and diverse molecular patterns, which involves profiling the hormone receptor status of the patient. Hormone receptor-positive subtypes such as the estrogen receptor-positive (ER^+) and progesterone receptor-positive subtypes are reliant on their respective hormones for cancer growth and proliferation (11). HER2-positive individuals exhibit upregulation of the receptor HER2 and/or amplification of the gene HER2 (12). Triple-negative BC (TNBC) is characterized by the lack of all three hormone receptors and is highly heterogenous with poorer prognosis compared with the other BC subtypes (13).

The heterogeneity in BC molecular subtypes reflects the different metabolic phenotypes of BC. Disruption of normal cell metabolism has underlying effects in breast carcinogenesis and tumorigenicity, which is the rationale behind the heterogeneity and aggressiveness of BC subtypes (14,15).

The hallmarks of cancer are a concept used to illustrate the framework in understanding cancer pathology (16). One distinct feature is the reprogramming of cellular metabolism. Cancer cells have the ability to exploit and rewire different metabolic pathways in order to sustain the increased nutritional and energy requirements for tumorigenic proliferation and metastasis (14). In a review by Hanahan (17), the author highlighted the deregulation of cellular metabolism as one of the eight core hallmarks of cancer. Deregulation of cell metabolism and cell signaling are caused as a result of metabolic reprogramming, characterized by increased synthesis of macromolecules and increased proliferation, giving rise to more aggressive cancer phenotypes and drug resistance (18). As aforementioned, BC cells have the ability to exhibit different metabolic phenotypes depending on their molecular subtypes. Intrinsic factors such as gene amplifications and mutations, and extrinsic factors such as hypoxia, oxidative stress and acidosis are contributing factors for the different metabolic phenotypes observed in BC (19). BC cells have the ability to alter glucose, lipid and amino acid metabolic pathways, which are usually regulated by genes to promote uncontrolled cell proliferation and induce breast carcinogenesis. For example, non-cancerous cells under normal conditions are able to catabolize glucose to produce ATP via the mitochondrial oxidative phosphorylation pathway. However, cancer cells have the preference of utilizing the glycolysis pathway as an alternative to produce energy and disrupt tumor microenvironments to promote carcinogenesis and cancer invasion, known as the Warburg phenomenon (20). It has come to the attention of researchers that microRNA (miRNA/miR) dysregulation occurs in various human diseases, including BC, and that miRNAs have the ability to influence the metabolism of cells by regulating various metabolic pathways for tumor growth and sustenance (21-23). Therefore, it has been proposed that dysregulated miRNA expression can be linked to the alteration of metabolic pathways in BC cells.

miRNAs are small, highly conserved, non-coding RNA sequences that are 18-25 nucleotides long and have the ability to exert biological effects by post-transcriptionally regulating mRNAs (24). miRNAs regulate gene expression by binding to the 3' untranslated region (3'-UTR) of the target mRNA (25). Various studies have revealed that dysregulation of miRNA levels contributes to tumor onset, growth and metastasis in individuals affected by BC (26-28). miRNA-mediated gene expression is important for normal cellular responses to environmental stresses. The deregulation of miRNA levels interrupts the normal regulation of oncogenic and tumor-suppressive target genes, which are implicated in the pathogenesis of BC tumors (29). Metabolic mechanisms and networks underlying BC heterogeneity are still poorly understood due to the inherent complexity of BC tumors. Therefore, further studies are required to gain a deeper understanding of the metabolic machinery of BC cells to stimulate future developments in BC diagnosis, BC prognosis and the identification of personalized treatments for subtype-specific BC. The present comprehensive review discusses miRNAs that are involved in BC cellular metabolism, including mainly glucose, lipid and amino acid metabolism, and also highlights future perspectives and clinical implications of miRNAs in BC metabolism.

2. Glucose metabolism in BC

Glucose is central to energy consumption in mammalian cells. It can be produced by breaking down complex molecules, carbohydrates, serving as primary metabolic fuel for mammals. In addition, glucose can be synthesized from non-carbohydrate sources, such as proteins and lipids, through gluconeogenesis, a process which occurs within mitochondria of liver cells (30). Glucose can also be synthesized through glycogenolysis where glycogen is broken down into glucose-1-phosphate and glucose. Glycogenolysis takes place in hepatocytes and myocytes, and is regulated by enzymes, phosphorylase kinase and glycogen phosphorylase (31). In addition, glucose metabolism also involves the process of glycogenesis, where glycogen, the principal storage form of glucose and primary source of non-oxidative glucose for skeletal muscle and the liver, is formed (32).

At the cellular level, glucose is essential in the production of ATP, which is the main source of energy for use and storage. ATP is synthesized through the process of cellular respiration, where glucose is catabolized into acetyl-CoA, producing high energy electron carriers that are oxidized during oxidative phosphorylation. ATP is regarded as the 'energy currency' as it provides readily released energy by breaking the bond of phosphate groups. It is required in a number of processes, including intracellular signaling, DNA and RNA synthesis, purinergic signaling, synaptic signaling, active transport, and muscle contraction (33).

Energy production in cancer cells has been found to be different (34). The major pathway of glucose metabolism in cancer cells is aerobic glycolysis, known as the Warburg effect (35). A review by Liberti and Locasale (36) stated that cancer cells increased glucose uptake and glucose fermentation to lactate with the purpose of promoting growth, survival and proliferation despite having functional mitochondria and oxygen. Furthermore, Pascale *et al* (37) mentioned that the Warburg effect is associated with tumor progression, as the aerobic glycolysis increased with the degree of malignancy. This reprogramming of metabolic pathways is closely related to the activation of proto-oncogenes, transcription factors and related signaling pathways (38). In addition, the aerobic glycolysis in tumor cells can be enhanced by expression of key glycolytic enzymes and glucose transporter proteins through the activation of oncogenes and tumor suppressor genes (39). miRNAs are essential in regulating glucose metabolism in BC cells, and are key factors of tumor growth and metastasis (40). As important targets of glucose metabolism in BC, some miRNAs are of great research value in the occurrence and development of BC.

miRNAs as regulators of glycolytic enzymes in BC. The regulation of glucose metabolism in BC cells by miRNAs has gained attention from researchers worldwide. Glycolysis is part of the glucose metabolic pathway, and it is the first step in cellular respiration, which entails the oxidation of glucose molecules

in the body (41). A series of glycolytic enzymes are involved in catabolizing the glucose molecules, and thus, pyruvates and water molecules are formed as the end products (42). Table I summarizes the glycolytic enzymes or genes targeted by miRNAs and the changes of BC cells following the expression of the miRNAs.

Hexokinase (HK) is the enzyme that catalyzes the first step of glycolysis, in which glucose molecules are phosphorylated into glucose-6-phosphate (43). Jiang *et al* (44) reported that miR-155 upregulated HK2 via two distinct mechanisms. Firstly, HK2 transcription was promoted by miR-155 via activation of STAT3. Following upregulation of miR-155 in BC cells, glucose consumption and lactate production were found to be increased, and pro-inflammatory cytokines such as TNF-α, IL-1β and IFN-γ were upregulated. In addition, miR-155 promoted HK2 expression at the post-transcriptional level by repressing miR-143 by targeting CCAAT/enhancer-binding protein β. The downregulation of miR-143 increased glucose consumption and lactate production, and thus, elevated the proliferation and migration of BC cells, as well as xenograft tumor growth (44). Another study by Liu *et al* (45) concluded that miR-216b inhibited the progression of BC by targeting HK2, which resulted in mTOR signaling pathway inactivation. The study also showed that increased levels of miR-216b following transfection of miR-216b mimics inhibited proliferation, migration and invasion in MCF-7 and MDA-MB-231 cells. In addition, HK2 silencing led to autophagy of BC cells, cell cycle arrest and apoptosis of BC cells (45). Furthermore, Li *et al* (46) demonstrated that Let-7b-5p restrained breast tumor growth and metastasis both *in vitro* and *in vivo* by suppressing HK2 expression. A decreased extracellular acidification rate (ECAR) and increased oxygen consumption were observed following Let-7b-5p upregulation (46).

