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

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 mammal 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-mRNAs), 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 he 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

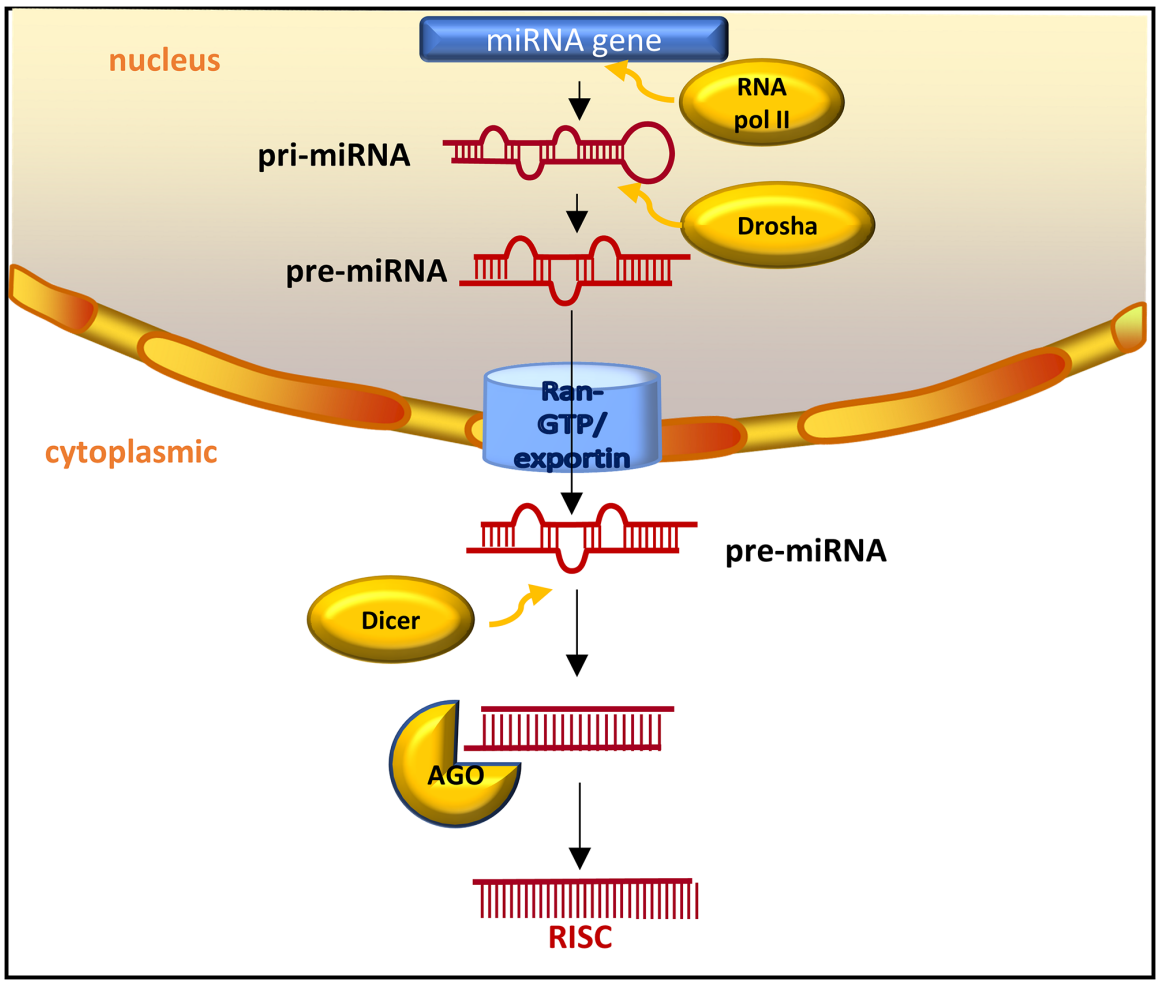

Figure 1. Schematic diagram of the generation of miRNAs. miRNAs, microRNAs; pre-miRNAs, precursor miRNAs; AGO, Argonaute; RISC, RNA-induced silencing complex.

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 H_2O and CO_2, 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 l 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 CO_2, through oxidative phosphorylation, which maximizes ATP production but does not meet the requirements of rapid cell proliferation. Notably, the rapid proliferation of tumor cells

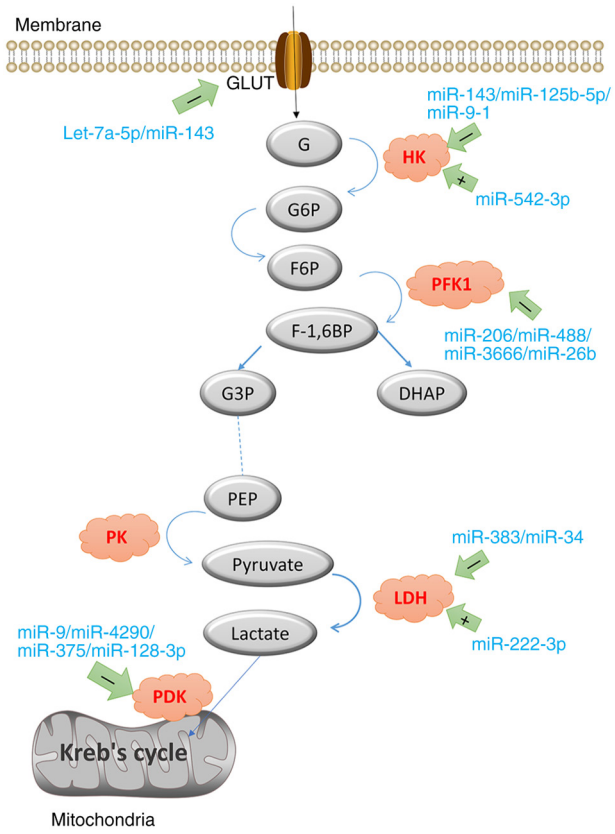

Figure 2. Glucose is transported into the cell by GLUT, and HK catalyzes the production of G-6-P. Phosphohexose isomerase catalyzes the production of F-6-P. PFK1 is further phosphorylated to form F-1, 6-BP, which is catalyzed by aldolase into DHAP and glyceraldehyde 3-phosphate. PEP is subsequently generated 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

