

Role of microRNAs in glycolysis in gynecological tumors (Review)

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Abstract. Gynecological malignancies are a leading cause of mortality among females worldwide, and difficulties in early diagnosis and acquired drug resistance constitute obstacles to effective therapies. Ovarian cancer causes more deaths than any other cancer of the female reproductive system. Specifically, in females aged 20 to 39 years, cervical cancer is the third leading cause of cancer-related mortality, and the incidence rates of cervical adenocarcinoma are increasing. Endometrial carcinoma is the most common gynecological cancer in developed countries, such as the United States. Vulvar cancer and uterine sarcomas are considered rare, and therefore require further investigation. Notably, the development of novel treatment options is critical. Previous research has revealed metabolic reprogramming as a distinct feature of tumor cells, which includes aerobic glycolysis. In this instance, cells produce adenosine triphosphate and various precursor molecules through glycolysis, despite oxygen levels being sufficient. This is to meet the energy required for rapid DNA replication. This phenomenon is also known as the Warburg effect. The Warburg effect results in an increased glucose uptake, lactate production and reduced pH values in tumor cells. The results of previous studies have demonstrated that microRNAs (miRNAs/miRs) regulate glycolysis, and participate in tumorigenesis and tumor progression via interactions with glucose transporters, essential enzymes, tumor suppressor genes, transcription factors and multiple cellular signaling pathways that play critical roles in glycolysis. Notably, miRNAs affect the levels of glycolysis in ovarian, cervical and endometrial cancers. The present review article provides a comprehensive overview of the literature surrounding miRNAs in the glycolysis of gynecological malignant cells. The present review also

aimed to determine the role of miRNAs as potential therapeutic options rather than diagnostic markers.

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1. Introduction

Gynecological malignancies, including cervical, ovarian, uterine, vulvar, vaginal and fallopian tube cancers, are among the leading cause of mortality among females worldwide; among these, ovarian, cervical and endometrial cancers are the most common (1). When these diseases are detected at an early stage, surgery is the primary and most effective treatment option. With the development of medical science, the earlier detection of endometrial cancer (2) and cervical cancer (3) has increased; however, ovarian cancer is often diagnosed in later stages, at which point, numerous treatment options are not available. Moreover, the recurrence and chemical resistance of ovarian cancer leads to poor treatment outcomes and a poor prognosis (4).

Ovarian cancer causes more deaths than any other type of cancer of the female reproductive system (5). According to the histological classification of female genital tumors established by the World Health Organization (6), the main histological categories of ovarian cancer are epithelial carcinoma, malignant ovarian germ cell tumor, sex cord-stromal carcinoma and metastatic ovarian cancer. Among these, epithelial carcinoma accounts for the majority of ovarian cancer cases (7). Epithelial carcinoma is also classified as serous, mucinous, endometrioid or transparent cells and certain other types of cancer. Notably, the most common type of epithelial carcinoma is high-grade serous ovarian cancer, which accounts for 75% of epithelial carcinoma-associated deaths (6). As ovarian cancer has no notable symptoms during the early stages, it is often not diagnosed until it reaches an advanced stage (5). In addition, ~75% of patients develop extensive peritoneal metastasis by the time of diagnosis, in stages III or IV. Despite an increased

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understanding of this type of cancer in recent years, the associated survival rate has not improved, due to these difficulties in early diagnosis (4). Notably the 5-year survival rate for patients with stage III or IV ovarian cancer is <30% (8). By contrast, the 5-year survival rates of patients diagnosed with stage I or II disease are as high as 70-90% (9). At present, tumor resection combined with platinum chemotherapy is the standard treatment option for ovarian cancer (10). Surgical tumor reduction combined with platinum and taxane chemotherapy may lead to clinical remission in up to 75% of cases (8). However, the majority of patients with advanced-stage ovarian cancer relapse or develop drug resistance, leading to treatment failure and mortality (10).

The results of previous studies indicated that the incidence and mortality rates of patients with cervical cancer have decreased with the increase in human papillomavirus (HPV) vaccines, and increases in global cervical cancer testing facilities. For women aged 20 to 39 years, cervical cancer is the third leading cause of cancer-related mortality (11-13). Notably, the incidence rates of adenocarcinoma have increased in young females aged <40 years. Moreover, the prevention, early detection and prognosis of cervical adenocarcinoma remain poor (14). It is well-established that pre-cervical or cervical cancers are caused by HPV infection. Notably, HPV is present in >90% of tumors (15), and is often transmitted through sexual activity. Cervical cancer progression is often associated with a persistent high-risk HPV infection (16). Lymph node metastasis is the primary mode of the distant metastasis of cervical cancer; however, blood transfer occurs relatively infrequently and during the late stages (17). The most common metastatic sites of cervical cancer are the lung and liver. In addition, the 5-year survival rate of patients with cervical cancer without metastasis is 91.5%, while the 5-year survival rate of patients with cervical cancer with metastasis is 16.5% (18).

Endometrial carcinoma is the most common gynecological cancer in developed countries, such as the United States, and the incidence rate of endometrial cancer continues to increase. At present, 67% of endometrial cancers are detected and confirmed in the early stages (19). Moreover, there are two types of endometrial cancer, namely, types I and II. Type I endometrial cancer may be caused by obesity, driven by estrogen and associated with the excessive proliferation of endometrial cells. Type I is more common, accounting for ~70% of endometrial cancer cases, and exhibits a lower risk. Patients with type I endometrial cancer often present with metabolic disorders, such as hyperlipidemia, hyperestrogenemia, diabetes or anovulation uterine bleeding. By contrast, type II endometrial cancer is not associated with obesity or endometrial hyperplasia, and is not associated with metabolic or endocrine diseases. Type II endometrial cancer is rare and highly invasive. Type I and II endometrial cancers can be distinguished histologically. Notably, type I tumor samples are often endometrioid cancers that are well-differentiated. Type II, however, is developed through endometrial atrophy, and the most common types are serous and clear cell adenocarcinoma. Premalignant forms differ for each type. The premalignant form of type I cancer is endometrial intraepithelial neoplasia, while the premalignant form of type II cancer is endometrial intraepithelial carcinoma (2,20).

Vulvar cancer is considered rare and accounts for only 5% of cancers of the female genital tract. Vulvar cancers are divided into a variety of types depending on their histology, among which, squamous cell carcinoma accounts for >85% of cases. Other rare histological types include basal cell carcinoma, Bartholin adenocarcinoma, extra mammary Paget's disease, sweat gland adenocarcinoma and intestinal adenocarcinoma (21,22). The results of a previous study demonstrated that risk factors for vulvar cancer include HPV infection, vulvar lichen sclerosis disease and vulvar intraepithelial neoplasia in young females. Imaging techniques, including pelvic magnetic resonance imaging, computed tomography (CT) or positron emission tomography/CT, and ultrasound, may be used to evaluate the condition of the patient (21). Vulvar cancer is often treated with surgery, followed by radiotherapy and chemotherapy.

Similarly, uterine sarcomas are rare, accounting for ~1% of all female genital tract malignancies, and 2 to 3% of all uterine cancers (23). Uterine sarcomas are categorized into the following two groups: i) Mesenchymal tumors and ii) mixed epithelial and mesenchymal tumors. Mesenchymal tumors include endometrial stromal sarcoma, leiomyosarcoma and undifferentiated endometrial or uterine sarcoma. Mixed epithelial and mesenchymal tumors include adenosarcoma and carcinosarcoma (21). The rarity of uterine sarcoma and its histopathological diversity result in a lack of agreement on risk factors and available treatment option (22). Patients with uterine sarcoma often present with abnormal uterine bleeding or pelvic pain. However, a definitive diagnosis requires biopsy or histopathological analysis.