Another glycolytic enzyme, namely pyruvate kinase (PK), has been extensively studied by numerous researchers in cancer metabolism (47-49). PK is a metabolic enzyme involved in the last step of the glycolysis process, catalyzing the irreversible transphosphorylation between phosphoenolpyruvate and ADP to produce pyruvate and ATP (50). Four PK isoforms have been identified: PK isoform L, PK isoform R, PKM1 and PKM2 (51). Among all isoforms, PKM2 has gained much interest as it can be identified as a cancer biomarker due to its expression in most human cancers (52). Wen *et al* (53) reported that the proliferation and colony formation of MCF-7 and MDA-MB-231 cells were inhibited by high miR-152 expression via inhibition of β-catenin and PKM2 expression. The authors revealed that, upon expression of insulin-like growth factor 1 (IGF-1), a binding protein that is involved in BC progression, β-catenin and PKM2 expression was induced. IGF-1-induced expression of β-catenin and PKM2 was shown to enhance the interaction between β-catenin and PKM2, leading to transcriptional activation of miR-152. Therefore, the results demonstrated a regulatory circuit among miR-152, β-catenin and PKM2 in BC (53). Xu *et al* (54) demonstrated that upon upregulation of miR-148a and miR-152, the levels of PKM2 were downregulated. Xu *et al* (54) also reported that miR-148a and miR-152 regulated the Warburg effect of BC cells, which was demonstrated by low glucose consumption and lactate production levels following the overexpression miR-148a and miR-152 cells. The authors proposed that the PKM2/NF-κB/miR-148a/miR-152 pathway could regulate tumor angiogenesis and cancer cell proliferation (54). Similar outcomes were reported by Yao *et al* (55) who revealed that the upregulation of let-7a-5p inhibited aerobic glycolysis and proliferation of MCF-7 and MDA-MB-231 cells, and decreased the protein levels of PKM2.

Phosphoglycerate kinase 1 (PGK1) is another pivotal glycolytic enzyme, which catalyzes the reversible transfer of a high-energy phosphate group from 1,3-biphosphoglycerate to ADP, producing 3-phosphoglycerate and ATP (56). Ye *et al* (57) demonstrated that miR-16-1-3p inhibited PGK1 expression, resulting in suppression of aerobic glycolysis by decreasing the glucose uptake, lactate and ATP production and ECAR, and increasing the oxygen consumption rate in BC cells. Furthermore, the downregulation of the phosphoglucomutase (PGM) family member PGM5 in patients with BC has also gained the attention of researchers. Ran *et al* (58) reported that miR-1224-3p, an oncogene that inhibited PGM5, caused an increase in the proliferation, migration and glycolytic function in BC cells. Another enzyme, namely lactate dehydrogenase A (LDHA), was found to be suppressed by miR-30a-5p, thus decreasing glucose uptake, lactate production, ATP generation and the ECAR of BC cells (59). Xiao *et al* (60) showed that miR-34a suppressed glycolysis and proliferation of BC cells by downregulating LDHA.

Another glycolytic enzyme, 6-phosphofructose-2-kinase (PFKFB3), which regulates glycolysis by controlling the levels of fructose-2,6-bisphosphate (F2,6BP), was found to be upregulated in BC, while miR-206 was downregulated (61). Further analysis has shown that miR-206 overexpression decreased PFKFB3 protein expression, cell proliferation and migration, as well as F2,6BP and lactate production of BC cells (61,62).

Phosphoglucose isomerase (PGI) is a key enzyme in glycolysis, which catalyzes the interconversion of glucose-6-phosphate and fructose-6-phosphate (63). Ahmad *et al* (64) demonstrated that PGI was downregulated following overexpression of miR-200s (miR-200a, miR-200b and miR-200c), leading to inhibition of wound healing, colony formation and metastasis in BC cells. Additionally, Guda *et al* (65) concluded that miR-211 is a robust inhibitor of the Warburg effect, and pyruvate dehydrogenase kinase 4 was silenced by miR-211. Following the upregulation of miR-211, decreased ECAR and increased OCR were reported in BC cells. The expression of miR-211 ultimately induced mitochondrial apoptosis through mitochondrial dysfunction (65).

Although the aforementioned studies demonstrated the role of miRNAs in regulating the glycolytic enzymes in BC cells, which could be useful in identifying alternative strategies for BC treatment, more investigations could be implemented to study other enzymes, such as aldolase, glyceraldehyde-3-phosphate dehydrogenase and enolase, and the associated miRNAs in the regulation of BC progression. Fig. 1 shows the aerobic glycolysis pathway with all the involved glycolytic enzymes, as well as the miRNAs that regulate the enzymatic reactions.

miRNAs that regulate gene expression in glucose metabolic pathways in BC. Studies in the past two decades have

Table I. Summary of miRNAs involved in BC glucose metabolism.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
Jiang *et al*, 2012	miR-155 and miR-143	HK2	Overexpression of miR-155 increased glucose consumption and lactate production in BC cells. Upregulationof miR-155 upregulated the GLUT1, HK2, PFK2, PGM2, PKM2, PDK1 and LDHA genes. miR-155 positively regulated HK2 protein expression at the post-transcriptional level. miR-155 suppressed miR-143 expression via targeting C/EBPβ, thus promoting the expression of HK2. Downregulation of miR-143 increased cell proliferation, survival and migration, and xenograft tumor growth.	miR-155 is an oncogene; miR-143 is a tumor suppressor	(44)
Liu *et al*, 2021	miR-216b	HK2	HK2 was highly expressed, while miR-216b expression was found to be low in BC tissues. The luciferase activity of pHK2 wild-type was inhibited by miR-216b mimic in cancer cells. miR-216b mimic inhibited cell proliferation, migration and invasion. High expression of miR-216b promoted cell cycle arrestand apoptosis by targeting HK2. miR-216b downregulated HK2 to block the mTOR signaling pathway. miR-216b upregulated Beclin1, Bax and LC3 but downregulated Bcl-2 and MMP-9.	Tumor suppressor	(45)
Li *et al*, 2023	Let-7b-5p	HK2	HK2 was a target of let-7b-5p in BC cells. Let-7b-5p suppressed HK2 expression. HK2 mRNA was downregulated when Let-7b-5p was overexpressed. Let-7b-5p overexpression led to reduced cell proliferation, migration and invasion in MDA-MB-231 and ZR75-1 cells. Let-7b-5p overexpression decreased extracellular acidification and increased cell oxygen consumption.	Tumor suppressor	(46)
Wen *et al*, 2017	miR-152	PKM2	miR-125 was downregulated in BC tissues and BC cell lines. Luciferase activity of β-catenin 3'-UTR was reduced by miR-152 overexpression. miR-152 overex-pression inhibited MCF7 and MDA-MB-231 cell proliferation. Overexpression of PKM2, abated miR-152-inhibited cell proliferation and colony formation. Overexpression of miR-152 repressed PKM2, β-catenin, IGF-1R and IRS-1 expression. β-catenin and PKM2 expression levels were detected in TNBC and TPBC.	Tumor suppressor	(53)
Xu *et al*, 2015	miR-148a and miR-152	PKM2	Expression of miR-148a and miR-152 decreased glucose consumption and lactate production. Expression of miR-148a and miR-152 decreased PKM2 expression. Expression of miR-148a and miR-152 led to a decrease in BC cell proliferation, colony formation and angiogenesis.	Tumor suppressor	(54)

Table I. Continued.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
Yao *et al*, 2019	Let-7a-5p	PKM2	PKM2 protein was found to be highly expressed in MFC-7 and MDA-MB-231 cells. Proliferation of MCF-7 and MDA-MB-231 cells was inhibited following let-7a-5p mimic treatment. MCF-7 and MDA-MD-231 BC cells transfected with let-7a-5p mimics exhibited reduced glucose uptake and lactate production. Let-7a-5p mimic transfection led to lower PKM2 protein expression in BC cells. Let-7a-5p decreased aerobic glycolysis through suppression of Stat3, with downstream effects on PKM2 expression.	Tumor suppressor	(55)
Ye *et al*, 2020	miR-16-1-3p	PGK1	miR-16-1-3p mimic reduced PGK1 protein expression in ZR75-1 and MDA-MB-231 cells. Overexpression of miR-16-1-3p led to a decrease in the ECAR and increased the cellular OCR. Overexpression of miR-16-1-3p suppressed BC cell proliferation, migration and invasion. Upregulation of miR-16-1-3p increased the expression levels of E-cadherin, and vimentin was reduced. miR-16-1-3p expression was negatively associated with BC lung metastasis. miR-16-1-3p was negatively associated with tumor size, nodal status and grade.	Tumor suppressor	(57)
Ran *et al*, 2021	miR-1224-3p	PGM5	miR-1224-3p inhibited PGM5 expression by directly targeting its 3'-UTR. miR-1224-3p promoted cell proliferation and migration by downregulating PGM5 expression in MCF7 and ZR75-1 cells. miR-1224-3p expression increased the expression levels of cyclin B, cyclin D1, Bcl-2, N-cadherin and vimentin, while it decreased the expression levels of p21, p53, Bax and E-cadherin. Overexpression of miR-1224-3p enhanced lactate, ATP and G6P production. miR-1224-3p expression promoted the expression of LDHA, but not LDHB.	Oncogene	(58)
Li *et al*, 2017	miR-30a-5p	LDHA	miR-30a-5p suppressed LDHA expression by directly targeting its 3'-UTR. miR-30a-5p expression decreased glucose uptake, lactate production, ATP generation and the ECAR, and increased oxygen levels. miR-30a-5p expression led to reduced tumor growth and metastasis.	Tumor suppressor	(59)
Xiao *et al*, 2016	miR-34a	LDHA	A 40% reduction in luciferase activity was observed in the wild-type 3'-UTR of LDHA group in MDA-MB-231 cells co-transfected with miR-34a mimic compared with cells	Tumor suppressor	(60)