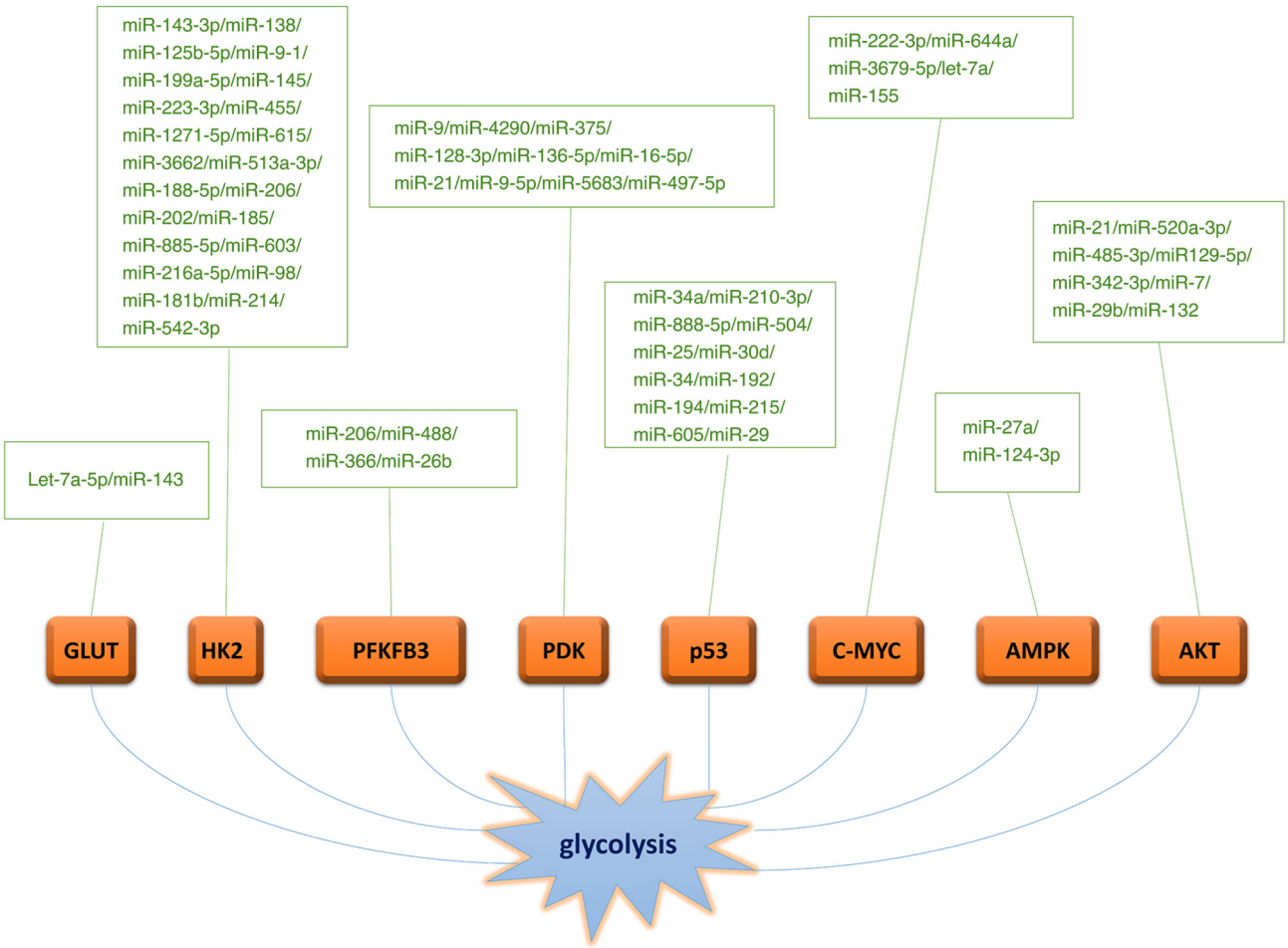

Figure 3. Downstream targets of miRNAs. miRNAs/miRs, microRNAs; GLUT, glucose transporter; HK2, hexokinase 2; PFKFB3, 6-phospho-fructo-2-kinase/fructose-2,6-biphosphatase 3; PDK, pyruvate dehydrogenase; AMPK, AMP kinase.

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-1α (HIF-1α) 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 chromatins 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 GULT1, 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 α1 telomerase of AMPK (AMPKα1). 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 glycol- 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, LNC00504 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 *et al*, 2020	miR-4500	Tumor promoter	Up	lncRNA-NEAT1	BZW1	Increased	Potential treatment	(139)
Liu *et al*, 2021	miR-128-3p	Tumor promoter	Up	lncRNA-OIP5-AS1	CCNG1	Increased	Potential treatment	(142)
Liu *et al*, 2020	miR-1244	Tumor promoter	Up	LINC00504		Increased treatment	Potential	(143)
Liu *et al*, 2021	miR-486-5p	Tumor promoter	Up	LINC00857	YAP1	Increased	Potential treatment	(146)
Li *et al*, 2022	miR-580-3p	Tumor promoter	Up	lncRNA-RMRP	MICU1	Increased	Potential treatment for chemical resistance	(157)
Teng *et al*, 2015	miR-29b	Tumor inhibitor	Down		AKT2/AKT3	Reduced	Potential treatment	(147)
Boscaro *et al*, 2022	miR-206	Tumor inhibitor	Down		PFKFB3	Reduced	Potential treatment for chemical resistance	(93)
Rao *et al*, 2020	miR-195	Tumor inhibitor	Down		MICU1	Reduced	Potential treatment	(154)
Han *et al*, 2017	miR-383	Tumor inhibitor	Down		LDHA	Reduced	Potential treatment	(158)
Lu *et al*, 2019	miR-603	Tumor inhibitor	Down		HK2	Reduced	Potential treatment	(86)
Rafat *et al*, 2021	miR-132	Tumor inhibitor	Down		PI3K, TGFβ, Ras, AKT, mTOR	Reduced	Potential treatment	(159)
Xiaohong *et al*, 2016	miR-203	Tumor promoter	Up		PDHB	Increased	Potential treatment	(163)
Hu *et al*, 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, *et al*, 2021	miR-214-5p	Tumor promoter	Up	lncRNA-TDRG1	SEMA4C	Increased	Potential treatment	(50)
Shao *et al*, 2021	miR-34a	Tumor promoter	Up	lncRNA-NEAT1	LDHA	Increased	Potential treatment	(164)
Li *et al*, 2021	miR-124-5p	Tumor promoter	Up	lncRNA-OIP5-AS1	IDH2/HIF-1α	Increased	Potential treatment	(165)
Li *et al*, 2019	miR-27a	Tumor promoter	Up		INPP1	Increased	Potential treatment	(169)
Zhang *et al*, 2016	miR-34a	Tumor inhibitor	Down		LDHA	Reduced	Potential treatment	(173)
Yang *et al*, 2016	miR-497	Tumor promoter	Up		TKT	Increased	Potential treatment for chemical resistance	(174)
Zhao *et al*, 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-1α, isocitrate dehydrogenase 2/hypoxia-inducible factor-1α; 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-11732™ 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 overexpression 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 overexpression. 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 TGFβ 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 *et al*, 2021	miR-455	Tumor promoter	Up	lncRNA-DLEU2	HK2	Increased	Potential treatment	(76)
Dong *et al*, 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-1α 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.

References

1. Dwivedi SKD, Rao G, Dey A, Mukherjee P, Wren JD and Bhattacharya R: Small non-coding-RNA in gynecological malignancies. Cancers 13: 1085, 2021.
2. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, Tatebe K and Veneris JL: Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin 69: 258-279, 2019.
3. Tsikouras P, Zervoudis S, Manav B, Tomara E, Iatrakis G, Romanidis C, Bothou A and Galazios G: Cervical cancer: Screening, diagnosis and staging. J BUON 21: 320-325, 2016.
4. Stewart C, Ralyea C and Lockwood S: Ovarian cancer: An integrated review. Semin Oncol Nurs 35: 151-156, 2019.
5. Shafabakhsh R and Asemi Z: Quercetin: A natural compound for ovarian cancer treatment. J Ovarian Res 12: 55, 2019.
6. Cree IA, White VA, Indave BI and Lokuhetty D: Revising the WHO classification: Female genital tract tumours. Histopathology 76: 151-156, 2020.
7. Devouassoux-Shisheboran M and Genestie C: Pathobiology of ovarian carcinomas. Chin J Cancer 34: 50-55, 2015.
8. Vergote I, González-Martín A, Ray-Coquard I, Harter P, Colombo N, Pujol P, Lorusso D, Mirza MR, Brasiuniene B, Madry R, *et al*: European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer. Ann Oncol 33: 276-287, 2022.