2. miRNAs and the Warburg effect

MicroRNAs (miRNAs/miRs). miRNAs are small, non-protein-coding RNAs that produce ~22 nucleotide-long sequences. These mediate post-transcriptional gene suppression via the inhibition of protein translation or the destabilization of target transcription, by recognizing the 3'untranslated region (UTR) of homologous mRNAs. Among the miRNAs, LIN-4 was the first to be discovered (24). Subsequently, additional miRNAs and their corresponding functions have been studied, and a miRNA database has been established (25). This database provides a unique name to a miRNA prior to its discovery, and the sequences of all published miRNAs are included. In total, ~25% of human miRNA genes are located in the introns of precursor miRNAs (pre-miRNAs), suggesting that the majority of miRNAs are not transcribed from their own promoters but are instead processed from introns (26). As illustrated in Fig. 1, the transcription of miRNAs is often carried out by RNA polymerase II, and the transcript is further processed using capping and polyadenylation (27). Two successive processing reactions transform transcripts into mature miRNAs (28). In mammals, one of the processing reactions involves the removal of stem rings from the rest of the pri-miRNA transcript in the nucleus. This is carried out by nuclear members of Drosha to create pre-miRNA products (27). The second process includes the active transportation of pre-miRNAs out of the nucleus via output receptor and RAS-related nuclear protein (RAN)-GTP. In the cytoplasm, the terminal ring is removed from the stem of pre-miRNA by Dicer, to create a mature miRNA

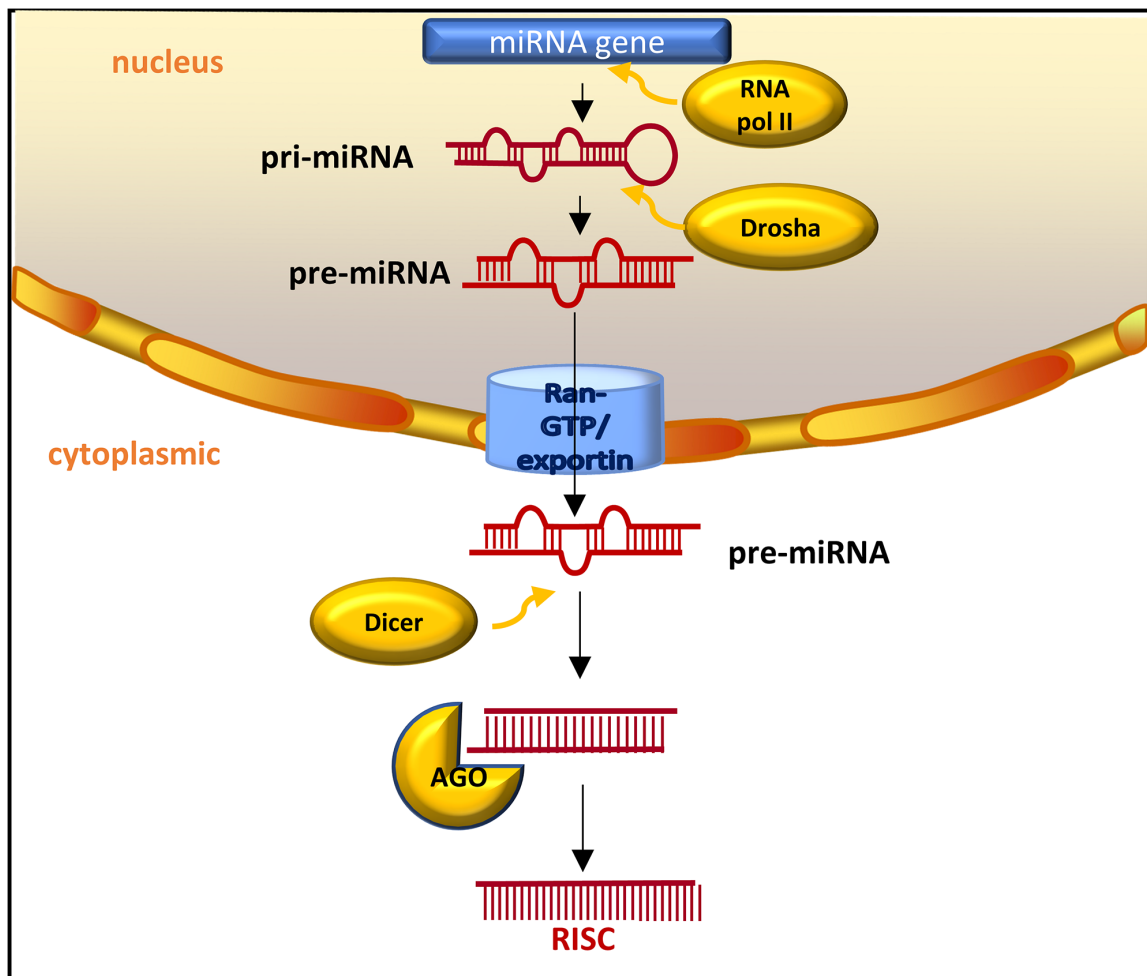


Figure 1. Schematic diagram of the generation of miRNAs. miRNAs, microRNAs; pre-miRNAs, precursor miRNAs; AGO, Argonaute; RISC, RNA-induced silencing complex.

double-stranded body with a length of ~22 base pairs (26,27). The mature miRNA double strand is an unstable entity; it is at a high speed when bound to the Argonaute (AGO) protein. Only one strand is retained, depending on the relative thermodynamic stability of the ends of each strand (28).

miRNAs bind to AGO and GW182 proteins to form RNA-induced silencing complexes (RISCs), that mediate gene expression and participate in various biologically critical processes (29). Notably, this process involves two mechanisms. Firstly, the target RNA contains sequences entirely complementary to miRNA, and is cleaved by ribonuclease in the RISC complex (30,31). Moreover, when the target RNA includes sequences that are not entirely complimentary to the miRNA, these are controlled in translation (30,32). Through these mechanisms, miRNAs are involved in multifarious biological impacts, such as cell growth, cell death, cell differentiation, cell apoptosis, intercellular signaling and cell metabolism, including fat metabolism (26,33-35). The present review will focus on the steps of glycolysis in gynecological tumor cells in which miRNAs are involved.

Warburg effect. Otto Heinrich Warburg (36,37) initially discovered the Warburg effect in the 1920s. This effect refers to the tendency of tumor cells to produce adenosine

triphosphate (ATP) through anaerobic glycolysis, even when sufficient oxygen is present (36,37). Normal cellular glucose metabolism can be divided into two phases and ten reactions. The first phase is the production of two propanose phosphates from glucose and the second phase is the conversion of propanose phosphate to pyruvate. The specific process displayed in Fig. 2. Under aerobic conditions, pyruvate is further oxidized and decomposed to form acetyl CoA in the mitochondria, which can be wholly oxidized into H₂O and CO₂ through the electron transfer chain and Krebs cycle to generate ATP (38). Pyruvate cannot be further oxidized in anoxic conditions and is reduced to lactate.