Table I. Continued.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
			co-transfected with scrambled oligonucleotides. A reduction in mRNA and protein levels of LDHA was observed in MCF7 and MDA-MB-231 cells upon transfection of miR-34a. miR-34a inhibited cell proliferation via targeting of LDHA.		
Ge *et al*, 2015	miR-206	PFKFB3	miR-206 bound directly with the 3'-UTR of PFKFB3 mRNA. miR-206 expression impeded fructose-2,6-bisphosphate production. Upregulation of miR-206 reduced lactate production, proliferation and migration of BC cells.	Tumor suppressor	(61)
Ahmad *et al*, 2011	miR-200s	PGI	PGI overexpression in MCF-10A cells led to downregulation of miR-200s (a, b and c) and upregulated ZEB1 and ZEB2 expression. Upregulation of miR-200s increased E-cadherin expression, and downregulated vimentin, ZEB1 and ZEB2. Upregulation of miR-200s inhibited wound healing and colony formation. Expression of miR-200s suppressed metastasis of BC cells.	Tumor suppressor	(64)
Guda *et al*, 2018	miR-211	PDK4	BC tumors showed increased positivity for PDK4 expression. PDK4 mRNA was silenced in miR-211-transfected BT-474 and MDA-MB-468 cells. miR-211-transfected BT-474 and MDA-MB-468 cells exhibited decreased expression levels of both PDK4 and HIF-1α. miR-211-transfected cells exhibited increased Bad, Bax, FADD, SMAC, p21, p27a, $p53_{s46}$ and $p53_{s392}$ expression. miR-211 transfection induced mitochondrial dysfunction, leading to apoptosis. miR-211 decreased the ECAR, and increased the OCR and spare respiratory capacity in BC cells.	Tumor suppressor	(65)
Zhai *et al*, 2022	miR-181a-5p	NDRG2	miR-181a-5p was found to be upregulated, while NDRG2 expression was low in BC tumor tissues. Downregulation of miR-181a-5p reduced glucose consumption and lactate production, and reduced metabolic enzyme activities and protein levels. miR-181a-5p reduced the relative luciferase activity in the wild-type NDRG2 group compared with mutant NDRG2 group. Overexpression of miR-181a-5p also elevated the levels of p-PTEN and p-AKT.	Oncogene	(67)
Lang *et al*, 2022	miR-4731-5p	PAICS	miR-4731-5p expression was found to be low in MCF-7 and MDA-MB-231 cells. miR-4731-5p expression suppressed the glycolysis rate, glucose consumption and lactic acid content. miR-4731-5p expression reduced PKM2, GLUT1 and vimentin expression, while it increased E-cadherin expression. miR-4731-5p expression inhibited cell migration and invasion. Decreased	Tumor suppressor	(68)

Table I. Continued.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
			PAICS expression observed in a luciferase assay upon miR-4731-5p mimic treatment showed that PAICS could be a potential target of miR-4731-5p. PAICS reversed the suppressive role of miR-4731-5p in glycolysis, migration and invasion of BC cells.		
Du *et al*, 2020	miR-210-3p	HIF-1α	miR-210-3p increased the ECAR and glycolytic capacity. miR-210-3p reduced the protein levels of GPD1L and CYGB. miR-210-3p expression promoted cell proliferation and inhibited cell apoptosis. miR-210-3p directly inhibits GPD1L to promote HIF-1α protein accumulation. miR-210-3p also decreased p53 protein expression by targeting CYGB.	Tumor suppressor	(71)
Jiang *et al*, 2022	miR-542-3p	HIF-1α	miR-542-3p expression was downregulated in BC tissue samples and cell lines. miR-542-3p directly targeted HIF-1α, where HIF-1α expression was decreased in cells transfected with miR-542-3p mimics. HIF-1α overexpression reversed the inhibitory effect of miR-542-3p, resulting in increased glycolysis and proliferation, and decreased apoptosis of BC cells.	Tumor suppressor	(72)
Cao *et al*, 2020	miR-487a	HIF-1α	circRNF20 was upregulated in BC tissues and cells. A luciferase reporter assay indicated that circRNF20 was closely combined with miR-487a and that circRNF20 acted as a miRNA sponge. The findings showed that circRNF20/miR-487a directly targeted HIF-1α in BC cells. Decreased miR-487a expression resulted in increased HIF-1α levels, which facilitated HK2 transcription, leading to increased glycolysis in BC cells.	Tumor suppressor	(73)
Zhao *et al*, 2018	miR-31	HDAC3	HDAC3 mRNA levels were found to be high in BC tissues compared with adjacent normal tissues. miR-31 was upregulated following knockdown of HDAC3. Decreased cell proliferation, LDH activity, glucose utilization and lactate production, and increased intracellular ATP levels were observed following HDAC3 downregulation. An inverse association was observed between HDAC3 expression and miR-31 mRNA expression in BC cells. HDAC3 was an oncogene that inhibited the tumor-suppressor miR-31.	Tumor suppressor	(74)

BC, breast cancer; C/EBPβ, CCAAT/enhancer-binding protein β; circRBM33, circular RNA RNA binding motif protein 33; circRNF20, circular RNA ring finger protein 20; CYGB, cytoglobin; ECAR, extracellular acidification rate; FADD, Fas associated via death domain; G6P, glucose 6-phosphate; GLUT1, glucose transporter 1; GPD1L, glycerol-3-phosphate dehydrogenase 1 like; HK2, hexokinase 2; HDAC3, histone deacetylase 3; HIF-1α, hypoxia-inducible factor 1α; IGF-1R, insulin-like growth factor 1 receptor; IRS-1, insulin receptor substrate 1; LDH, lactate dehydrogenase; miRNA/miR, microRNA; NDRG2, N-Myc downstream-regulated gene-2; OCR, oxygen consumption rate; p-, phosphorylated; PAICS, phosphoribosyl aminoimidazole succinocarboxamide synthase; PDK4, pyruvate dehydrogenase lipoamide kinase 4; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGI, phosphoglucomutase 1; PGK1, phosphoglycerate kinase 1; PGM5, phosphoglucomutase 5; pHK2, plasmid of hexokinase 2; PKM2, pyruvate kinase M2; SMAC, second mitochondria-derived activator of caspase; TNBC, triple-negative BC; TPBC, triple-positive BC; UTR, untranslated region; ZEB, zinc finger E-box binding homeobox.

