

Role of miRNA-424 in Cancers

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Abstract: microRNA (miRNA) is an important part of non-coding RNA that regulates gene expression at a posttranscriptional level. miRNA has gained increasing interest in recent years, both in research and clinical fields. miRNAs have been found to play an important role in various diseases, particularly cancer. Aberrant miR-424 expression is found in several tumors where they can function as either oncogenes or tumor-suppressor genes. Meanwhile, miR-424 is also affected by the reorganization of many other non-coding RNAs such as lncRNA and circRNA. Several studies have found that miR-424 participates in proliferation, differentiation, apoptosis, invasion, angiogenesis, and drug resistance, and plays an important role in the tumorigenesis and progression of tumors. This review will focus on the recent progress of research on miR-424 in tumors.

Keywords: miRNAs, miR-424, tumor, regulation, carcinogenesis, cancer progression

Introduction

MicroRNA (miRNA) has been the subject of many studies since its discovery in 1993.¹ miRNA is an important class of non-coding RNA that function as post-transcriptional regulators of gene expression in cells by repressing and fine-tuning protein output. Although miRNA accounts for only 1% of the human genome, it regulates one-third of the gene expression in humans.^{2–4} miRNAs are ubiquitous in eukaryotes, and are highly conservative, time-series, and tissue-cell specific. miRNAs are composed of a large group of non-coding small RNAs (approximately 21–23nt).⁵ miRNA formation comprises three main steps: transcription, maturation, and functional complex assembly. The gene encoding miRNA in the nucleus is first transcribed under the catalysis of RNA polymerase II to form a primary transcript with a cap structure (5MGpppG) and a poly-A tail (PolyA) of several hundred nucleotides in length.⁶ The primary transcript is further processed into a single precursor pre-miRNA, with a stem-loop structure containing only 70–100 nt under the action of the RNase family enzyme Drosha. The pre-miRNA is then transported to the cytoplasm by HASTY (HST), a homolog of the export protein Exportin-5.^{7–9} In conjunction with the RNaseIII family enzyme Dicer, the pre-miRNA is processed to form double-stranded miRNA, which subsequently forms double strand mature miRNA.¹⁰ Mature miRNAs combine with a ribonucleoprotein complex similar to RISC (RNA-induced silencing complex) to form miRNP, which recognizes target genes.^{9,11} After miRNA is loaded into the RISC complex, it functions in the regulation of gene expression. miRNA recognizes binding sites on the mRNA 3'UTR through its seed sequence (nucleotides 2–8 at the 5' end), carries RISC, and inhibits protein expression. The three main functions of miRNA are transcriptional repression, and mRNA cleavage or degradation.^{12–14} Existing studies have found

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that approximately 30% of human protein expression is regulated by miRNAs.¹⁵ By interacting with the 3'UTR, miRNA can simultaneously regulate the expression of many genes, thereby regulating signaling pathways at multiple levels.^{16,17}

Evidence increasingly suggests that miR-424 plays an important role in different types of diseases, including sperm damage,¹⁸ psoriasis,¹⁹ amyotrophic lateral sclerosis (ALS),²⁰ insulin resistance,²¹ and acute respiratory distress syndrome (ARDS).²² However, the research on miR-424 is more abundant in cases of tumors involving early diagnosis, development, treatment, prognosis. This review focuses on the role of miR-424 in tumor progression.

Dual Regulatory Function of miRNA-424

The expression level of miR-424 in tumors can be either high or low, highlighting its multiple roles. Due to differences in expression, it is possible to diagnose disease and predict prognosis by detecting the amount of miRNA-424 in the blood or other body fluids.

Multilateral statistical evaluations have repeatedly confirmed the combination of highly specific biomarkers composed of four urine microRNAs (miR-424, miR-423, miR-660, and let7-i) as indicators to distinguish breast cancer patients from healthy controls, with sensitivity of 98.6% and specificity of 100%. This is of great significance for the non-invasive auxiliary diagnosis of breast cancer.²³ Meanwhile, currently basing on the PSA to diagnose prostate cancer is limited. A previous study identified that a low expression level of miR-424-3p was associated with the invasive phenotype and recurrence of prostate cancer.^{24,25} It can be detected by miR-424 combined with PSA value and prostate volume to assist in the diagnosis of prostate cancer in patients with elevated PSA.²⁶

In addition to studies on endocrine organs, the association between miRNAs and digestive system tumors has also been explored. The overall survival rate of pancreatic adenocarcinoma (PAAD) is associated with miRNAs including miR-424, which may have the potential to become a prognostic biomarker for PAAD.²⁷ Several studies have found that miR-424-5p is a tumor suppressor miRNA in hepatocellular carcinoma (HCC), and miR-424-5p is closely related to cell proliferation and invasion.^{28–30} Furthermore, it has been shown that miR-424 can predict the recurrence of liver cancer after liver transplantation,

and that low expression of miR-424 is an independent prognostic factor of relapse, primarily through promoting the migration, invasion, and proliferation of HCC cells.³¹ In the respiratory system, it has been shown that high expression of miR-424 indicates a worse prognosis for patients with non-small cell lung cancer.³²

In summary, a large number of studies have found that the expression level of miRNA-424 in different tumors has significance in the diagnosis and prognosis of tumors.