9. Steinberga I, Jansson K and Sorbe B: Quality indicators and survival outcome in Stage IIIB-IVB epithelial ovarian cancer treated at a single institution. In Vivo 33: 1521-1530, 2019.
10. Zhang C and Liu N: Noncoding RNAs in the glycolysis of ovarian cancer. Front Pharmacol 13: 855488, 2022.
11. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, *et al*: American Cancer Society, American Society for Colposcopy and cervical pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 62: 147-172, 2012.
12. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2022. CA Cancer J Clin 72: 7-33, 2022.
13. Xu HH, Wang K, Feng XJ, Dong SS, Lin A, Zheng LZ and Yan WH: Prevalence of human papillomavirus genotypes and relative risk of cervical cancer in China: A systematic review and meta-analysis. Oncotarget 9: 15386-15397, 2018.
14. Bray F, Carstensen B, Møller H, Zappa M, Zakelj MP, Lawrence G, Hakama M and Weiderpass E: Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 14: 2191-2199, 2005.
15. Li H, Wu X and Cheng X: Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol 27: e43, 2016.
16. Crosbie EJ, Einstein MH, Franceschi S and Kitchener HC: Human papillomavirus and cervical cancer. Lancet 382: 889-899, 2013.
17. Han X, Wen H, Ju X, Chen X, Ke G, Zhou Y, Li J, Xia L, Tang J, Liang S and Wu X: Predictive factors of para-aortic lymph nodes metastasis in cervical cancer patients: A retrospective analysis based on 723 para-aortic lymphadenectomy cases. Oncotarget 8: 51840-51847, 2017.
18. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, Gavin A, Visser O and Bray F: Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 103: 356-387, 2018.
19. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, Chon HS, Chu C, Cohn D, Crispens MA, *et al*: Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 16: 170-199, 2018.
20. Kajo K, Vallová M, Biró C, Bognár G, Macháleková K, Závodná K, Galbavý Š and Žúbor P: Molecular pathology of endometrial carcinoma-a review. Cesk Patol 51: 65-73, 2015 (In Czech).
21. Miccò M, Sala E, Lakhman Y, Hricak H and Vargas HA: Imaging features of uncommon gynecologic cancers. AJR Am J Roentgenol 205: 1346-1359, 2015.
22. Di Fiore R, Suleiman S, Pentimalli F, O'Toole SA, O'Leary JJ, Ward MP, Conlon NT, Sabol M, Ozretić P, Erson-Bensan AE, *et al*: Could MicroRNAs be useful tools to improve the diagnosis and treatment of rare gynecological cancers? A Brief overview. Int J Mol Sci 22: 3822, 2021.
23. Mbatani N, Olawaiye AB and Prat J: Uterine sarcomas. Int J Gynaecol Obstet 143 (Suppl 2): S51-S58, 2018.
24. Lee RC, Feinbaum RL and Ambros V: The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75: 843-854, 1993.
25. Griffiths-Jones S: The microRNA registry. Nucleic Acids Res 32 (Database Issue): D109-D111, 2004.
26. Bartel DP: MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 116: 281-297, 2004.
27. Kim VN: MicroRNA biogenesis: Coordinated cropping and dicing. Nat Rev Mol Cell Biol 6: 376-385, 2005.
28. Carthew RW and Sontheimer EJ: Origins and mechanisms of miRNAs and siRNAs. Cell 136: 642-655, 2009.
29. Riedmann LT and Schwentner R: miRNA, siRNA, piRNA and argonautes: News in small matters. RNA Biol 7: 133-139, 2010.
30. Brennecke J, Hipfner DR, Stark A, Russell RB and Cohen SM: Bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila. Cell 113: 25-36, 2003.
31. Zeng Y, Wagner EJ and Cullen BR: Both natural and designed micro RNAs can inhibit the expression of cognate mRNAs when expressed in human cells. Mol Cell 9: 1327-1333, 2002.
32. Doench JG, Petersen CP and Sharp PA: siRNAs can function as miRNAs. Genes Dev 17: 438-442, 2003.
33. Xu P, Vernooy SY, Guo M and Hay BA: The drosophila microRNA Mir-14 suppresses cell death and is required for normal fat metabolism. Curr Biol 13: 790-795, 2003.
34. Krützfeldt J and Stoffel M: MicroRNAs: A new class of regulatory genes affecting metabolism. Cell Metab 4: 9-12, 2006.
35. Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JTand Dang CV: c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature 458: 762-765, 2009.
36. Warburg O: On the origin of cancer cells. Science 123: 309-314, 1956.
37. Warburg O: The chemical constitution of respiration ferment. Science 68: 437-443, 1928.
38. Rolfe DF and Brown GC: Cellular energy utilization and molecular origin of standard metabolic rate in mammals. Physiol Rev 77: 731-758, 1997.
39. Vander Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324: 1029-1033, 2009.
40. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S and Thompson CB: Beyond aerobic glycolysis: Transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci USA 104: 19345-19350, 2007.
41. Fantin VR, St-Pierre J and Leder P: Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 9: 425-434, 2006.
42. Shim H, Chun YS, Lewis BC and Dang CV: A unique glucose-dependent apoptotic pathway induced by c-Myc. Proc Natl Acad Sci USA 95: 1511-1516, 1998.
43. Birsoy K, Wang T, Chen WW, Freinkman E, Abu-Remaileh M and Sabatini DM: An essential role of the mitochondrial electron transport Chain in cell proliferation is to enable aspartate synthesis. Cell 162: 540-551, 2015.
44. Kopp F and Mendell JT: Functional classification and experimental dissection of long noncoding RNAs. Cell 172: 393-407, 2018.
45. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, *et al*: The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res 22: 1775-1789, 2012.
46. Ulitsky I and Bartel DP: lincRNAs: Genomics, evolution, and mechanisms. Cell 154: 26-46, 2013.
47. Chen F, Chen J, Yang L, Liu J, Zhang X, Zhang Y, Tu Q, Yin D, Lin D, Wong PP, *et al*: Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol 21: 498-510, 2019.
48. Gao YL, Zhao ZS, Zhang MY, Han LJ, Dong YJ and Xu B: Long noncoding RNA PVT1 facilitates cervical cancer progression via negative regulating of miR-424. Oncol Res 25: 1391-1398, 2017.
49. Wang S, Hui Y, Li X and Jia Q: Silencing of lncRNA CCDC26 restrains the growth and migration of glioma cells in vitro and in vivo via targeting miR-203. Oncol Res 26: 1143-1154, 2018.
50. Li X, Zhang C and Tian Y: Long non-coding RNA TDRG1 promotes hypoxia-induced glycolysis by targeting the miR-214-5p/SEMA4C axis in cervical cancer cells. J Mol Histol 52: 245-256, 2021.
51. Xiao L, Wang W, Zhao J, Xu H, Li S and Yang X: lncRNA MALAT1 promotes cell proliferation and invasion by regulating the miR-101/EZH2 axis in oral squamous cell carcinoma. Oncol Lett 20: 164, 2020.
52. Erratum: Long Non-coding RNA CASC2 serves as A ceRNA of microRNA-21 to promote pdcd4 expression in oral squamous cell carcinoma [Corrigendum]. Onco Targets Ther 12: 9569, 2019.
53. Yu Q, Xiang L, Chen Z, Liu X, Ou H, Zhou J and Yang D: MALAT1 functions as a competing endogenous RNA to regulate SMAD5 expression by acting as a sponge for miR-142-3p in hepatocellular carcinoma. Cell Biosci 9: 39, 2019.
54. Holman GD: Chemical biology probes of mammalian GLUT structure and function. Biochem J 475: 3511-3534, 2018.
55. Simpson IA, Appel NM, Hokari M, Oki J, Holman GD, Maher F, Koehler-Stec EM, Vannucci SJ and Smith QR: Blood-brain barrier glucose transporter: Effects of hypo- and hyperglycemia revisited. J Neurochem 72: 238-247, 1999.
56. Yu M, Yongzhi H, Chen S, Luo X, Lin Y, Zhou Y, Jin H, Hou B, Deng Y, Tu L and Jian Z: The prognostic value of GLUT1 in cancers: A systematic review and meta-analysis. Oncotarget 8: 43356-43367, 2017.
57. Maher F, Vannucci SJ and Simpson IA: Glucose transporter proteins in brain. FASEB J 8: 1003-1011, 1994.