Despite sufficient levels of oxygen in tumor cells, the cells continue to turn pyruvate into lactic acid, which is known as aerobic glycolysis. In addition, tumor cells exhibit an increased glucose uptake. Therefore, the production of lactic acid by pyruvate increases and the pH value of tumor cells decreases. The results of a previous study demonstrated that this may be due to tumor cells living in environments rich in glucose and other nutrients, indicating that there is no ATP deficiency. On the other hand, tumor cells may convert all glucose into CO₂ through oxidative phosphorylation, which maximizes ATP production but does not meet the requirements of rapid cell proliferation. Notably, the rapid proliferation of tumor cells

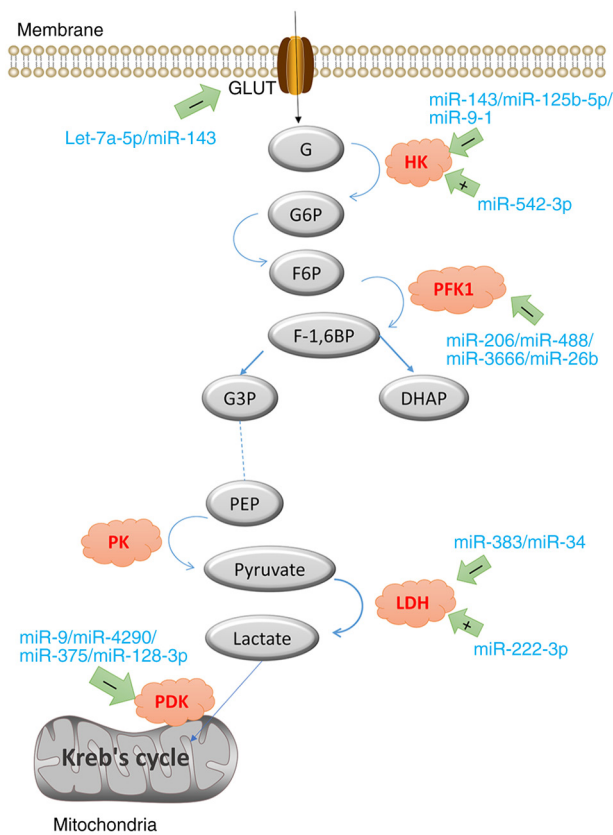


Figure 2. Glucose is transported into the cell by GLUT, and HK catalyzes the production of G-6-P. Phosphohexose isomerase catalyzes the production of F-6-P. PFK1 is further phosphorylated to form F-1, 6-BP, which is catalyzed by aldolase into DHAP and glyceraldehyde 3-phosphate. PEP is subsequently generated through multiple reversible reactions, and PEP is converted to pyruvate with PK catalysis. The + symbol indicates promotion, and the - symbol indicates inhibition. miR, miRNA; GLUT, glucose transporter; HK, hexokinase; G-6-P, glucose 6 phosphate; F-6-P, fructose 6-phosphate; PFK1, phosphofructokinase L; F-1, 6-BP, fructose 1,6-diphosphate; DHAP, dihydroxyacetone phosphate; PEP, phosphoenolpyruvate; PK, pyruvate kinase; LDH, lactate dehydrogenase; PDK, pyruvate dehydrogenase.

requires numerous substances, such as nucleotides, lipids and amino acids (39). In addition, glucose produces acetyl coenzyme A and ribose, which are used for nucleotide biosynthesis for rapid DNA replication (40,41). However, the requirements of the Warburg effect in cancer have yet to be fully elucidated (41-43).

3. miRNAs and glycolysis

Upstream regulation of miRNAs

Long non-coding RNAs (lncRNAs). lncRNAs are transcripts >200 nucleotides in length, that cannot be translated into proteins (44). lncRNAs contain intergene transcripts and enhancer RNA (45). The results of a previous study demonstrated that lncRNAs play a role in regulating gene expression during transcription or post-transcription, such as *cis*-trans transcriptional regulation, and the regulation of the organization of nuclear domain and protein/RNA molecules (46). On the other hand, lncRNAs also bind with proteins to regulate protein activity. For example, complementary pairing with miRNA bases regulates the abundance or activity of miRNA to affect its function (44). lncRNAs are vital in various biological

processes of carcinogenesis (47), and are closely associated with numerous human diseases (48,49).

The results of a previous study demonstrated that the expression levels of lncRNA-TDRG1, determined using reverse transcription-quantitative PCR (RT-qPCR), were increased in cervical cancer cells (50). Under conditions of hypoxia, tests of the trans hole, glucose, lactic acid and functional loss demonstrated that lncRNA-TDRG1 knockdown inhibited glycolysis and the progression of cervical cancer. The results obtained from a bioinformatics database revealed the association between lncRNA-TDRG1 and miR-214-5p, and miR-214-5p and signaling protein 4C (SEMA4C), and this was confirmed using a dual-luciferase reporter assay. The results of that study demonstrated that lncRNA-TDRG1 regulated the expression of miR-214-5p by sponging miR-214-5p. Subsequently, miR-214-5p binds to SEMA4C to regulate the corresponding levels, and regulates glycolysis and the growth of cervical cancer cells (50).

Similarly, the results of another study demonstrated that lncRNA-MALAT1 promoted the glycolysis and metastasis of oral squamous cell carcinoma (OSCC) cells, by targeting miR-101/EZH2 (51). By contrast, lncRNA-CASC2 expression was decreased in OSCC cells, and inhibited tumor cell replication by targeting miRNA-21 (52). In hepatocellular carcinoma, lncRNA-MALAT1 has been found to regulate glycolysis and the progression of hepatocellular carcinoma through sponging miR-142-3p (53).

Downstream targets of miRNAs

Glucose transporter (GLUT). The Warburg effect begins with the transport of extracellular glucose into the cell. Glucose requires specific membrane transporters, and the GLUT family plays an essential role in transportation. GLUT provides glucose for cellular metabolism and maintains a constant blood glucose level (54). A total of 14 glucose transporters have been identified in mammals using genome sequencing. The 14 subtypes are divided into three groups. GLUT1-4 and GLUT14 constitute the first group, and GLUTs 5, 7, 9 and 11 constitute the second group. Group 3 includes GLUTs 6, 8, 10, 12 and 13. GLUT1 is the most crucial subtype, and it exists in the majority of human cells, particularly at the blood-brain barrier (55). GLUT1 is expressed in numerous types of cancer (56). GLUT2 mainly plays a role in the liver and pancreas, GLUT3 primarily exists in the brain (57), and GLUT4 mainly exists in fat, heart and skeletal muscle (58).

The results of a previous study demonstrated that GLUT12 was significantly upregulated in triple-negative breast cancer (TNBC), compared with other types of breast cancer. In addition, GLUT12 is key in adjusting TNBC cell proliferation, wound healing and transportation measurements (59). Notably, five miRNAs were identified as targets of GLUT12 using the TargetScan and miRanda databases. Results of western blot analysis and dual-luciferase assays demonstrated that Let-7a-5p inhibited GLUT12 at the highest levels. Moreover, Let-7a-5p directly inhibited GLUT12 through binding to the 3'-UTR of GLUT12. Thus, Let-7a-5p is considered a tumor inhibitor (60). Similarly, Let-7a-5p demonstrated an inhibitory effect in TNBC. Following Let-7a-5p overexpression, both glucose uptake and lactic acid production were reduced in TNBC cells. In summary, Let-7a-5p inhibited glycolysis and