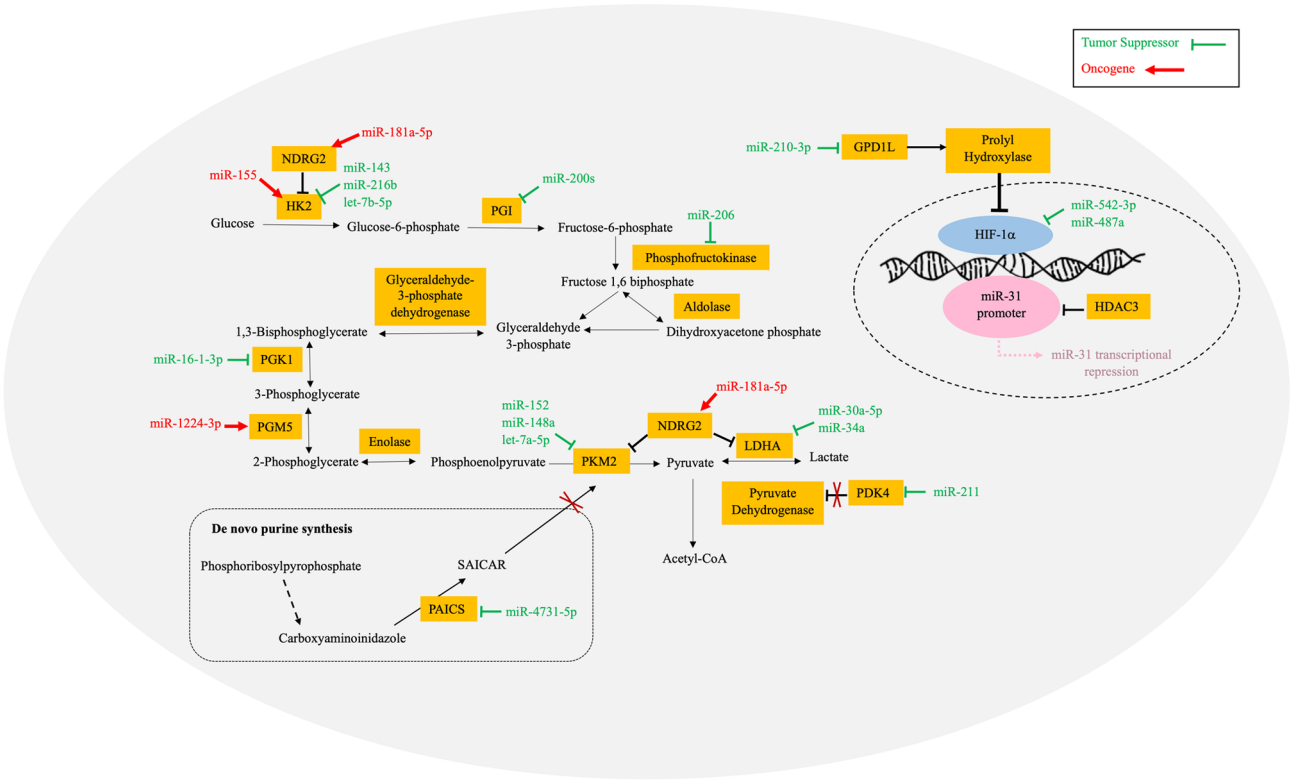

Figure 1. miRNAs associated with glucose metabolism in breast cancer cells. Glucose is converted into lactate via a series of glycolytic enzymes (yellow boxes). These enzymes are regulated by a number of miRNAs. GPD1L, glycerol-3-phosphate dehydrogenase; HDAC3, histone deacetylase 3; HIF-1α, hypoxia-inducible factor 1α; HK, hexokinase; LDH, lactate dehydrogenase; miRNA/miR, microRNA; NDRG2, N-Myc downstream-regulated gene-2; PAICS, phosphoribosyl aminoimidazole succinocarboxamide synthase; PDK4, pyruvate dehydrogenase lipoamide kinase 4; PGI, phosphoglucose isomerase; PGK, phosphoglycerate kinase; PGM, phosphoglucomutase; PKM2, pyruvate kinase M2; SAICAR, phosphoribosylaminoimidazolesuccinocarboxamide.

documented the transcriptional regulators in aerobic glycolysis of cancers, namely hypoxia-inducible factor 1 (HIF-1) (66), HK2 (43), histone deacetylase-3 (HDAC3) (67), phosphoribosyl aminoimidazole carboxylase and phosphoribosyl aminoimidazole succinocarboxamide synthase (PAICS) (68). All the aforementioned genes serve crucial roles in cellular aerobic glycolysis, and miRNAs have been found to regulate the expression levels of said genes.

HIF-1 is a heterodimeric transcription factor that consists of two subunits, namely HIF-1α and HIF-1β (69). HIF-1 serves a key role in reprogramming of cancer metabolism by activating transcription of genes encoding glucose transporters and glycolytic enzymes, which take up glucose and convert it to lactate (70). In a study by Du *et al* (71), the upregulation of miR-210-3p, glucose uptake, production of lactate and the ECAR were promoted in MDA-MB-231 and Hs578T cells. The authors proposed that miR-210-3p targeted glycerol-3-phosphate dehydrogenase 1 like to sustain the stability of HIF-1α, and cytoglobin repressed p53 activity (71). Another study by Jiang *et al* (72) revealed that miR-542-3p expression was downregulated in BC tissues and cell lines. miR-542-3p overexpression inhibited glycolysis and proliferation, and promoted apoptosis of BC cells by directly targeting HIF-1α. However, HIF-1α overexpression could reverse the inhibitory effect of miR-542-3p, resulting in enhanced glycolysis and cancer cell proliferation, and decreased apoptosis of BC cells (72). Cao *et al* (73) highlighted the circular RNA ring finger protein 20 (circRNF20)/miR-487a/HIF-1α/HK2 axis in BC progression and the Warburg effect. The authors revealed that cirRNF20 acted as a sponge of miR-487a, where the decreased expression of miR-487a led to the upregulation of HIF-1α levels, which promoted the transcription of HK2, resulting in increased glycolysis in BC cells (73).

Zhao *et al* (74) suggested that the repression of HDAC3 by miR-31 upregulation led to decreased cell proliferation, glucose utilization and lactate production in BC cells. Furthermore, Zhai *et al* (67) proposed that upregulation of miR-181a-5p led to the downregulation of N-Myc downstream-regulated gene-2, which promoted cell proliferation, invasion and glycolysis of BC cells via the PTEN/AKT signaling pathway. Lang *et al* (68) reported that the glycolysis and epithelial-mesenchymal transition (EMT) of BC cells were inhibited by miR-4731-5p through the reduction of PAICS-induced phosphorylation of focal adhesion kinase.

3. Amino acid and glutamine metabolism in BC

Amino acids are essential nutrients that serve important roles in the regulation of essential cellular functions such as protein and nucleotide synthesis needed for cellular proliferation. Other than being the building blocks for protein synthesis, amino acids are also essential for the production of non-essential amino acids to facilitate other metabolic pathways such as glucose and lipid conversion (75). Amino acids are also important in the production of nitrogen-containing metabolite precursors that are used for the synthesis of nucleic acids and neurotransmitters, as well

as activation of important pathways such as nutrient transport, epigenetic regulation and ferroptosis regulation (76-78). All these roles that amino acids serve highlight the extensive effects of amino acid metabolism in cells (79). The enhanced ability of cancer cells to acquire and exploit nutrients results in a greater demand for amino acids to supply and sustain the increased energy requirements of the tumor (80).

Glutamine, in particular, is a non-essential amino acid with high versatility and is abundantly available within the human body (81). Glutamine serves an integral role in cancer amino acid metabolism as it serves as the major nitrogen and carbon source for amino acid, lipid and nucleic acid biosynthesis (82). The heavy reliance on glutamine for tumor survival and proliferation in cancer cells is known as the 'glutamine addiction' phenotype (83). Glutamine metabolism is closely linked to various metabolic networks that are essential for cancer cell survival (84). Glutaminolysis is the process of conversion whereby glutamine is catabolized through various metabolic enzymes, namely phosphate-dependent glutaminase (GLS) and glutamate dehydrogenase 1, to yield glutamate and other tricarboxylic acid (TCA) cycle metabolites for ATP generation or macromolecule synthesis (85). Oncogenes such as MYC have the ability to stimulate glutamine consumption and metabolism through gene activation or miRNA regulation by upregulating GLS (86). BC tissues reportedly exhibit increased levels of glutamate compared with normal breast tissues, highlighting the dysregulation of glutamine metabolism and the importance of glutamine in BC (87). Previous studies have reported that glutamine and/or glutamate dependence contributes to invasiveness in other human cancer types, including pancreatic cancer, prostate cancer and natural killer T-cell lymphoma (88-90). It is crucial to understand that glutamine requirements in cancer cells are highly heterogenous and that there are various factors that could collectively influence the role of glutamine in cancer (91). Altered amino acid and glutamine metabolic profiles could be unique in different molecular subtypes and stages of BC, guiding biomarker identification and drug development for personalized treatment of BC (92).

miRNAs as regulators of metabolic enzymes in BC amino acid and glutamine metabolism. Aminotransferases, also known as transaminases, are important metabolic enzymes that catalyzes the interconversion of amino acids to allow repurposing of relevant amino acid derivatives essential for cellular function (93). Transaminases such as GLS, glutamine synthetase and branched-chain amino acid transaminase 1, and other key metabolic enzymes, such as glutamate dehydrogenase, have been reported to be deregulated in BC amino acid metabolism (94-97). Although there are various scientific works that have investigated the relationship among amino acid metabolism, its metabolic enzymes and BC (94,98-100), there is no study yet that focused on the role of miRNAs in the regulation of BC amino acid metabolism by specifically targeting these metabolic enzymes.

miRNAs as regulators of gene expression in BC amino acid and glutamine pathways. Transporters are membrane bound proteins that serves mediatory roles in amino acid metabolism by engaging in amino acid transfer in and out of the cell required for cellular function and signaling (101). To meet the increased amino acid demand, cancer cells can modulate the expression of specific amino acid transporters to suit their metabolic needs (79). Solute carrier family 7 member 11 (SLC7A11) is a well-known amino acid transporter, functioning as an antiporter by exchanging cystine for glutamate to facilitate glutathione biosynthesis and reduce reactive oxygen species (ROS)-mediated stress in cells (102). As such, SLC7A11 is also implicated in ROS homeostasis and ferroptosis regulation in BC (103). miRNAs such as miR-5096 (102), miR-26b (104) and miR-382-5p (105) have been reported to directly target SLC7A11 at the SLC7A11 3'-UTR and regulate its expression in BC cells, thus influencing BC amino acid metabolism.