58. James DE, Strube M and Mueckler M: Molecular cloning and characterization of an insulin-regulatable glucose transporter. Nature 338: 83-87, 1989.
59. Shi Y, Zhang Y, Ran F, Liu J, Lin J, Hao X, Ding L and Ye Q: Let-7a-5p inhibits triple-negative breast tumor growth and metastasis through GLUT12-mediated warburg effect. Cancer Lett 495: 53-65, 2020.
60. Tang R, Yang C, Ma X, Wang Y, Luo D, Huang C, Xu Z, Liu P and Yang L: MiR-let-7a inhibits cell proliferation, migration, and invasion by down-regulating PKM2 in gastric cancer. Oncotarget 7: 5972-5984, 2016.
61. Zhang T, Zhang Z, Li F, Ping Y, Qin G, Zhang C and Zhang Y: Correction: miR-143 regulates memory T cell differentiation by reprogramming T cell metabolism. J Immunol 201: 2165-2175, 2018.
62. Ciscato F, Ferrone L, Masgras I, Laquatra C and Rasola A: Hexokinase 2 in cancer: A prima donna playing multiple characters. Int J Mol Sci 22: 4716, 2021.
63. Peschiaroli A, Giacobbe A, Formosa A, Markert EK, Bongiorno-Borbone L, Levine AJ, Candi E, D'Alessandro A, Zolla L, Finazzi Agrò A and Melino G: miR-143 regulates hexokinase 2 expression in cancer cells. Oncogene 32: 797-802, 2013.
64. Wolf A, Agnihotri S, Micallef J, Mukherjee J, Sabha N, Cairns R, Hawkins C and Guha A: Hexokinase 2 is a key mediator of aerobic glycolysis and promotes tumor growth in human glioblastoma multiforme. J Exp Med 208: 313-326, 2011.
65. Zhou P, Chen WG and Li XW: MicroRNA-143 acts as a tumor suppressor by targeting hexokinase 2 in human prostate cancer. Am J Cancer Res 5: 2056-2063, 2015.
66. Gregersen LH, Jacobsen A, Frankel LB, Wen J, Krogh A and Lund AH: MicroRNA-143 down-regulates Hexokinase 2 in colon cancer cells. BMC Cancer 12: 232, 2012.
67. Chen J, Yu Y, Li H, Hu Q, Chen X, He Y, Xue C, Ren F, Ren Z, Li J, *et al*: Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer. Mol Cancer 18: 33, 2019.
68. Yu T, Li G, Wang C, Gong G, Wang L, Li C, Chen Y and Wang X: MIR210HG regulates glycolysis, cell proliferation, and metastasis of pancreatic cancer cells through miR-125b-5p/HK2/PKM2 axis. RNA Biol 18: 2513-2530, 2021.
69. Li Y, Wang Y, Fan H, Zhang Z and Li N: miR-125b-5p inhibits breast cancer cell proliferation, migration and invasion by targeting KIAA1522. Biochem Biophys Res Commun 504: 277-282, 2018.
70. Liu S, Chen Q and Wang Y: MiR-125b-5p suppresses the bladder cancer progression via targeting HK2 and suppressing PI3K/AKT pathway. Hum Cell 33: 185-194, 2020.
71. Hui L, Zhang J and Guo X: MiR-125b-5p suppressed the glycolysis of laryngeal squamous cell carcinoma by down-regulating hexokinase-2. Biomed Pharmacother 103: 1194-1201, 2018.
72. Xu QL, Luo Z, Zhang B, Qin GJ, Zhang RY, Kong XY, Tang HY and Jiang W: Methylation-associated silencing of miR-9-1 promotes nasopharyngeal carcinoma progression and glycolysis via HK2. Cancer Sci 112: 4127-4138, 2021.
73. Guo W, Qiu Z, Wang Z, Wang Q, Tan N, Chen T, Chen Z, Huang S, Gu J, Li J, *et al*: MiR-199a-5p is negatively associated with malignancies and regulates glycolysis and lactate production by targeting hexokinase 2 in liver cancer. Hepatology 62: 1132-1144, 2015.
74. Yoshino H, Enokida H, Itesako T, Kojima S, Kinoshita T, Tatarano S, Chiyomaru T, Nakagawa M and Seki N: Tumor-suppressive microRNA-143/145 cluster targets hexokinase-2 in renal cell carcinoma. Cancer Sci 104: 1567-1574, 2013.
75. Zhao Y, Zhong R, Deng C and Zhou Z: Circle RNA circABCB10 modulates PFN2 to promote breast cancer progression, as well as aggravate radioresistance through facilitating glycolytic metabolism via miR-223-3p. Cancer Biother Radiopharm 36: 477-490, 2021.
76. Dong P, Xiong Y, Konno Y, Ihira K, Kobayashi N, Yue J and Watari H: Long non-coding RNA DLEU2 drives EMT and glycolysis in endometrial cancer through HK2 by competitively binding with miR-455 and by modulating the EZH2/miR-181a pathway. J Exp Clin Cancer Res 40: 216, 2021.
77. Zhang B, Chen J, Cui M and Jiang Y: LncRNA ZFAS1/miR-1271-5p/HK2 promotes glioma development through regulating proliferation, migration, invasion and apoptosis. Neurochem Res 45: 2828-2839, 2020.
78. Sun L, Wang P, Zhang Z, Zhang K, Xu Z, Li S and Mao J: MicroRNA-615 functions as a tumor suppressor in osteosarcoma through the suppression of HK2. Oncol Lett 20: 226, 2020.
79. Ye J, Xiao X, Han Y, Fan D, Zhu Y and Yang L: MiR-3662 suppresses cell growth, invasion and glucose metabolism by targeting HK2 in hepatocellular carcinoma cells. Neoplasma 67: 773-781, 2020.
80. Li C, Yu Z and Ye J: MicroRNA-513a-3p regulates colorectal cancer cell metabolism via targeting hexokinase 2. Exp Ther Med 20: 572-580, 2020.
81. Ding Z, Guo L, Deng Z and Li P: Circ-PRMT5 enhances the proliferation, migration and glycolysis of hepatoma cells by targeting miR-188-5p/HK2 axis. Ann Hepatol 19: 269-279, 2020.
82. Jia KG, Feng G, Tong YS, Tao GZ and Xu L: miR-206 regulates non-small-cell lung cancer cell aerobic glycolysis by targeting hexokinase 2. J Biochem 167: 365-370, 2020.
83. Wang J, Chen J, Sun F, Wang Z, Xu W, Yu Y, Ding F and Shen H: miR-202 functions as a tumor suppressor in hepatocellular carcinoma by targeting HK2. Oncology Lett 19: 2265-2271, 2020.
84. Liu C, Cai L and Li H: miR-185 regulates the growth of osteosarcoma cells via targeting Hexokinase 2. Mol Med Rep 20: 2774-2782, 2019.
85. Xu F, Yan JJ, Gan Y, Chang Y, Wang HL, He XX and Zhao Q: miR-885-5p negatively regulates warburg effect by silencing hexokinase 2 in liver cancer. Mol Ther Nucleic Acids 18: 308-319, 2019.
86. Lu J, Wang L, Chen W, Wang Y, Zhen S, Chen H, Cheng J, Zhou Y, Li X and Zhao L: miR-603 targeted hexokinase-2 to inhibit the malignancy of ovarian cancer cells. Arch Biochem Biophys 661: 1-9, 2019.
87. Liu Y, Huo Y, Wang D, Tai Y, Li J, Pang D, Zhang Y, Zhao W, Du N and Huang Y: MiR-216a-5p/Hexokinase 2 axis regulates uveal melanoma growth through modulation of Warburg effect. Biochem Biophys Res Commun 501: 885-892, 2018.
88. Zhu W, Huang Y, Pan Q, Xiang P, Xie N and Yu H: MicroRNA-98 Suppress Warburg Effect by Targeting HK2 in Colon Cancer Cells. Dig Dis Sci 62: 660-668, 2017.
89. Li LQ, Yang Y, Chen H, Zhang L, Pan D and Xie WJ: MicroRNA-181b inhibits glycolysis in gastric cancer cells via targeting hexokinase 2 gene. Cancer Biomark 17: 75-81, 2016.
90. Zhang K, Zhang M, Jiang H, Liu F, Liu H and Li Y: Down-regulation of miR-214 inhibits proliferation and glycolysis in non-small-cell lung cancer cells via down-regulating the expression of hexokinase 2 and pyruvate kinase isozyme M2. Biomed Pharmacother 105: 545-552, 2018.
91. Kim J, Park MW, Park YJ, Ahn JW, Sim JM, Kim S, Heo J, Jeong JH, Lee M, Lim J and Moon JS: miR-542-3p Contributes to the HK2-mediated high glycolytic phenotype in human glioma cells. Genes 12: 633, 2021.
92. Atsumi T, Chesney J, Metz C, Leng L, Donnelly S, Makita Z, Mitchell R and Bucala R: High expression of inducible 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (iPFK-2; PFKFB3) in human cancers. Cancer Res 62: 5881-5887, 2002.
93. Boscaro C, Baggio C, Carotti M, Sandonà D, Trevisi L, Cignarella A and Bolego C: Targeting of PFKFB3 with miR-206 but not mir-26b inhibits ovarian cancer cell proliferation and migration involving FAK downregulation. FASEB J 36: e22140, 2022.
94. Ge X, Lyu P, Cao Z, Li J, Guo G, Xia W and Gu Y: Overexpression of miR-206 suppresses glycolysis, proliferation and migration in breast cancer cells via PFKFB3 targeting. Biochem Biophys Res Commun 463: 1115-1121, 2015.
95. Deng X, Li D, Ke X, Wang Q, Yan S, Xue Y, Wang Q and Zheng H: Mir-488 alleviates chemoresistance and glycolysis of colorectal cancer by targeting PFKFB3. J Clin Lab Anal 35: e23578, 2021.
96. Wang J, Li X, Xiao Z, Wang Y, Han Y, Li J, Zhu W, Leng Q, Wen Y and Wen X: MicroRNA-488 inhibits proliferation and glycolysis in human prostate cancer cells by regulating PFKFB3. FEBS Open Bio 9: 1798-1807, 2019.
97. Chen L, Cao Y, Wu B and Cao Y: MicroRNA-3666 suppresses cell growth in head and neck squamous cell carcinoma through inhibition of PFKFB3-mediated warburg effect. Onco Targets Ther 13: 9029-9041, 2020.
98. Du JY, Wang LF, Wang Q and Yu LD: miR-26b inhibits proliferation, migration, invasion and apoptosis induction via the downregulation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 driven glycolysis in osteosarcoma cells. Oncol Rep 33: 1890-1898, 2015.
99. Sheng W, Xu W, Ding J, Li L, You X, Wu Y and He Q: Curcumol inhibits the malignant progression of prostate cancer and regulates the PDK1/AKT/mTOR pathway by targeting miR-9. Oncol Rep 46: 246, 2021.