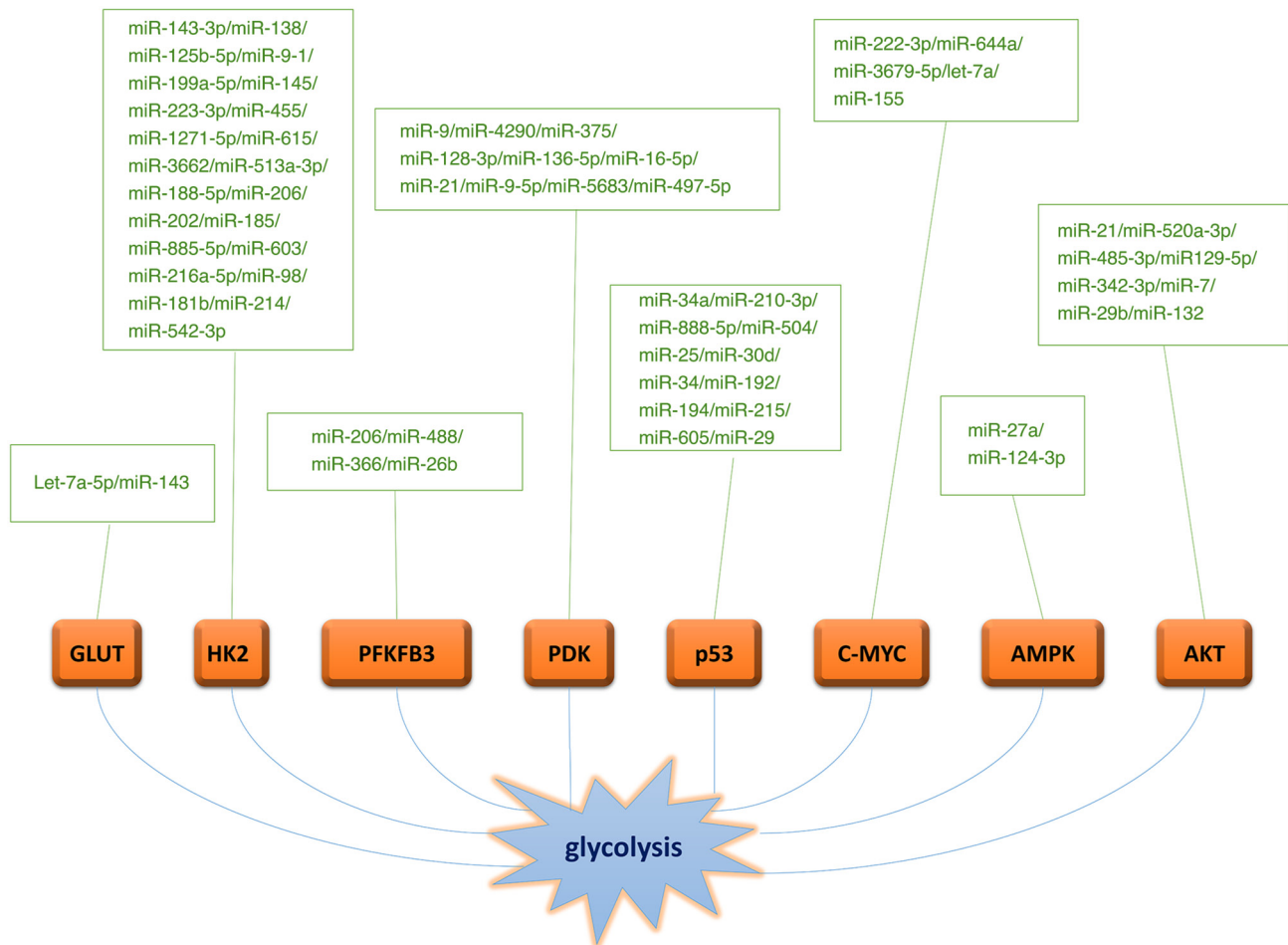


Figure 3. Downstream targets of miRNAs. miRNAs/miRs, microRNAs; GLUT, glucose transporter; HK2, hexokinase 2; PFKFB3, 6-phospho-fructo-2-kinase/fructose-2,6-biphosphatase 3; PDK, pyruvate dehydrogenase; AMPK, AMP kinase.

prevented TNBC cell propagation, transfer and migration through targeting GLUT12.

In addition to affecting tumor cell proliferation and migration, miRNA targets GLUT to adjust T-cell polarization. Notably, miR-143 ultimately inhibits glycolysis in T-cells and regulates T-cell polarization via directly targeting and inhibiting GLUT-1 (Fig. 3) (61).

Hexokinase (HK). HK is the key enzyme in glucose metabolism. It phosphorylates glucose to form G-6-P, which is an irreversible process. There are four subtypes of HK; however, only HK2 is associated with tumor development (62), and increased levels of HK2 are a characteristic of numerous tumors (63,64). In several types of cancer, including prostate (65), colon (66) and gallbladder cancer (67), increased HK2 expression levels have been observed, promoting tumor growth and metastasis. In addition, miR-143 inhibits HK2 expression through the recognition of specific sequences in the 3'UTR of HK2 (63), thus inhibiting cellular glucose metabolism. Moreover, miR-138 also affects HK1 expression through the identification of a specific motif in HK1 mRNA 3'UTR; however, HK1 does not play a role in tumor development (63), and studies are limited.

In pancreatic cancer (68), breast cancer (69) and bladder cancer (70), miR-125b-5P plays a role as a tumor-inhibiting miRNA that targets HK2 and inhibits HK2 expression (71).

Subsequently, this reduces ATP levels, glucose uptake and lactic acid release from tumor cells. HK2 also plays a role in the propagation, transfer, migration and glycolysis of tumor cells. In addition, miR-9-1 was determined to directly target the 3'UTR of HK2 to inhibit translation; thus, controlling tumor cell growth, metastasis and glycolysis (72). At present, through the determination of dual luciferase reporter genes, alternate miRNAs may inhibit cancer through targeting HK2 in different tumors. For example, miR-199a-5p (73), miR-145 (74), miR-223-3p (75), miR-455 (76), miR-1271-5p (77), miR-615 (78), miR-3662 (79), miR-513a-3p (80), miR-188-5p (81), miR-206 (82), miR-202 (83), miR-185 (84), miR-885-5p (85), miR-603 (86), miR-216a-5p (87), miR-98 (88), miR-181B (89) and miR-214 (90) may target HK2.

By contrast, certain miRNAs may promote tumor cells. For example, miR-542-3p promotes HK2-mediated glycolysis in human glioma cells, aids tumor cell growth and metastasis, and leads to a poor prognosis in patients with glioma (91).

6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3). Using dual-luciferase and bioinformatics analyses, the results of previous studies revealed PFKFB3 as a rate-limiting enzyme that regulates glycolysis. In addition, the levels of PFKFB3 are significantly increased in a variety of human tumors, ultimately expanding the glycolysis levels of

tumor cells, and the corresponding levels of proliferation and metastasis (92,93). miR-206 interacts directly with the 3'UTR of PFKFB3 mRNA. The overexpression of miR-206 obstructs the production of fructose-2,6-bisphosphatase (F-2, 6-BP), reduces lactic acid production, and reduces cell propagation and tumor migration (94). In other types of cancer, such as colorectal cancer, miR-488 directly targets PFKFB3, and PFKFB3 mRNA levels are inhibited by miR-488. This results in decreased glucose uptake and lactate secretion, increased sensitivity to chemotherapy drugs, and decreased proliferation, invasion, and migration (95,96). miR-3666 and miR-26b also reduce the rate of glycolysis through inhibiting the activity of PFKFB3; thus, contributing to tumor inhibition (97,98).