In another study by Wang *et al* (106), miR-149-5p was reported to modulate the expression of solute carrier family 1 member 5 (SLC1A5) via circular RNA septin 9. SLC1A5 is a transporter protein involved in glutamine uptake and glutamate dehydrogenase 1 expression in BC (97,107). Wang *et al* (106) demonstrated the tumor-suppressing effect miR-149-5p exerted on BC tumor formation and BC progression by abating glutamine consumption and glutamine metabolism in BC via decreased SLC1A5 expression.

ER^+ BC is one of the most commonly diagnosed BC molecular subtypes among individuals diagnosed with BC (108). Msheik *et al* (109) reported downregulated gene expression of solute carrier family 7 member 5 (SLC7A5) in the presence of miR-126 compared with other selected targets such as plexin B2, CRK protooncogene, polo-like kinase 2, sprouty-related EVH1 domain containing 1 and insulin receptor substrate 1 in ER^+ BC. SLC7A5, also known as L-amino acid transporter 1, is a neutral amino acid transporter responsible for transporting large, bulky amino acids such as leucine and glutamine, which are required for ER^+ BC proliferation (110,111). Upregulation of SLC7A5 expression has been observed in various BC subtypes, and has been associated with BC development and poor prognosis (92,112-114). The results of Msheik *et al* (109) highlighted the inverse relationship between miR-126 and SLC7A5, where miR-126 exerted its tumor-suppressive effects by targeting SLC7A5 mRNA and affecting SLC7A5 expression, resulting in dysregulated amino acid metabolism due to changes in amino acid levels. In another study, Bacci *et al* (115) investigated the relationship between miR-23b-3p and amino acid transporters in ER^+ BC. Solute carrier family 6 member 4 (SLC6A14) is a neutral and basic amino acid transporter responsible for mediating essential amino acid transport across cellular membranes. In ER^+ BC, SLC6A14 expression was observed to be downregulated following miR-23b-3p upregulation, resulting in impaired amino acid metabolism. The altered amino acid metabolic pathway allowed increased influx of acidic amino acids, such as glutamate and aspartate, through alternative amino acid transporters such as solute carrier family 1 member 2. Along with enhanced autophagic flux, miR-23b-3p upregulation could confer more aggressive phenotypes and chemoresistance in ER^+ BC (115). In a different study looking into signaling pathways, Delgir *et al* (116) reported downregulation of miR-3163 levels in human BC tissues compared with normal adjacent breast tissues. *In silico* analysis revealed that miR-3163 regulated target genes involved in important cellular pathways, such as the Wnt, Hedgehog and MAPK signaling pathways, which are key regulators of cellular metabolism,

including glutamine metabolism in BC. Therefore, miR-3163 was implied to be considerably involved in BC glutamine metabolism, development and progression (116).

Circulating miRNAs secreted in extracellular vesicles (EVs) have also been implicated in cancer by post-transcriptionally regulating gene expression in cells to promote cancer formation, malignant transformation, angiogenesis and metastasis (117-120). A study conducted on BC patient-derived cancer-associated fibroblasts treated with MDA-MB-231 EV-encapsulated miR-105 revealed decreased expression of the MAX interactor 1, dimerization protein (MXI1) gene along with elevated levels of the MYC protein. These observed changes in MXI1 and MYC expression due to the presence of miR-155 ultimately enhanced glutamine consumption, glutaminolysis and metabolite transport in BC *in vivo* models (80).

One major obstacle in BC therapy are the varied sensitivities in chemotherapeutic responses observed in different individuals due to the heterogenous nature of BC (121). Muciño-Olmos *et al* (122) utilized multicellular tumor spheroids (MCTs) from the BC cell line MCF7 to study miRNA-mRNA interactive pairs that serve a regulatory role in cellular metabolism in various metabolic phenotypes of MCF7 MCTs observed during different cell cycle stages. The authors reported downregulation of miR-663a and miR-1184 along with upregulation of glutamate-ammonia ligase and phosphoglycerate mutase 1 mRNAs, respectively, resulting in overall decreased amino acid biosynthesis in proliferative MCTs. In monoculture cells, miR-320c and miR-940 were found to inhibit phosphoribosyl pyrophosphate synthetase 1 and pyrroline-5-carboxylate reductase 1 mRNAs, respectively, to downregulate amino acid biosynthesis. miR-320c, miR-19a-3p, miR-454-3p and miR-1226-3p also contributed to the downregulation of amino acid degradation by regulating their respective target mRNAs in monoculture cells. As a consequence, dysregulated expression of all these miRNAs led to altered metabolic pathways and rapid cancer cell proliferation (122). Table II shows the miRNAs involved in the regulation of amino acid and glutamine metabolism in BC cell physiology.

4. Lipid metabolism in BC

Lipids are a diverse class of hydrophobic organic biomolecules that include fatty acids (FAs), glycerides, non-glyceride lipids and lipoproteins, all of which are vital in maintaining cellular integrity and serving as energy reserves to fuel cellular activity (123). FAs are the major components in the structural make up of complex lipid molecules and can be synthesized *de novo* from different carbon sources derived from other metabolic pathways. Alternatively, FAs can also be acquired exogenously through the diet (124). Structural variations seen among complex lipids and FAs often result in functional differences, which could directly influence cellular metabolism (125). Various biological metabolites such as triacylglycerol, diacylglycerol, monoacylglycerol and acyl-CoAs generated from lipid metabolism are also important energy sources and modulators of cellular signaling that governs cellular growth, proliferation, differentiation, apoptosis, survival and membrane homeostasis (123,126).

Lipid metabolism is tightly regulated by a series of enzyme-catalyzed reactions and comprises various different pathways, including but not limited to, FA transport, *de novo* synthesis, FA storage, FA mobilization and FA b-oxidation (127). Cancer cells upregulate lipid metabolism to support oncogenic development, such as malignant transformation, cancer development, metastatic colonization and therapeutic resistance (128). *De novo* lipogenesis (DNL) is of particular importance when discussing lipid metabolism in cancer. TCA cycle-derived citrate acts as a substrate for ATP citrate lyase (ACLY), providing acetyl-CoA for FA biogenesis. Palmitate formed from acetyl-CoA and malonyl-CoA undergoes further processing and elongation to form FA chains, such as saturated FAs and monosaturated FAs, which can be utilized as building blocks for cellular membranes and for cellular activity (129). Fig. 2 illustrates the DNL and cholesterol synthesis pathways that are regulated by a number of miRNAs, enzymes and genes. Cells usually depend on circulating exogenous lipids and FAs to fuel normal cellular activity and lipid storage. However, cancer cells preferentially utilize endogenous FAs to support oncogenic growth, proliferation and metastasis (130). The term 'lipogenic phenotype' has been used to characterize the phenotypic alteration observed in cancer cells with enhanced DNL and increased endogenous FA levels regardless of circulating exogenous FA levels (131).

miRNAs as regulators of metabolic enzymes in BC lipid metabolism. Lipogenic enzymes, including FA synthase (FASN), ACLY and acetyl-CoA carboxylase (ACACA), are responsible for cellular lipid metabolism and have been implicated in BC cancer development and survival, and thus, are recognized as potential targets for drug discovery in cancer therapeutics (132-134). For instance, FASN, an enzyme responsible for catalyzing endogenous long-chain FAs, has been reported to be upregulated in BC cells, and is associated with tumorigenesis and metastasis, leading to poor BC prognosis (135). Table III summarizes the targeted enzymes and genes regulated by miRNAs and the effects in BC lipid metabolism following miRNA expression in BC cells.