100. Qian Y, Wu X, Wang H, Hou G, Han X and Song W: MicroRNA-4290 suppresses PDK1-mediated glycolysis to enhance the sensitivity of gastric cancer cell to cisplatin. Braz J Med Biol Res 53: e9330, 2020.
101. Tsukamoto Y, Nakada C, Noguchi T, Tanigawa M, Nguyen LT, Uchida T, Hijiya N, Matsuura K, Fujioka T, Seto M and Moriyama M: MicroRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14-3-3zeta. Cancer Res 70: 2339-2349, 2010.
102. Jia-Yuan X, Wei S, Fang-Fang L, Zhi-Jian D, Long-He C and Sen L: miR-375 inhibits the proliferation and invasion of nasopharyngeal carcinoma cells by suppressing PDK1. Biomed Res Int 2020: 9704245, 2020.
103. Qu C, Yan C, Cao W, Li F, Qu Y, Guan K, Si C, Yu Z and Qu Z: miR-128-3p contributes to mitochondrial dysfunction and induces apoptosis in glioma cells via targeting pyruvate dehydrogenase kinase 1. IUBMB Life 72: 465-475, 2020.
104. Huang Y, Zheng S, Lin Y and Ke L: Circular RNA circ-ERBB2 elevates the warburg effect and facilitates triple-negative breast cancer growth by the MicroRNA 136-5p/pyruvate dehydrogenase Kinase 4 axis. Mol Cell Biol 41: e0060920, 2021.
105. Zhao Z, Ji M, Wang Q, He N and Li Y: miR-16-5p/PDK4-mediated metabolic reprogramming is involved in chemoresistance of cervical cancer. Mol Ther Oncolytics 17: 509-517, 2020.
106. Guda MR, Asuthkar S, Labak CM, Tsung AJ, Alexandrov I, Mackenzie MJ, Prasad DV and Velpula KK: Targeting PDK4 inhibits breast cancer metabolism. Am J Cancer Res 8: 1725-1738, 2018.
107. Si T, Ning X, Zhao H, Zhang M, Huang P, Hu Z, Yang L and Lin L: microRNA-9-5p regulates the mitochondrial function of hepatocellular carcinoma cells through suppressing PDK4. Cancer Gene Ther 28: 706-718, 2021.
108. Miao Y, Li Q, Sun G, Wang L, Zhang D, Xu H and Xu Z: MiR-5683 suppresses glycolysis and proliferation through targeting pyruvate dehydrogenase kinase 4 in gastric cancer. Cancer Med 9: 7231-7243, 2020.
109. Feng L, Cheng K, Zang R, Wang Q and Wang J: miR-497-5p inhibits gastric cancer cell proliferation and growth through targeting PDK3. Biosci Rep 39: BSR20190654, 2019.
110. Cheung EC and Vousden KH: The role of p53 in glucose metabolism. Curr Opin Cell Biol 22: 186-191, 2010.
111. Yang L, Zhang B, Wang X, Liu Z, Li J, Zhang S, Gu X, Jia M, Guo H, Feng N, *et al*: P53/PANK1/miR-107 signalling pathway spans the gap between metabolic reprogramming and insulin resistance induced by high-fat diet. J Cell Mol Med 24: 3611-3624, 2020.
112. Le MT, Teh C, Shyh-Chang N, Xie H, Zhou B, Korzh V, Lodish HF and Lim B: MicroRNA-125b is a novel negative regulator of p53. Genes Dev 23: 862-876, 2009.
113. Gopu V, Fan L, Shetty RS, Nagaraja MR and Shetty S: Caveolin-1 scaffolding domain peptide regulates glucose metabolism in lung fibrosis. JCI Insight 5: e137969, 2020.
114. Zou S, Rao Y and Chen W: miR-885-5p plays an accomplice role in liver cancer by instigating TIGAR expression via targeting its promoter. Biotechnol Appl Biochem 66: 763-771, 2019.
115. Tang J, Chen L, Qin ZH and Sheng R: Structure, regulation, and biological functions of TIGAR and its role in diseases. Acta Pharmacol Sin 42: 1547-1555, 2021.
116. Jones M and Lal A: MicroRNAs, wild-type and mutant p53: More questions than answers. RNA Biol 9: 781-791, 2012.
117. Dang CV: MYC on the path to cancer. Cell 149: 22-35, 2012.
118. Broecker-Preuss M, Becher-Boveleth N, Bockisch A, Dührsen U and Müller S: Regulation of glucose uptake in lymphoma cell lines by c-MYC- and PI3K-dependent signaling pathways and impact of glycolytic pathways on cell viability. J Transl Med 15: 158, 2017.
119. Zhai S, Xu Z, Xie J, Zhang J, Wang X, Peng C, Li H, Chen H, Shen B and Deng X: Epigenetic silencing of LncRNA LINC00261 promotes c-myc-mediated aerobic glycolysis by regulating miR-222-3p/HIPK2/ERK axis and sequestering IGF2BP1. Oncogene 40: 277-291, 2021.
120. Ebron JS, Shankar E, Singh J, Sikand K, Weyman CM, Gupta S, Lindner DJ, Liu X, Campbell MJ and Shukla GC: MiR-644a disrupts oncogenic transformation and warburg effect by direct modulation of multiple genes of tumor-promoting pathways. Cancer Res 79: 1844-1856, 2019.
121. Luan W, Wang Y, Chen X, Shi Y, Wang J, Zhang J, Qian J, Li R, Tao T, Wei W, *et al*: PKM2 promotes glucose metabolism and cell growth in gliomas through a mechanism involving a let-7a/c-Myc/hnRNPA1 feedback loop. Oncotarget 6: 13006-13018, 2015.