Pyruvate dehydrogenase kinase (PDK). PDK phosphorylates pyruvate dehydrogenase and converts glucose metabolism from OXPHOS to glycolysis, resulting in increased lactate production. There are four subtypes of PDK in human cells (PDK1, PDK2, PDK3 and PDK4), each highly expressed in different tumors. The results of a dual-luciferase reporter gene assay demonstrated that miRNA-9, as a tumor suppressor, directly targets PDK1, reduces the levels of glycolysis and inhibits the development of prostate cancer (99). miR-4290 has been shown to enhance cisplatin sensitivity in gastric cancer cells by inhibiting PDK1-mediated glycolysis (100). miRNA-375 was the most downregulated miRNA in gastric cancer cells, and its ectopic expression significantly inhibited cell survivability through a caspase-mediated apoptosis pathway. Moreover, high miR-375 expression levels inhibited the expression of PDK1 (101). In nasopharynx cancer, PDK1 is the target of miR-375, and tumor development is negatively associated with miR-375 expression levels (102). The results obtained from the Interactive Analysis of Gene Expression Profiling database demonstrated that PDK1 levels were markedly increased in glioma tissues. The downstream target of miR-128-3p is PDK1, and miR-128-3p overexpression interfered with the Warburg effect in neuroglioma cells by decreasing PDK1 expression, and inhibiting the occurrence and development of glioma (103).

In TNBC cells, PDK4, as a downstream target of miR-136-5p, has been found to be downregulated, subsequently reducing the Warburg effect and inhibiting the proliferation and metastasis of TNBC cells (104). In cervical cancer, miR-16-5p targets PDK4 to reduce glycolysis levels and chemical resistance (105). Other human tumor cells that also target PDK4 and inhibit expression include miR-21 (106), miR-9-5p (107) and miR-5683 (108).

In gastric cancer tissues, PDK3 levels are increased, and miR-497-5p directly downregulates PDK3, thereby inhibiting the proliferation and growth of cells (109).

p53. p53 is one of the most common tumor suppressor genes. In the process of normal development, p53 activity is often low. p53 pathway deactivation occurs in tumors, as it functions in inhibiting cell proliferation and in controlling metabolism. Thus, p53 plays a role in resisting high levels of glycolysis of tumor cells, and aiding in the adaptation to metabolic stress. p53 activity aids in preventing the occurrence and development of cancer, and provides a basis for the development of novel tumor therapies (110-112).

The activation of p53 induces a variety of non-coding miRNAs, including miR-34a. The results of previous studies demonstrated that p53 overexpression reduces the expression

levels of HK2, pyruvate kinase M (PKM), phosphofructokinase 1 (PFKP), PFKFB3 and hypoxia-inducible factor-1 α (HIF-1 α) in cells, by inducing the upregulation of miR-34a expression; thus, inhibiting the Warburg effect. This ultimately impacts the proliferation and metastasis of tumor cells (113). TP53-inducible glycolysis and apoptosis regulator (TIGAR), an apoptosis and glycolysis regulatory factor, is a downstream target of p53, that controls cell metabolism and prevents programmed cell death. TIGAR primarily functions as a F-2, 6-BP to inhibit the Warburg effect. In liver tumors, miR-885-5p and the associated precursors bind to TIGAR promoter binding sites, alter local chromatin construction, and subsequently adjust the levels of TIGAR (114,115). miR-125b is a negative regulator of p53 (112). Other miRNAs that act on p53, such as miR-504, miR-25 and miR-30d, inhibit its expression by directly binding to the 3'UTR of p53 mRNA. By contrast, miR-34, miR-215, miR-194, miR-605, miR-192 and miR-29 affect the regulation of p53, leading to the indirect activation of p53 (116).

c-myc. C-myc is an oncogenic transcription factor that is overexpressed in numerous cancer types, and is involved in cell metabolism and proliferation processes, including nucleotide metabolism, glucose metabolism and, glutamine metabolism. Notably, c-myc also participates in ribosomal and mitochondrial biogenesis. Myc functions as an oncogene in the development of numerous human cancers (117,118). Therefore, the inhibition of c-myc may exhibit potential in glucose metabolism in tumor cells, thus providing a basis for the development of novel treatment option (118).

The results of previous studies have demonstrated an association between c-myc and miRNAs. For example, miR-222-3p indirectly activates c-myc and c-myc target genes, such as GLUT1, HK2 and lactate dehydrogenase A (LDHA) (119). miR-644a directly inhibits c-myc, thereby inhibiting the Warburg effect and proliferation (120). Through miRNA target prediction, c-myc was identified as a potential target of Let-7a, which inhibits the glucose metabolism activity of tumor cells through inhibiting c-myc (121). miR-3679-5p indirectly regulates c-myc by inhibiting the transcription of neuronal precursor cell-expressed developmentally downregulated 4, an E3 ligase, leading to c-myc stability and Warburg effect increases, thus driving chemical resistance in lung cancer (122). The results of a previous study demonstrated that miR-155-deficient cells possess reduced genes that play a role in the Warburg effect, and exhibit reduced HK2, LDHA and PKM2 expression levels. Further results demonstrated that the downregulation of c-myc controls the PIK3R1-PDK1/Akt-Foxo3a pathway; however, there is no miR-155 binding domain in c-myc. These associations have yet to be fully elucidated (123).

AMP kinase (AMPK). AMPK plays a role as a metabolic master switch, regulating three major types of metabolisms in metabolic tissues, such as muscles and the liver. AMPK is also a stabilizer of organic energy in cells. AMPK harmonizes and balances various metabolic pathways, including glucose uptake and mitochondrial biogenesis, and ultimately regulates cell and organ tissue growth (124).

The results of previous studies demonstrated that the human tumor suppressor, liver kinase B1 (LKB1), directly activates AMPK by encoding serine/threonine kinases, suggesting that the LKB1-AMPK axis may be an essential cancer inhibitory

pathway (125,126). Epstein Barr virus (EBV)-miR-bart1-5p, a miRNA encoded by EBV-Barts, binds to the $\alpha 1$ telomerase of AMPK (AMPK $\alpha 1$). This activates the mTOR/HIF1 pathway to affect angiogenesis, leading to angiogenesis and glycolysis in tumor cells. This leads to the propagation, transfer and migration of tumor cells (127). The results of a previous study demonstrated that miR-27a inhibited the AMPK pathway, enhanced mTOR signaling, and functioned synergistically with oncogenes and tumor cell metabolic regulators, leading to enhanced glycolysis, unrestricted growth and chemical resistance (128). By contrast, aryl camphor flavone increased miR-124-3p expression in glioma cells by activating the reactive oxygen species (ROS)/AMPK signaling pathway, inducing apoptosis and inhibiting cell glycolysis (129).

AKT. AKT, also known as protein kinase B, is a serine/threonine kinase with three subtypes in mammalian cells. AKT is stimulated by various growth factors to become phosphorylated (p)-AKT, which affects multiple cellular functions and is a crucial regulator of pro-growth signals (130). The results of a previous study demonstrated that increased AKT and p-AKT expression levels were associated with the appearance, development and prognosis of various human tumors (131). Another study verified that proteins of the PI3K/AKT/mTOR signaling pathway were highly expressed in tumors (130). This pathway regulates essential processes in tumor cell development, such as substance metabolism and cytoskeletal remodeling metastasis. The reduced activity of the PI3K/AKT/mTOR signaling pathway decreases the levels of glycolysis in tumor cells. Notably, miR-21 and miR-520a-3p act by reducing the expression levels of PKM2 and LDHA in the glycolysis pathway to reduce glycolysis in tumor cells (132,133). In addition, miR-485-3p binds to AKT3 mRNA and downregulates glycolysis and migration-associated proteins expression by suppressing the activation of the AKT3/mTOR pathway, and inhibiting cell glycolysis, propagation and migration (134).