Wang *et al* (136) identified miR-15 and miR-16-1, both belonging to the miRNA cluster miR-15-16-1, located on chromosome 13q14, as miRNAs with tumor-suppressing abilities that contribute to FASN inhibition in BC. The miR-15-16-1 cluster markedly decreased endogenous FASN expression by directly targeting the FASN mRNA at the FASN 3'-UTR in MDA-MB-231 BC cell lines, which inhibited BC cell proliferation (136). Wahdan-Alaswad *et al* (137) demonstrated that miR-193b directly targeted the FASN-3'-UTR mRNA transcript in TNBC cells. A rapid increase in miR-193b expression due to metformin treatment facilitated the downregulation of the expression of FASN proteins associated with FA and cholesterol synthesis. Furthermore, decreased levels of FASN proteins induced apoptosis and decreased mammosphere formation in TNBC cells compared with normal cells (137).

miRNAs as regulators of gene expression in BC lipid metabolism pathways. ACLY is a lipogenic enzyme responsible for FA synthesis regulation. Increased ACLY expression has been associated with BC development and could be a potential prognostic biomarker for BC recurrence (138). Liu *et al* (139) demonstrated that overexpression of miR-22 in MCF-7 BC cell lines could potentially inhibit BC progression and

Table II. Summary of miRNAs involved in amino acid and glutamine metabolism.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
Yan *et al*, 2018	miR-105	MYC, MXI1	High expression of miR-105 induced MYC signaling activation and downregulated MXI1 in BC cells. Expression of miR-105 increased the ECAR, and enhanced glucose and glutamine consumption. High expression of miR-105 reduced lactic acid and ammonium production in cells. Overexpression of miR-105 enhanced glycolysis and glutaminolysis.	Oncogene	(80)
Liu *et al*, 2011	miR-26b	SLC7A11	Clinical BC samples and BC cell lines were found to have low miR-26b expression. High expression of miR-26b led to increased apoptosis in MCF-7 cells. miR-26b repressed the expression of endogenous SLC7A11. miR-26b overexpression reduced cancer cell viability.	Tumor suppressor	(104)
Sun *et al*, 2021	miR-382-5p	SLC7A11	miR-382-5p expression was found to be low, while SLC7A11 expression was high in clinical BC tissue. Overexpression of miR-382-5p reduced T47D cell viability and colony formation. Upon miR-382-5p mimic treatment, apoptosis of T47D cells was induced. Levels of ferum (II) ion, iron and lipid reactive oxygen species were increased by miR-382-5p expression in T47D cells.	Tumor suppressor	(105)
Msheik *et al*, 2022	miR-126	SLC7A5	miR-126 was downregulated in ER^+ BC tissues from patients both above and below 40 years old. miR-126 overexpression reduced MCF-7 cell proliferation and mammosphere forming ability. miR-126 overexpression downregulated SLC7A5 mRNA levels in MCF-7 cells. High miR-126 expression was associated with improved overall survival of patients with ER^+ BC.	Tumor suppressor	(109)
Bacci *et al*, 2019	miR-23b-3p	SLC6A14	Overexpression of miR-23b-3p in BC cells led to downregulation of SLC6A14 and low amino acid uptake. High miR-23b-3p expression supports the aggressive phenotype of BC cells.	Tumor suppressor	(115)

BC, breast cancer; ECAR, extracellular acidification rate; ER, estrogen receptor; miRNA/miR, microRNA; MXI1, MAX interactor 1, dimerization protein; SLC6A14, solute carrier family 6 member 4; SLC7A5, solute carrier family 7 member 5; SLC7A11, solute carrier family 7 member 11.

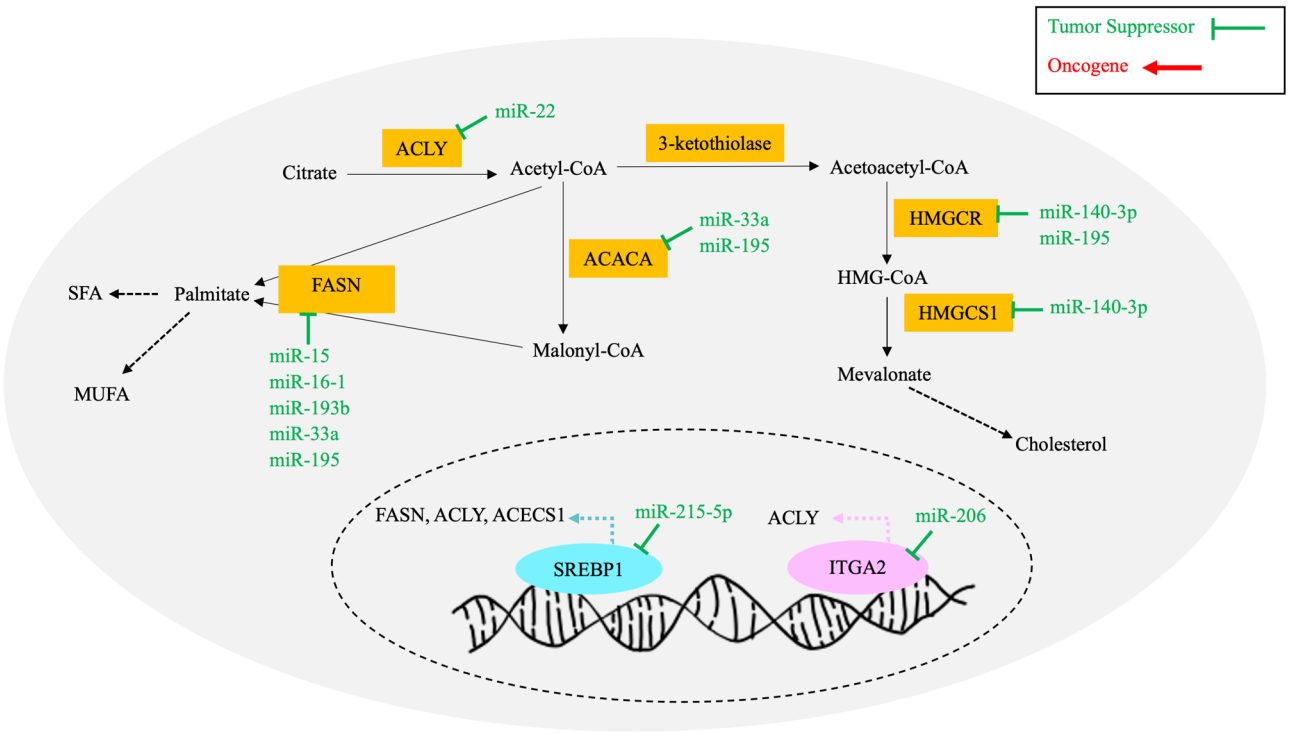

Figure 2. miRNAs involved in lipid metabolism pathways in breast cancer cells. Citrate from the tricarboxylic acid cycle is converted into fatty acids chains and cholesterol by a number of enzymatic pathways. These enzymes (in yellow), transcription factor (in cyan) and integrin gene (in pink) are regulated by miRNAs. ACACA, acetyl-CoA carboxylase; ACECS1, acetyl Co-A synthetase 1; ACLY, ATP citrate lyase; FASN, fatty acid synthase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HMGCS1, hydroxy-3-methylglutaryl-CoA synthase 1; ITGA2, integrin α-2; miRNA/miR, microRNA; MUFA, monosaturated fatty acid; SFA, saturated fatty acid; SREBP1, sterol regulatory element-binding protein 1.

proliferation via downregulation of the expression of the proto-oncogene *ACLY*. Despite miR-22 showing independent tumor-suppressing abilities in BC, cell tumor formation was enhanced when both miR-22 and ACLY were overexpressed. Therefore, these results demonstrated the possibility of miR-22 exerting oncogenic effects when coupled with ACLY expression (139).

Integrin α-2 (ITGA2) is an integrin gene that encodes the surface integrin receptor CD49b, and is suspected to be involved in BC lipid metabolism (140). Adorno-Cruz *et al* (140) reported that miR-206 inhibited transcription of ITGA2 by directly binding to the 3'-UTR of the ITGA2 mRNA. BC cells with miR-206 overexpression exhibited decreased CD49b levels. Downregulation of the ACLY gene was observed in ITGA2-knockdown TNBC cell models compared with controls. ACLY enzyme expression and the cellular concentration of acetyl-CoA were observed to be reduced following ITGA2 knockdown. Therefore, miR-206 might have an effect on CD49b signaling pathways and ACLY expression, which may ultimately affect lipid metabolism pathways in BC (140).