122. Wang H, Wang L, Pan H, Wang Y, Shi M, Yu H, Wang C, Pan X and Chen Z: Exosomes derived from macrophages enhance aerobic glycolysis and chemoresistance in lung cancer by stabilizing c-Myc via the Inhibition of NEDD4L. Front Cell Dev Biol 8: 620603, 2020.
123. Kim S, Lee E, Jung J, Lee JW, Kim HJ, Kim J, Yoo HJ, Lee HJ, Chae SY, Jeon SM, *et al*: microRNA-155 positively regulates glucose metabolism via PIK3R1-FOXO3a-cMYC axis in breast cancer. Oncogene 37: 2982-2991, 2018.
124. Ojuka EO: Role of calcium and AMP kinase in the regulation of mitochondrial biogenesis and GLUT4 levels in muscle. Proc Nutr Soc 63: 275-278, 2004.
125. Shackelford DB and Shaw RJ: The LKB1-AMPK pathway: Metabolism and growth control in tumour suppression. Nat Rev Cancer 9: 563-575, 2009.
126. Hardie DG: AMP-activated/SNF1 protein kinases: Conserved guardians of cellular energy. Nat Rev Mol Cell Biol 8: 774-785, 2007.
127. Lyu X, Wang J, Guo X, Wu G, Jiao Y, Faleti OD, Liu P, Liu T, Long Y, Chong T, *et al*: EBV-miR-BART1-5P activates AMPK/mTOR/HIF1 pathway via a PTEN independent manner to promote glycolysis and angiogenesis in nasopharyngeal carcinoma. PLoS Pathog 14: e1007484, 2018.
128. Barisciano G, Colangelo T, Rosato V, Muccillo L, Taddei ML, Ippolito L, Chiarugi P, Galgani M, Bruzzaniti S, Matarese G, *et al*: miR-27a is a master regulator of metabolic reprogramming and chemoresistance in colorectal cancer. Br J Cancer 122: 1354-1366, 2020.
129. Zhaohui W, Yingli N, Hongli L, Haijing W, Xiaohua Z, Chao F, Liugeng W, Hui Z, Feng T, Linfeng Y and Hong J: Amentoflavone induces apoptosis and suppresses glycolysis in glioma cells by targeting miR-124-3p. Neurosci Lett 686: 1-9, 2018.
130. Wang L, Guo W, Ma J, Dai W, Liu L, Guo S, Chen J, Wang H, Yang Y, Yi X, *et al*: Aberrant SIRT6 expression contributes to melanoma growth: Role of the autophagy paradox and IGF-AKT signaling. Autophagy 14: 518-533, 2018.
131. Vivanco I and Sawyers CL: The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat Rev Cancer 2: 489-501, 2002.
132. Sun Y, Liu W, Zhao Q, Zhang R, Wang J, Pan P, Shang H, Liu C and Wang C: Down-regulating the expression of miRNA-21 inhibits the glucose metabolism of A549/DDP cells and promotes cell death through the PI3K/AKT/mTOR/HIF-1α pathway. Front Oncol 11: 653596, 2021.
133. Pan C, Liu Q and Wu X: HIF1α/miR-520a-3p/AKT1/mTOR feedback promotes the proliferation and glycolysis of gastric cancer cells. Cancer Manage Res 11: 10145-10156, 2019.
134. Wang Q, Liu MJ, Bu J, Deng JL, Jiang BY, Jiang LD and He XJ: miR-485-3p regulated by MALAT1 inhibits osteosarcoma glycolysis and metastasis by directly suppressing c-MET and AKT3/mTOR signalling. Life Sci 268: 118925, 2021.
135. Carnero A, Blanco-Aparicio C, Renner O, Link W and Leal JF: The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. Curr Cancer Drug Targets 8: 187-198, 2008.
136. Zhai Z, Mu T, Zhao L, Li Y, Zhu D and Pan Y: MiR-181a-5p facilitates proliferation, invasion, and glycolysis of breast cancer through NDRG2-mediated activation of PTEN/AKT pathway. Bioengineered 13: 83-95, 2022.
137. Liu W, Kang L, Han J, Wang Y, Shen C, Yan Z, Tai Y and Zhao C: miR-342-3p suppresses hepatocellular carcinoma proliferation through inhibition of IGF-1R-mediated Warburg effect. Onco Targets Ther 11: 1643-1653, 2018.
138. Wang B, Sun F, Dong N, Sun Z, Diao Y, Zheng C, Sun J, Yang Y and Jiang D: MicroRNA-7 directly targets insulin-like growth factor 1 receptor to inhibit cellular growth and glucose metabolism in gliomas. Diagn Pathol 9: 211, 2014.
139. Xu H, Sun X, Huang Y, Si Q and Li M: Long non-coding RNA NEAT1 modifies cell proliferation, colony formation, apoptosis, migration and invasion via the miR-4500/BZW1 axis in ovarian cancer. Mol Med Rep 22: 3347-3357, 2020.
140. Xu M, Zhou K, Wu Y, Wang L and Lu S: Linc00161 regulated the drug resistance of ovarian cancer by sponging microRNA-128 and modulating MAPK1. Mol Carcinog 58: 577-587, 2019.
141. Zhao J, Li D and Fang L: MiR-128-3p suppresses breast cancer cellular progression via targeting LIMK1. Biomed Pharmacother 115: 108947, 2019.
142. Liu Y, Fu X, Wang X, Liu Y and Song X: Long non-coding RNA OIP5-AS1 facilitates the progression of ovarian cancer via the miR-128-3p/CCNG1 axis. Mol Med Rep 23: 388, 2021.