As a PTEN binding protein, N-myc downstream-regulated gene 2 (NDRG2) regulates PTEN phosphatase through dephosphorylation. In addition, PIP3, the primary substrate of PTEN, phosphorylates AKT. Thus, PTEN/PI3K/AKT is an essential axis for controlling propagation, migration and metabolism (135). miR-181a-5p binds to NDRG2 and promotes migration and glycolysis through stimulating the PTEN/AKT axis, ultimately leading to a poor prognosis (136).

Insulin-like growth factor-1 receptor (IGF-1R) is a carcinogen that stimulates cell propagation and metabolism and is upregulated in numerous tumors. miRNA-342-3p and miR-7 inhibit the IGF-1R-mediated PI3K/AKT/GLUT1 signaling pathway through directly binding with the 3'UTR of IGF-1R; thus, reducing glucose uptake (137,138).

4. miRNAs and glycolysis in gynecological cancers

Ovarian cancer. As presented in Table I, various miRNAs play differential roles in the glycolysis of ovarian cancer cells. The results of a previous study demonstrated that the levels of lncRNA-NEAT1 in ovarian cancer were notably increased, and the proliferation, invasion and glycolysis of ovarian cancer were markedly inhibited following NEAT1 knockdown (139). In addition, StarBase database prediction and a dual-luciferase reporter assay were used to verify that NEAT1 was the sponge

of miR-4500, and alkaline leucine zipper and w2-domain protein 1 (BZW1) were direct targets of miR-4500. miR-4500 silencing reversed the suppressive effects of NEAT1 knockdown on ovarian cancer, whereas the overexpression of BZW1 reversed the suppressive effects of miR-4500 on the tumor. Notably, NEAT1 accelerated the occurrence and development of ovarian cancer via the miR-4500/BZW1 axis. Thus, NEAT1 may exhibit potential in the treatment of ovarian cancer; however, further investigations are required (139). lncRNA OPA-interacting protein 5 antisense transcript 1 (lncRNA-OIP5-AS1) is also elevated in ovarian cancer. As previously demonstrated, OIP5-AS1 knockdown inhibited the migration and glycolysis of ovarian cancer, and accelerated programmed cell death. The results obtained using StarBase, TargetScan and a dual-luciferase reporter assay demonstrated that OIP5-AS1 indirectly regulated cyclin G1 (CCNG1) levels by sponging miR-128-3p. Moreover, miR-128-3p suppressed the progression of numerous cancers (140,141). Subsequent experiments demonstrated that miR-128-3p knockdown alleviated the decrease in glucose consumption and lactic acid production, enhanced apoptosis, and prevented cell migration caused by CCNG1 knockdown. These results demonstrated that OIP5-AS1 functions as a carcinogen in the development of ovarian cancer through the miR-128-3p/CCNG1 axis, which may act as a basis for the development of novel therapeutic options for ovarian cancer (142). The results of an RT-qPCR analysis demonstrated that lncRNA-LINC00504 expression was upregulated in ovarian cancer. In addition, the results of further assays demonstrated that LINC00504 was overexpressed in ovarian cancer, which promoted cell proliferation and upregulated PDK1, PKM2 and HK2, thereby increasing the levels of glycolysis in cells. Moreover, LINC00504 reduced the expression of miR-1244 through sponging. In summary, LINC00504 promotes ovarian cancer cell development and glycolysis through targeting miR-1244, suggesting that LINC00504 may function as a therapeutic target for ovarian cancer (143).

Previous research has demonstrated that the Hippo signaling pathway is associated with tumor development. As a critical oncogene of the Hippo pathway (144,145), yes1-associated transcriptional regulator (YAP1) is targeted by miR-486-5p, and miR-486-5p binds to LINC00857 in ovarian cancer, and inhibits the progression and glycolysis of ovarian cancer. Thus, LINC00857 inactivates the Hippo pathway. Notably, LINC00857 regulates ovarian cancer development through sponging miR-486-5p and upregulating YAP1, through regulation of the Hippo signaling pathway (146).

miR-29b functions as a tumor inhibitor in numerous types of cancer, and the expression of this miRNA was reduced in epithelial ovarian cancer (147). Using dual-luciferase reporter gene detection, the results demonstrated that miR-29b bound directly to AKT2/AKT3 3'UTR and inhibited the corresponding expression. Activated AKT promotes GLUT and HK expression, to increase the activity of phosphofructokinase (148); thus, stimulating the glucose to lactic acid metabolism pathway. This ultimately promotes the replication and migration of tumor cells. Therefore, it was hypothesized that miR-29b may negatively regulate AKT to reduce glycolysis levels and inhibit tumor development in epithelial ovarian cancer. The results of a previous study demonstrated that miR-29b silencing

Table I. miRNAs and glycolysis in ovarian cancer.

Authors, year	miRNA	Role	Expression	Upstream	Downstream	Glycolysis	Value	(Refs.)
Xu <i>et al</i> , 2020	miR-4500	Tumor promoter	Up	lncRNA-NEAT1	BZW1	Increased	Potential treatment	(139)
Liu <i>et al</i> , 2021	miR-128-3p	Tumor promoter	Up	lncRNA-OIP5-AS1	CCNG1	Increased	Potential treatment	(142)
Liu <i>et al</i> , 2020	miR-1244	Tumor promoter	Up	LINC00504		Increased treatment	Potential	(143)
Liu <i>et al</i> , 2021	miR-486-5p	Tumor promoter	Up	LINC00857	YAP1	Increased	Potential treatment	(146)
Li <i>et al</i> , 2022	miR-580-3p	Tumor promoter	Up	lncRNA-RMRP	MICU1	Increased	Potential treatment for chemical resistance	(157)
Teng <i>et al</i> , 2015	miR-29b	Tumor inhibitor	Down		AKT2/ AKT3	Reduced	Potential treatment	(147)
Boscaro <i>et al</i> , 2022	miR-206	Tumor inhibitor	Down		PFKFB3	Reduced	Potential treatment for chemical resistance	(93)
Rao <i>et al</i> , 2020	miR-195	Tumor inhibitor	Down		MICU1	Reduced	Potential treatment	(154)
Han <i>et al</i> , 2017	miR-383	Tumor inhibitor	Down		LDHA	Reduced	Potential treatment	(158)
Lu <i>et al</i> , 2019	miR-603	Tumor inhibitor	Down		HK2	Reduced	Potential treatment	(86)
Rafat <i>et al</i> , 2021	miR-132	Tumor inhibitor	Down		PI3K, TGFβ, Ras, AKT, mTOR	Reduced	Potential treatment	(159)
Xiaohong <i>et al</i> , 2016	miR-203	Tumor promoter	Up		PDHB	Increased	Potential treatment	(163)
Hu <i>et al</i> , 2019	miR-1180	Tumor promoter	Up		SFRP1	Increased	Potential treatment	(161)

miRNA/miR, microRNA; lncRNA-NEAT1, long non-coding RNA Nuclear-enriched abundant transcript 1; lncRNA-OIP5-AS1, long non-coding RNA OPA-interacting protein 5 antisense transcript 1; lncRNA-RMRP, long non-coding RNA component of mitochondrial RNA processing endoribonuclease; BZW1, w2-domain protein 1; CCNG1, cyclin G1; YAP1, yes1-associated transcriptional regulator; MICU1, mitochondrial calcium uptake 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; LDHA, lactate dehydrogenase A; HK2, hexokinase 2; PDHB, pyruvate dehydrogenase E1 subunit beta; SFRP1, secreted frizzled-related protein 1.

upregulated the mRNA expression of AKT2/3, PKM2 and HK2, and increased glucose intake and lactate production in ovarian cancer cells. On the other hand, miR-29b overexpression demonstrated the reverse effects (147). Thus, these results demonstrated that miR-29b plays a key role in regulating the Warburg effect, and in the replication and migration of ovarian cancer cells through impacting the expression of AKT. This may provide a theoretical basis for the development of novel treatment options for epithelial ovarian cancer.