Previous studies have reported that cancer cells have a preference in synthesizing FA via DNL for membrane and energy production to support rapid cell proliferation (141,142). A study conducted by Singh *et al* (143) identified FASN, ACACA and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) transcripts as direct gene targets of miR-195 in BC. Overexpression of miR-195 decreased cellular levels of cholesterol and triglycerides by reducing the gene expression of FASN, ACACA and HMGCR transcripts in MCF-7 BC cell lines. These results confirmed that miR-195 directly targeted key genes involved in the regulation of DNL and cholesterol biosynthesis, and dysregulated miR-195 expression might have implications in BC tumorigenesis and progression (143).

Cholesterol is a vital component in lipid rafts that regulates various cell signaling pathways such as cell binding and cholesterol biosynthesis that are implicated in cancer cell migration and metastasis (144,145). There are two key enzymes involved in the cholesterol synthesis pathway: HMGCR and hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1) (146). The tumor suppressor miRNA miR-140-3p-1 was found to be downregulated during TNBC progression in a study by Bhardwaj *et al* (147). Further analysis also revealed that miR-140-3p-1 directly bound to HMGCR and HMGCS1 gene transcripts at the 3'-UTR to repress transcript activity, ultimately impacting enzyme and cholesterol levels, which could contribute to BC development or progression (147).

Sterol regulatory element-binding proteins (SREBPs) are a family of transcription factors that are involved in cellular lipid metabolism by activating genes that encode integral lipogenic enzymes needed for the synthesis of FAs and choles terol (148). The tumor suppressor miRNA miR-215-5p was reported to negatively regulate SREBP1 expression by directly binding to the 3'-UTR of the SREBP1 mRNA in BC cells by Wu *et al* (149). SREBP1 was highly expressed in MCF-7 and MDA-MB-231 cells, and patients with BC compared with controls following the downregulation of miR-215-5p levels. Furthermore, SREBP1 expression stimulated lipid metabolism by increasing the expression of lipogenic enzymes such

Table III. Summary of miRNAs involved in BC lipid metabolism.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
Wang *et al*, 2016	miR-15	FASN	miR-15 directly targeted the 3'-UTR of FASN mRNA. FASN mRNA expression was downregulated in the presence of miR-15. miR-15 decreased endogenous FASN expression and reduced FA synthesis. miR-15 expression was linked to inhibition of BC cell proliferation.	Tumor suppressor	(136)
	miR-16-1	FASN	miR-16-1 directly targeted the 3'-UTR of FASN mRNA. FASN mRNA expression was downregulated in the presence of miR-16-1. miR-16-1 decreased endogenous FASN expression and reduced FA synthesis. miR-16-1 expression was linked to inhibition of BC cell proliferation.	Tumor suppressor	
Wahdan-Alaswad *et al*, 2014	miR-193b	FASN	miR-193b directly targeted the 3'-UTR of FASN mRNA. Overexpression of miR-193b caused downregulated FASN protein expression in TNBC cells. Decreased levels of FASN protein induced apoptosis and decreased mammosphere formation in metformin-treated TNBC cells.	Tumor suppressor	(137)
Liu *et al*, 2018	miR-22	ACLY	miR-22 directly targeted the 3'-UTR of ACLY mRNA. miR-22 overexpression reduced ACLY gene expression in MCF-7 cells. Simultaneous overexpression of both miR-22 and ACLY was associated with enhanced tumor formation in MCF-7 cells. Decreased ACLY expression led to citrate accumulation, affecting lipid and glucose metabolism pathways. Downregulation of the ACLY enzyme stunted BC cell proliferation.	Tumor suppressor (independent) and oncogene (coupled)	(139)
Adorno-Cruz *et al*, 2020	miR-206	ITGA2	miR-206 directly targeted the 3'-UTR of ITGA2 mRNA. miR-206 overexpression led to decreased ITGA2 gene expression in TNBC cells. Suppressed ITGA2 expression resulted in downregulation of the ACLY enzyme and acetyl-CoA levels in MDA-MB-231 cells. Low miR-206 levels and high levels of ITGA2 and ACLY were associated with poor survival of patients with ER^- or high-grade BC.	Tumor suppressor	(140)
Singh *et al*, 2015	miR-195	FASN, ACACA, HMGCR	miR-195 directly targeted FASN, ACACA and HMGCR gene transcripts at the 3'-UTR. miR-195 overexpression resulted in reduced FASN, ACACA and HMGCR expression in MCF-7 cells. A decreased cellular concentration of cholesterol and triglycerides was	Tumor suppressor	(143)

Table III. Continued.

First author/s, year	miRNA	Target	Findings	miRNA as oncogene/ tumor suppressor	(Refs.)
			observed following miR-195 overexpression. miR-195 inhibited cell proliferation, migration and invasion, and attenuated EMT.		
Bhardwaj *et al*, 2018	miR-140-3p-1	HMGCR, HMGCS1	miR-140-3p directly binds to HMGCR and HMGCS1 transcripts at the 3'-UTR to suppress their activity. Decreased miR-140-3p-1 levels and high expression of HMGCR and HMGCS1 transcripts were associated with TNBC progression and poor patient prognosis.	Tumor suppressor	(147)
Wu *et al*, 2022	miR-215-5p	SREBP1	miR-215-5p directly targeted the 3'-UTR of SREBP1 mRNA. Downregulation of miR-215-5p resulted in increased SREBP1 gene and protein expression in BC cells. miR-215-5p expression caused inhibition of FASN, ACLY and ACECS1 expression via SREBP1, resulting in attenuation of EMT in BC cells.	Tumor suppressor	(149)

ACACA, acetyl-CoA carboxylase; ACECS1, acetyl Co-A synthetase 1; ACLY, ATP citrate lyase; BC, breast cancer; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; FA, fatty acid; FASN, fatty acid synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HMGCS, 3-hydroxy-3-methylglutaryl-CoA synthase; ITGA2, integrin α-2; miRNA/miR, microRNA; SREBP1, sterol regulatory element-binding protein 1; TNBC, triple-negative BC; UTR, untranslated region.

as FASN, ACLY and acetyl Co-A synthetase 1 to promote cell migration, invasion and EMT in BC. On the other hand, miR-215-5p exerted its antitumor effect by downregulating SREBP1 expression and inhibiting lipid metabolism in BC cells. The results of the study highlighted the role of the miR-215-5p/SREBP1 axis in the regulation of BC lipid metabolism, resulting in attenuation of EMT in BC cells (149).

5. Future perspectives and clinical implications of miRNAs in BC metabolism

Early-onset BC was reported to be among the cancers with the highest mortality rate and disease burden in the year 2019 (150). BC has relatively higher survival rate compared with other cancer types when detected early; however, extensive genetic heterogeneity between primary and disseminated BC due to genomic evolution occurring during BC development could result in poor prognostic outcomes and strong limitations in diagnosing and treating patients with BC (151). Early BC detection and diagnosis are important for effective therapeutic management to improve the overall survival and decrease the mortality rate of patients with BC. Although mammograms and ultrasounds are commonly used for initial diagnosis of the tumor, the existing probability of acquiring false-positive or false-negative results cannot be overlooked (152). Furthermore, expensive and invasive procedures such as tissue biopsies are often performed to confirm tumor malignancy, and such procedures are often accompanied by physical discomfort, contributing to the psychological and financial burden of the patient (153). Therefore, researchers have shifted their focus to less invasive and more accessible approaches for early BC detection and risk prediction in the form of human biofluids, including blood, saliva and urine (154-157).

Since the identification of miRNAs in 1993 (158), various studies have investigated the potential diagnostic, prognostic and therapeutic values of miRNAs in BC (159-166). As aforementioned, miRNAs are capable of regulating numerous major metabolic pathways in BC by modulating the expression of genes, enzymes and transporters, contributing to cancer development (53,71,104,136,143). These aberrant miRNA profiles can be used to highlight the disturbances in metabolic homeostasis and to characterize these distinct metabolic changes that are uniquely observed in BC. Identification of differential miRNA signatures by miRNA expression profiling has been useful in BC classification, risk stratification and clinical management (167). miR-155 and miR-21 are examples of frequently dysregulated miRNAs found in BC as reported in various cancer research studies (168-171), with well-established sensitivity and specificity values determining their potential as diagnostic biomarkers (159). Furthermore, miRNAs could be potential prognostic biomarkers for monitoring cancer recurrence and metastasis in order to improve the outcomes and survival of patients with BC (160). Previous studies have reported aberrant miRNA expression related

to metastasis status, dissemination and prognosis to predict patient outcomes and overall survival in BC (161-163). In addition, miRNA-based cancer therapies utilize the oncogenic and tumor-suppressive properties of miRNAs via synthetic oligonucleotides to either restore tumor suppressor miRNA function or inhibit upregulated oncogenic miRNAs in BC (164). The development of individualized treatment for patients with BC is made possible by utilizing the function of miRNAs as cancer cell gene regulators (165). A Taiwanese study demonstrated that miR-125a-5p directly targeted histone deacetylase 4 (HDAC4) to reduce BC tumor growth, metastasis and angiogenesis in mouse models, suggesting the potential of developing miR-125a-5p as a drug candidate for the drug target HDAC4 (166). Although promising, further research and validation should be performed to assess and establish the disease and subtype specificity values of miRNAs as diagnostic and prognostic biomarkers in BC, and miRNA-based therapeutics as treatment options for BC.