143. Liu Y, He X, Chen Y and Cao D: Long non-coding RNA LINC00504 regulates the Warburg effect in ovarian cancer through inhibition of miR-1244. Mol Cell Biochem 464: 39-50, 2020.
144. Goto H, Nishio M, To Y, Oishi T, Miyachi Y, Maehama T, Nishina H, Akiyama H, Mak TW, Makii Y, *et al*: Loss of Mob1a/b in mice results in chondrodysplasia due to YAP1/TAZ-TEAD-dependent repression of SOX9. Development 145: dev159244, 2018.
145. Wu DW, Wang YC, Wang L, Chen CY and Lee H: A low microRNA-630 expression confers resistance to tyrosine kinase inhibitors in EGFR-mutated lung adenocarcinomas via miR-630/YAP1/ERK feedback loop. Theranostics 8: 1256-1269, 2018.
146. Lin X, Feng D, Li P and Lv Y: LncRNA LINC00857 regulates the progression and glycolysis in ovarian cancer by modulating the Hippo signaling pathway. Cancer Med 9: 8122-8132, 2020.
147. Teng Y, Zhang Y, Qu K, Yang X, Fu J, Chen W and Li X: MicroRNA-29B (mir-29b) regulates the Warburg effect in ovarian cancer by targeting AKT2 and AKT3. Oncotarget 6: 40799-40814, 2015.
148. Young CD, Nolte EC, Lewis A, Serkova NJ and Anderson SM: Activated Akt1 accelerates MMTV-c-ErbB2 mammary tumourigenesis in mice without activation of ErbB3. Br Cancer Res 10: R70, 2008.
149. Kotowski K, Rosik J, Machaj F, Supplitt S, Wiczew D, Jabłońska K, Wiechec E, Ghavami S and Dzięgiel P: Role of PFKFB3 and PFKFB4 in cancer: Genetic basis, impact on disease development/progression, and potential as therapeutic targets. Cancers 13: 909, 2021.
150. Mondal S, Roy D, Sarkar Bhattacharya S, Jin L, Jung D, Zhang S, Kalogera E, Staub J, Wang Y, Xuyang W, *et al*: Therapeutic targeting of PFKFB3 with a novel glycolytic inhibitor PFK158 promotes lipophagy and chemosensitivity in gynecologic cancers. Int J Cancer 144: 178-189, 2019.
151. Chakraborty PK, Mustafi SB, Xiong X, Dwivedi SKD, Nesin V, Saha S, Zhang M, Dhanasekaran D, Jayaraman M, Mannel R, *et al*: MICU1 drives glycolysis and chemoresistance in ovarian cancer. Nat Commun 8: 14634, 2017.
152. Singh R, Yadav V, Kumar S and Saini N: MicroRNA-195 inhibits proliferation, invasion and metastasis in breast cancer cells by targeting FASN, HMGCR, ACACA and CYP27B1. Sci Rep 5: 17454, 2015.
153. Yang Y, Li M, Chang S, Wang L, Song T, Gao L, Hu L, Li Z, Liu L, Yao J and Huang C: MicroRNA-195 acts as a tumor suppressor by directly targeting Wnt3a in HepG2 hepatocellular carcinoma cells. Mol Med Rep 10: 2643-2648, 2014.
154. Rao G, Dwivedi SKD, Zhang Y, Dey A, Shameer K, Karthik R, Srikantan S, Hossen MN, Wren JD, Madesh M, *et al*: MicroRNA-195 controls MICU1 expression and tumor growth in ovarian cancer. EMBO Rep 21: e48483, 2020.
155. Cao HL, Liu ZJ, Huang PL, Yue YL and Xi JN: lncRNA-RMRP promotes proliferation, migration and invasion of bladder cancer via miR-206. Eur Rev Med Pharmacol Sci 23: 1012-1021, 2019.
156. Hongfeng Z, Andong J, Liwen S, Mingping B, Xiaowei Y, Mingyong L and Aimin Y: lncRNA RMRP knockdown suppress hepatocellular carcinoma biological activities via regulation miRNA-206/TACR1. J Cell Biochem 121: 1690-1702, 2020.
157. Li L, Zeng S, Guo L, Huang P, Xi J, Feng J, Li Q, Li Y, Xiao X, Yan R and Zhang J: Long noncoding RNA RMRP contributes to paclitaxel sensitivity of ovarian cancer by regulating miR-580-3p/MICU1 signaling. J Oncol 2022: 8301941, 2022.
158. Han RL, Wang FP, Zhang PA, Zhou XY and Li Y: miR-383 inhibits ovarian cancer cell proliferation, invasion and aerobic glycolysis by targeting LDHA. Neoplasma 64: 244-252, 2017.
159. Rafat M, Moraghebi M, Afsa M and Malekzadeh K: The outstanding role of miR-132-3p in carcinogenesis of solid tumors. Hum Cell 34: 1051-1065, 2021.
160. Cooper SJ, von Roemeling CA, Kang KH, Marlow LA, Grebe SK, Menefee ME, Tun HW, Colon-Otero G, Perez EA and Copland JA: Reexpression of tumor suppressor, sFRP1, leads to antitumor synergy of combined HDAC and methyltransferase inhibitors in chemoresistant cancers. Mol Cancer Ther 11: 2105-2115, 2012.
161. Hu J, Zhao W, Huang Y, Wang Z, Jiang T and Wang L: MiR-1180 from bone marrow MSCs promotes cell proliferation and glycolysis in ovarian cancer cells via SFRP1/Wnt pathway. Cancer Cell Int 19: 66, 2019.
162. Gu ZW, He YF, Wang WJ, Tian Q and Di W: MiR-1180 from bone marrow-derived mesenchymal stem cells induces glycolysis and chemoresistance in ovarian cancer cells by upregulating the Wnt signaling pathway. J Zhejiang Univ Sci B 20: 219-237, 2019.
163. Xiaohong Z, Lichun F, Na X, Kejian Z, Xiaolan X and Shaosheng W: MiR-203 promotes the growth and migration of ovarian cancer cells by enhancing glycolytic pathway. Tumour Biol 37: 14989-14997, 2016.
164. Shao X, Zheng X, Ma D, Liu Y and Liu G: Inhibition of lncRNA-NEAT1 sensitizes 5-Fu resistant cervical cancer cells through de-repressing the microRNA-34a/LDHA axis. Biosci Rep 41: BSR20200533, 2021.
165. Li L, Ma Y, Maerkeya K, Reyanguly D and Han L: LncRNA OIP5-AS1 regulates the warburg effect through miR-124-5p/IDH2/HIF-1α pathway in cervical cancer. Front Cell Dev Biol 9: 655018, 2021.
166. Luo W, Zhang D, Ma S, Wang C, Zhang Q, Wang H, He K and Liu Z: miR-27a is highly expressed in H1650 cancer stem cells and regulates proliferation, migration, and invasion. J Cancer Res Ther 14 (Suppl): S1004-S1011, 2018.
167. Jiang G, Shi W, Fang H and Zhang X: miR-27a promotes human breast cancer cell migration by inducing EMT in a FBXW7-dependent manner. Mol Med Rep 18: 5417-5426, 2018.
168. Li W, Yu ZX and Ma BF: The increase of miR-27a affects the role of cisplatin on proliferation and migration capacities of liver cancer cells. Eur Rev Med Pharmacol Sci 22: 5490-5498, 2018.
169. Li P, Zhang Q and Tang H: INPP1 up-regulation by miR-27a contributes to the growth, migration and invasion of human cervical cancer. J Cell Mol Med 23: 7709-7716, 2019.
170. Zhang S, Chen P, Huang Z, Hu X, Chen M, Hu S, Hu Y and Cai T: Sirt7 promotes gastric cancer growth and inhibits apoptosis by epigenetically inhibiting miR-34a. Sci Rep 5: 9787, 2015.
171. Gougelet A, Sartor C, Bachelot L, Godard C, Marchiol C, Renault G, Tores F, Nitschke P, Cavard C, Terris B, *et al*: Antitumour activity of an inhibitor of miR-34a in liver cancer with β-catenin-mutations. Gut 65: 1024-1034, 2016.
172. Hermeking H: The miR-34 family in cancer and apoptosis. Cell Death Differ 17: 193-199, 2010.
173. Zhang R, Su J, Xue SL, Yang H, Ju LL, Ji Y, Wu KH, Zhang YW, Zhang YX, Hu JF and Yu MM: HPV E6/p53 mediated down-regulation of miR-34a inhibits Warburg effect through targeting LDHA in cervical cancer. Am J Cancer Res 6: 312-320, 2016.
174. Yang H, Wu XL, Wu KH, Zhang R, Ju LL, Ji Y, Zhang YW, Xue SL, Zhang YX, Yang YF and Yu MM: MicroRNA-497 regulates cisplatin chemosensitivity of cervical cancer by targeting transketolase. Am J Cancer Res 6: 2690-2699, 2016.
175. Yang X and Wu X: miRNA expression profile of vulvar squamous cell carcinoma and identification of the oncogenic role of miR-590-5p. Oncol Rep 35: 398-408, 2016.
176. de Melo Maia B, Lavorato-Rocha AM, Rodrigues LS, Coutinho-Camillo CM, Baiocchi G, Stiepcich MM, Puga R, de A Lima L, Soares FA and Rocha RM: microRNA portraits in human vulvar carcinoma. Cancer Prev Res (Phila) 6: 1231-1241, 2013.
177. Gonzalez Dos Anjos L, de Almeida BC, Gomes de Almeida T, Mourão Lavorato Rocha A, De Nardo Maffazioli G, Soares FA, Werneck da Cunha I, Baracat EC and Carvalho KC: Could miRNA signatures be useful for predicting uterine sarcoma and carcinosarcoma prognosis and treatment? Cancers (Basel) 10: 315, 2018.
178. Tyagi K, Mandal S and Roy A: Recent advancements in therapeutic targeting of the Warburg effect in refractory ovarian cancer: A promise towards disease remission. Biochim Biophys Acta Rev Cancer 1876: 188563, 2021.
179. Hietanen S, Lain S, Krausz E, Blattner C and Lane DP: Activation of p53 in cervical carcinoma cells by small molecules. Proc Natl Acad Sci USA 97: 8501-8506, 2000.
180. Guan XY, Guan XL and Jiao ZY: Improving therapeutic resistance: Beginning with targeting the tumor microenvironment. J Chemother 34: 492-516, 2022.
181. Arvizo RR, Moyano DF, Saha S, Thompson MA, Bhattacharya R, Rotello VM, Prakash YS and Mukherjee P: Probing novel roles of the mitochondrial uniporter in ovarian cancer cells using nanoparticles. J Biol Chem 288: 17610-17618, 2013.
182. Khan S, Chib R, Shah BA, Wani ZA, Dhar N, Mondhe DM, Lattoo S, Jain SK, Taneja SC and Singh J: A cyano analogue of boswellic acid induces crosstalk between p53/PUMA/Bax and telomerase that stages the human papillomavirus type 18 positive HeLa cells to apoptotic death. Eur J Pharmacol 660: 241-248, 2011.