The results of previous studies demonstrated that PFKFB3 was overexpressed in human cancers, such as in ovarian cancer, where the upregulation of PFKFB3 expression promoted cell growth and migration and enhanced chemotherapeutic resistance (149,150). Using a dual-luciferase assay, the results of a

previous study demonstrated that miR-206 reduced the levels of PFKFB3 by binding with the 3'UTR, miR-206 overexpression prevented the proliferation and migration of ovarian cancer by downregulating the PFKFB3 levels. In addition, the results of another study demonstrated that miR-206 downregulated PFKFB3 expression and negatively regulated focal adhesion kinase (FAK) post-transcription. These results indicated that miR-206 exhibits numerous roles, and may be used to control ovarian cancer characterized by FAK overexpression and resistance to chemotherapy (93).

Mitochondrial calcium uptake 1 (MICU1) is a protein in the inner membrane of the mitochondria that inhibits calcium ions from entering. However, in ovarian cancer, MICU1 overexpression increases glycolysis and enhances cellular

Table II. miRNAs and glycolysis in cervical cancer.

Authors, year	miRNA	Role	Expression	Upstream	Downstream	Glycolysis	Value	(Refs.)
Li, <i>et al</i> , 2021	miR-214-5p	Tumor promoter	Up	lncRNA-TDRG1	SEMA4C	Increased	Potential treatment	(50)
Shao <i>et al</i> , 2021	miR-34a	Tumor promoter	Up	lncRNA-NEAT1	LDHA	Increased	Potential treatment	(164)
Li <i>et al</i> , 2021	miR-124-5p	Tumor promoter	Up	lncRNA-OIP5-AS1	IDH2/HIF-1 α	Increased	Potential treatment	(165)
Li <i>et al</i> , 2019	miR-27a	Tumor promoter	Up		INPP1	Increased	Potential treatment	(169)
Zhang <i>et al</i> , 2016	miR-34a	Tumor inhibitor	Down		LDHA	Reduced	Potential treatment	(173)
Yang <i>et al</i> , 2016	miR-497	Tumor promoter	Up		TKT	Increased	Potential treatment for chemical resistance	(174)
Zhao <i>et al</i> , 2020	miR-16-5p	Tumor inhibitor	Down		PDK4	Reduced	Potential treatment for chemical resistance	(105)

miRNA/miR, microRNA; lncRNA-TDRG1, long non-coding RNA testis developmental related gene 1; lncRNA-NEAT1, long non-coding RNA nuclear-enriched abundant transcript 1; lncRNA-OIP5-AS1, long non-coding RNA OPA-interacting protein 5 antisense transcript 1; SEMA4C, signaling protein 4C; LDHA, lactate dehydrogenase A; IDH2/HIF-1 α , isocitrate dehydrogenase 2/hypoxia-inducible factor-1 α ; INPP1, inositol polyphosphate 1-phosphatase; TKT, transketolase; PDK4, pyruvate dehydrogenase kinase.

chemotherapy resistance. Moreover, MICU1 plays a role in the low survival rates of patients with ovarian cancer (151), highlighting its potential use as a target in the treatment of ovarian cancer. miR-195 is a tumor inhibitor in various types of cancer (152,153), and its expression is reduced in seven different ovarian cancer cell lines (OVCAR4, A2780-CP20, TYK-NU(JCRB0234.0), TYK-NU.CPr(JCRB0234.1), OVSAHO(JCRB1046), ATCC CRL-11732TM and FTE188). Notably, MICU1 expression was significantly increased in six of these cancer cells, compared with standard cell lines (152). It was demonstrated that miR-195 targeted the MICU1 3'UTR in healthy cells, leading to decreased MICU1 expression. Moreover, intracellular lactic acid levels were significantly reduced in ovarian cancer cell lines following miR-195 over-expression or MICU1 knockdown, suggesting that glycolysis was inhibited (154). It was also demonstrated that miR-195 expression levels maintained calcium homeostasis and reduced the glycolysis of ovarian cancer cells by regulating MICU1; thus, inhibiting cell growth and migration. Tumor growth experiments in female athymic mice revealed that miR-195 prolonged the *in vivo* survival of ovarian cancer models in mice, and the re-expression of MICU1 in cells reversed the tumor growth-inhibiting phenotype caused by miR-195 over-expression. These results suggest that miR-195 extends overall survival in ovarian cancer patients by targeting MICU1 (154). In addition, lncRNA component of mitochondrial RNA processing endoribonuclease (lncRNA-RMRP) functions as a tumor activator in various types of cancer (155,156), and also increases MICU1 expression by sponging miR-580-3p,

thus promoting glycolysis and paclitaxel resistance in ovarian cancer (157).

Similarly, miR-383, miR-603 and miR-132 are inhibitors of several human cancers, and their expression levels are significantly decreased. The results of previous studies demonstrated that the ectopic levels of miR-383 inhibit LDHA mRNA expression by binding with the 3'UTR of LDHA. Moreover, miR-603 directly targets HK2 expression. miR-132 affects PI3K and TGF β signaling pathways or Ras, AKT and mTOR oncogene expression. Notably, these miRNAs promote cell apoptosis, reduce glucose consumption and lactic acid production, and inhibit cell proliferation and invasion (86,158,159).

By contrast, miR-203 and miR-1180 expression have been shown to be increased in ovarian cancer tissues, compared with healthy tissues. miR-203 mainly targets the 3'UTR of pyruvate dehydrogenase B, while secreted frizzled-related protein 1, a tumor inhibitor (160), acts as a direct target gene of miR-1180, and activates the Wnt signaling pathway following miR-1180-induced inhibition (161,162). Notably, miRNAs promote glucose consumption and lactate production in tumor cells to increase glycolysis. This leads to cell colony growth, migration and invasion (163).

Cervical cancer. The roles of numerous miRNAs in the development of cervical cancer are presented in Table II. The results of a previous study demonstrated that hypoxic-responsive lncRNA-TDRG1 expression was increased in cervical cancer. Subsequently, the interactive association between miR-214-5p, lncRNA-TDRG1 and signaling SEMA4C was analyzed. The

Table III. miRNAs and glycolysis in endometrial carcinoma.

Authors, year	miRNA	Role	Expression	Upstream	Downstream	Glycolysis	Value	(Refs.)
Dong <i>et al.</i> , 2021	miR-455	Tumor promoter	Up	lncRNA-DLEU2	HK2	Increased	Potential treatment	(76)
Dong <i>et al.</i> , 2021	miR-181a	Tumor promoter	Up	HK2	HK2	Increased	Potential treatment	(76)

miRNA/miR, microRNA; lncRNA-DLEU2, long non-coding RNA deleted in lymphocytic leukemia 2; HK2, hexokinase 2.

levels of lncRNA-TDRG1, miR-214-5p, SEMA4C and HK2 were evaluated using western blot analysis and RT-qPCR. Under conditions of hypoxia, lncRNA-TDRG1 knockdown inhibited glycolysis and the migration of cervical cancer. Moreover, miR-214-5p knockdown or SEMA4C overexpression reversed tumor inhibition. In conclusion, lncRNA-TDRG1 acts on miR-214-5p to affect SEMA4C expression, glycolysis and the migration of cervical cancer cells (50). Compared with healthy cells, NEAT1 expression levels have been found to be increased in cervical cancer cells, which affect the levels of miR-34a, leading to dysglycolysis and 5-fluorouracil resistance. Bioinformatics prediction using TargetScan revealed that LDHA was a close target of miR-34a-5p, and miR-34a and LDHA mRNA expression were negatively correlated. The NEAT1-mediated miR-34a/LDHA axis may act as a latent treatment for chemotherapy-resistant cervical cancer (164). lncRNA-OIP5-AS1 is considered a hypoxic-responsive lncRNA. In addition, OIP5-AS1 inhibits miR-124-5p to promote Isocitrate dehydrogenase 2 (IDH2) expression, and IDH2 promotes the Warburg effect in cervical cancer cells through regulating HIF-1 α expression (165).