The concept of metabolic reprogramming observed in malignant cells has been gaining widespread interest due to advances in cancer metabolomics (172). 'Omics'-based approaches, including metabolomics, proteomics, transcriptomics and genomics, have a wide range of applications in cancer research, including but not limited to improving the understanding of underlying mechanisms that lead to BC pathology, and also aid in the identification of potential diagnostic and prognostic markers, and novel drug targets for BC therapy (173). Metabolomics is an emerging, high-throughput technique used in cancer research with the purpose of measuring and detecting changes in metabolite levels present in a metabolome or a given biological sample during malignant cell proliferation and transformation (174). Metabolite detection is often performed using techniques such as liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry and nuclear magnetic resonance (175). The metabolome of an organism is largely defined by its genome, and thus, alterations in the respective genome of an individual due to diseases such as cancer often show a reflective result in the cellular function and metabolomic profile of said individual (176).

Metabolites such as glutamine have been observed to be upregulated due to the enhanced expression of the amino acid transporter SLC1A5 in more aggressive forms of BC, with varying glutamine and β-alanine profiles observed between ER^+ and ER^- patients with BC (177). Furthermore, 20 different metabolites involved in arginine, proline, glycerophospholipid, phenylalanine, tyrosine and tryptophan metabolism pathways have been observed to be deregulated in patients with IDC compared with healthy patients (178). Thus, dysregulated metabolite profiles are capable of differentiating between healthy individuals and patients with breast cancer (178). Metabolomic profiling has also been used as an effective diagnostic tool for cancer biomarker detection and stratification of cancer subtypes in lung, colorectal and cervical cancer (179-181), further accentuating the idea that metabolic profiles have the potential of being utilized as promising biosignatures in BC. The multifaceted nature of BC tumors means they can be challenging to treat due to the diverse clinical presentations and tumor responses to anticancer therapy. In BC therapeutics, metabolomic studies could help with the identification of metabolic pathways responsible for mechanisms involved in cancer drug resistance and anticancer drug responses. As reported by Granit *et al* (182), the lipid metabolism metabolite valproic acid has been found to enhance the anticancer effect of cisplatin in order to counter cisplatin resistance in TNBC cells.

Despite their advantages, '-omics' based approaches do not come without its limitations. Xiao *et al* (183) highlighted the limitations of using transcriptomic and genomic data in metabolic research. As metabolic regulatory networks in cancer cells are complex, solely relying on either transcriptomic or genomic data to characterize the complexity of cancer is often proven to be insufficient or unreliable (183). The inherent complexity of BC tumors among different individuals due to inter- and intra-tumor heterogeneity poses challenges in genotype and phenotype mapping. Therefore, by merging metabolomic-, transcriptomic- and genomic-based approaches, this research gap could be minimized to improve BC characterization and BC subtype refinement for further applications in precision medicine and to enhance diagnostic and prognostic accuracy in BC (184). Furthermore, operating analytical equipment and data analysis can be complicated, and thus, advanced bioinformatics knowledge and skills might be required for more accurate interpretation and analysis of data. Furthermore, study limitations, including selection of internal controls, selection of mass spectrometers and analysis equipment, and sample sizes, need to be optimized to obtain reliable and valid results (183,184).

Molecular heterogeneity of BC tumors still poses a challenge to overcome in BC treatment prediction and patient prognosis. miRNAs can regulate metabolism in tumors either directly or indirectly by modulating genes and/or enzymes involved in these pathways. With the knowledge that dysregulated miRNA profiles reflect changes in metabolism, unique metabolic profiles can be generated to assist with understanding the pathology behind BC subtypes (23). There have been numerous studies that have analyzed the involvement of miRNAs in BC metabolism in different BC molecular subtypes (109,115,137). For example, the studies by Msheik *et al* (109) and Bacci *et al* (115) both looked into the role of miRNAs affecting amino acid transporters and amino acid metabolism in ER^+ BC. miR-216 upregulation coupled with decreased expression of its target, SLC7A5, was shown to be associated with improved overall survival in patients with ER^+ BC (109). Additionally, altered amino acid metabolism due to miR-23b-3p overexpression resulted in endocrine therapy resistance in ER^+ BC, offering targetable pathways to predict and combat endocrine therapy resistance in ER^+ BC (115). The results of these studies showed that miRNAs could be potential prognostic and predictive biomarkers by targeting the amino acid metabolic dependencies observed in ER^+ BC to possibly monitor patient prognosis and predict treatment responses in patients with ER^+ BC (109,115). TNBC is a BC subtype with poor patient prognosis and has been clinically challenging to treat due to its non-hormone-dependent nature (13). A study on miR-193b showed that miR-193b directly targeted the FASN enzyme, which is needed for TNBC cell survival (137). The metformin-induced upregulation of miR-193b resulted in decreased FASN levels, followed by TNBC cell death (137). The findings of the study provided an insight into the therapeutic effect of miRNAs on targetable metabolic pathways in

aggressive BC subtypes such as TNBC (137). HER2-positive BC is another BC subtype with poor patient prognosis and response to treatment (185). To the best of our knowledge, there have been no studies that focused on the role of miRNAs in HER2-positive BC metabolism to date. The combination of metabolic footprinting and miRNA profiling has potential in BC subtype stratification refinement and also provides opportunities for identifying novel drug targets for subtype-specific BC treatment approaches (186). However, no studies could be found comparing metabolic profiles between BC subtypes and investigating the differential role of miRNAs according to these metabolic profiles thus far.

Research towards understanding the roles miRNAs serve in BC metabolism is still in its early stages, with more that remains to be investigated. The aforementioned studies have shown evidence that miRNAs hold indisputable influence over BC metabolism, and thus, such insights into the cellular function of BC pathology is information worth seeking. The combination of metabolomics, transcriptomics and genomics could be a valuable diagnostic and prognostic tool in BC when properly validated and implemented in clinical settings. Further studies on cancer metabolism integrating '-omics' based approaches and multiomic data could create reformative and promising avenues for future BC diagnostics, prognostics and therapeutics, which will ultimately improve the precision of BC treatment and reduce the global disease burden of BC.

6. Conclusion

BC is a highly heterogenous malignancy that affect millions of women worldwide regardless of their age and ethnicity, placing a substantial disease burden on the global population. In the advent of scientific technological advancement, miRNAs have garnered considerable attention amongst researchers as promising non-invasive biomarkers for early diagnosis and prognosis of BC, and as emerging therapeutic targets for individualized BC treatment in a subtype-specific manner. The present review highlights the pivotal role miRNAs serve in regulating and reprogramming cellular metabolism in BC. miRNAs have been shown to be implicated in major metabolism pathways, including glucose, amino acid, glutamine and lipid metabolism pathways, by inhibiting or promoting gene expression and metabolic enzyme expression in BC through their oncogenic and/or tumor-suppressive abilities. The complex interplay between miRNAs and metabolic cell signaling pathways contributes to BC tumorigenesis and oncogenic development, conferring more 'aggressive' BC phenotypes such as increased invasiveness and metastasis, high risk of relapse and therapeutic resistance, which could be clinically challenging to treat. Advances in understanding pathophysiological mechanisms of miRNAs in BC metabolic dysregulation by implementing '-omics'-based approaches in scientific research can instigate future breakthroughs in cancer therapeutics and provide potential developments in precision medicine for subtype-specific BC treatment to further improve clinical outcomes and patient survival in BC.

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Authors' contributions

WXL conceived the idea for the manuscript. WXL and BSY drafted the manuscript, and designed the tables and figures. The manuscript was revised by YKC, RM, GCT and MIAW. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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