183. Yuan Y, Li H, Pu W, Chen L, Guo D, Jiang H, He B, Qin S, Wang K, Li N, *et al*: Cancer metabolism and tumor microenvironment: Fostering each other? Sci China Life Sci 65: 236-279, 2022.
184. Hashemian SM, Pourhanifeh MH, Fadaei S, Velayati AA, Mirzaei H and Hamblin MR: Non-coding RNAs and exosomes: Their role in the pathogenesis of sepsis. Mol Ther Nucleic Acids 21: 51-74, 2020.
185. Razavi ZS, Tajiknia V, Majidi S, Ghandali M, Mirzaei HR, Rahimian N, Hamblin MR and Mirzaei H: Gynecologic cancers and non-coding RNAs: Epigenetic regulators with emerging roles. Crit Rev Oncol Hematol 157: 103192, 2021.
186. Bonneau E, Neveu B, Kostantin E, Tsongalis GJ and De Guire V: How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market. EJIFCC 30: 114-127, 2019.
187. Fatmi A, Chabni N, Cernada M, Vento M, González-López M, Aribi M, Pallardó FV and García-Giménez JL: Clinical and immunological aspects of microRNAs in neonatal sepsis. Biomed Pharmacother 145: 112444, 2022.
188. Gumusoglu-Acar E, Gunel T, Hosseini MK, Dogan B, Tekarslan EE, Gurdamar B, Cevik N, Sezerman U, Topuz S and Aydinli K: Metabolic pathways of potential miRNA biomarkers derived from liquid biopsy in epithelial ovarian cancer. Oncol Lett 25: 142, 2023.