Inositol polyphosphate 1-phosphatase (INPP1) is an enzyme involved in glycolysis and lipid metabolism. Using RT-qPCR, the results demonstrated that INPP1 mRNA expression was increased in cervical cancer. In addition, INPP1 overexpression enhanced cell viability and facilitated cell irradiation. Results of wound healing and translocation assays demonstrated that migration and invasion rates were significantly increased following INPP1 was overexpression. Moreover, results of a dual-luciferase reporter assay demonstrated that miR-27a binds with the 3'UTR of INPP. miR-27a is highly expressed in a variety of cancer cells and is essential in the invasion of cancer (166-168). The results of a previous study demonstrated that miR-27a expression was increased cervical cancer, and was positively associated with INPP1. Notably, miR-27a is upregulated in cervical cancer cells and promotes the overexpression of INPP1. This regulates cell metabolic reprogramming and promotes aerobic glycolysis, ultimately increasing the viability of cervical cancer cells (169). Thus, miR-27a and INPP1 may function as potential biomarkers for cervical cancer.

By contrast, miR-34a expression is often reduced in tumors (170,171), and plays a crucial role in tumor suppression. Notably, miR-34a regulates a variety of target genes involved in cell replication, differentiation and apoptosis, and interferes with the processes involved in cancer cell metastasis and chemical tolerance (172). The results of the measurement of

lactate production and glucose consumption demonstrated that cervical cancer cells with exogenous miR-34a consume less glucose, highlighting that miR-34a prevents the aerobic glycolysis of cervical cancer cells (173). The results obtained using the miRNA target prediction program, miRbase, demonstrated that LDHA is a downstream target of miR-34a. In addition, the ectopic expression of miR-34a or LDHA knockdown reduced tumor growth and invasion (173). Thus, it was hypothesized that miR-34a may play an inhibitory role in cervical cancer, and may exhibit potential in the treatment of cervical cancer.

The results of a previous study demonstrated that miRNA-497 regulated ROS and glutathione levels by targeting the transketolase enzyme involved in the pentose phosphate pathway and subsequently promoting cisplatin chemical resistance in cervical cancer (174). miR-16-5p directly binds to PDK4. The inhibition of miR-16-5p has been shown to lead to an increased expression of PDK4, which activates glycolytic metabolic activity and enhances chemoresistance in cervical cancer (105). Therefore, miR-497 and miR-16-5p may exhibit potential as targets in the treatment of chemical resistance in cervical cancer.

Endometrial carcinoma. The roles of miRNAs in endometrial cancer are presented in Table III. Notably, HK2 is upregulated in various types of cancer, such as endometrial cancer. HK2 expression is significantly increased in high-risk endometrial cancer cells, suggesting that HK2 expression is associated with the prognosis of endometrial cancer. Numerous prediction algorithms have revealed that miR-455 and miR-181a may bind to the 3'UTR of HK2, and miR-455 directly inhibits HK2 expression. In addition, lncRNA deleted in lymphocytic leukemia 2 (lncRNA-DLEU2) binds EZH2 and increases the corresponding expression while silencing miR-181a. Subsequently, this increases HK2 levels and promotes glycolysis (76). In conclusion, DLEU2 affects the progression of endometrial cancer through targeting the miR-455/HK2 and EZH2/miR-181a/HK2 axis, which may exhibit potential in the treatment of endometrial cancer.

Other gynecological tumors. At present, research focused on the expression of miRNAs in vulvar carcinoma is limited. The results of a previous study demonstrated that miR-182-5p, miR-183-5p and miR-590-5p were upregulated, and miR-103a-3p, miR-107 and miR-603 were downregulated in vulvar squamous cell carcinoma (175). Moreover, miR-19-b1-5p and miR-223-5p downregulation were previously found to be associated with the presence of lymph node

metastasis (176). However, the role and molecular mechanisms of miRNAs in glycolysis, and their potential to predict treatment outcomes in patients with uterine sarcoma have yet to be fully elucidated. The results of a previous study demonstrated that the downregulation of miR-10a-5p and miR-125a-5p, and the upregulation of miR-34c-5p and miR-196a-5p were associated with the prognosis of patients with uterine leiomyosarcoma (177). In endometrial stromal sarcoma, the downregulation of miR-23-3p and let-7b-5p, and the upregulation of miR-372-3p and miR-373-3p were associated with poor survival outcomes. The expression levels of miR-210-3p, miR-301a-3p and miR-335-5p were increased in patients with tumor metastasis and recurrence (177).

5. Conclusions and future perspectives

It has been demonstrated that miRNAs are involved in the glycolysis in ovarian, cervical and endometrial cancers. However, there is a lack of consensus on the involvement of miRNAs in vulvar cancer, uterine sarcoma, or other rare gynecological tumors. The incidence of cancer, development mechanisms and the early diagnosis of ovarian cancer are complex (178). Recurrence and challenges in both diagnosis and treatment processes affect invasive cervical cancer and endometrial carcinoma, and lead to a poor prognosis (179). Although previous studies have focused on improving potential treatment options and prognosis (180-182), further investigations are required.

The consumption and metabolism of glucose during glycolysis in tumor cells leads to an increased glucose uptake, lactic acid production, changes in the tumor microenvironment and an increased ATP production. All of the aforementioned factors may promote tumor progression, invasion, metastasis and chemical resistance (183,184). Therefore, glycolysis may exhibit potential as a novel drug target. The results of previous studies have demonstrated that miRNAs participate in the glycolysis process, and inhibit or promote glycolysis through lncRNA-mediated regulation. miRNAs act on transporters and critical enzymes in the glycolysis process, and also target multiple cellular signaling pathways, tumor suppressor genes and transcription factors (1,185-187). However, the interaction between various factors during glycolysis remains to be fully elucidated.

In conclusion, miRNAs are vital in the glycolysis of tumor cells. Future investigations will aim to explore additional miRNA-targeting molecules and mechanisms and continue to explore metabolic reprogramming in other gynecological tumors. Currently, a number of preclinical trials have indicated the potential of targeted miRNAs for cancer treatment. For example, tumor growth experiments in female athymic mice revealed that miR-195 prolonged the *in vivo* survival of ovarian cancer models in mice, and the re-expression of MICU1 in cells reversed the tumor growth-inhibiting phenotype caused by miR-195 overexpression. These results suggest that miR-195 extends the overall survival of patients with ovarian cancer by targeting MICU1 (154). There is currently a lack of clinical trials to verify the feasibility and effectiveness of miRNA-targeted drugs in gynecological cancer patients. Further studies are also required to aim at exploring potential biomarkers, and provide novel theoretical platforms for the treatment of cancer.

At the same time, targeting miRNAs in the diagnosis of gynecological tumors also warrants attention. miRNAs whose expression is clearly dysregulated in serum and tissues, and whose target genes and pathways are associated with tumors, are screened by enrichment analysis may play a key role in cancer diagnosis (188).

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QC drafted and revised the manuscript. JT designed and supervised the study. SS and NL collected the data for inclusion in the review and designed the tables. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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