Function of miR-424 and Roles in Tumor Progression

MicroRNA regulates gene expression at the post-transcription level and is involved in regulating several key processes including cell proliferation, apoptosis, stem cell differentiation, invasion and metastasis, and other physiological and pathological processes. As mentioned above, the expression of miR-424 in tumors is closely related to the occurrence and development of disease. At the same time, a large number of studies have found that by changing the expression of miR-424 in tumors to regulate different target genes, cell function can also be altered.

Multiplication, Invasion, and Migration

Tumor proliferation, invasion and migration are complex processes with multiple factors and steps that involve oncogenes, tumor suppressor genes, signal transduction genes, and numerous cytokines and regulatory factors. Studies have found that miRNAs play different functions in different diseases. For instance, in the nervous system, glioma is one of the most deadly malignant tumors, in which miR-424 plays a role in suppressing cancer in glioma cells and is down-regulated by DNA methylation.³³ Further research found that miR-424 can inhibit cell migration and epithelial-mesenchymal transition (EMT) by targeting KIF23 in glioma.³⁴ Moreover, in the reproductive system, based on the exact relationship between HPV infection and cervical cancer, studies have found that in HPV (+) cervical cancer cells, CHK1 and Wee1, the two targets of miR-424, are suppressed. These factors have important roles in DNA damage repair,³⁵ and further research found that regulating CHK1 can affect cervical cancer cell migration and invasion, apoptosis, and cell cycle changes. Furthermore, miR424-5p can target KDM5B through the Notch signaling pathway to influence cervical cancer cell proliferation.^{36,37} In endometrial

cancer, miR-424 can inhibit cell proliferation by targeting E2F7, increase cell apoptosis, and cause cell cycle arrest³⁸. Another study found that miR-424 can inhibit cell invasion and sphere formation by inhibiting MMSET, as well as inhibiting cell migration, invasion, and EMT by down-regulating doublecortin-like kinase 1 (DCLK1). miR-424 can also target G protein-coupled estrogen receptor -1 (GPER-1), which in turn affects the PI3K/AKT signaling pathway to regulate cell proliferation.³⁹⁻⁴²

In summary, a large number of studies on the female reproductive system have indicated that miR-424 is involved in regulating the malignant biological behavior of tumors by regulating the expression of target genes, which may become an important marker for tumor diagnosis and prognosis, and may even have potential as an anti-tumor adjuvant therapy.

In nasopharyngeal carcinoma, miR-424-5p acts an oncogene that promotes the aggressive progression of laryngosquamous cell carcinoma (LSCC), and a high miR-424-5p level is significantly associated with poor differentiation, advanced tumors, and cervical lymph node metastasis.⁴³ In oral squamous cell carcinoma, it has been found that miR-424-5p is involved in cell migration and invasion by negatively regulating the expression of SOCS2.⁴⁴ Meanwhile, studies in a variety of digestive system tumors have found that miR-424 can either promote or suppress cancer. miR-424-5p is a carcinogen in colorectal cancer (CRC) that directly promotes proliferation and metastasis by targeting SCN4B, CCNE1, AKT3, and Rictor.⁴⁵⁻⁴⁸ In the field of hepatobiliary carcinoma, it has been found that miR-424-5p can inhibit the metastasis and invasion of intrahepatic cholangiocarcinoma by targeting ARK5. Moreover, in liver cancer, miR-424 can inhibit the proliferation and invasion of tumors by targeting TRIM29, YAP1, and c-Myb, while miR-424-5p can also target ICAT and inhibit tumor progression by reversing the EMT process of primary liver cancer.^{28,49-52} Another group has found that miR-424 inhibits tumor growth by inhibiting the Akt3/E2F3 axis in liver cancer tissues.⁵³ Other studies have found that in hepatoma cells, the transcription of miR-424 and miR-503 increases after thyroid hormone binds to its receptor, further confirming its role in promoting tumor proliferation and invasion.⁵⁴ miR-424 targets TGFBR3, thereby promoting EMT and migration of tongue squamous cell carcinoma (TSCC).⁵⁵ miR-424-5p is involved in the invasion and metastasis of esophageal squamous cell carcinoma (ESCC) through the SMAD7 pathway; therefore, the upregulation of miR-424-5p may

reduce the invasion and metastasis of the tumor.⁵⁶ miR-424-5p affects the ERK1/2 signaling pathway by negatively regulating SOCS6 in pancreatic cancer, thereby increasing proliferation, migration, and invasion, and inhibiting apoptosis.⁵⁷

There are relatively few studies on miR-424 in the urinary system. In prostate cancer, a study has found that low expression of miR-424-3p is closely related to increased invasiveness.²⁴ Moreover, the expression level of miR-424 was shown to significantly correlate with aggressive tumor growth, advanced clinical stage, and poor prognosis of bladder cancer.⁵⁸ In kidney cancer, miR-424 and miR-381 jointly target WEE1, up-regulate the activity of Cdc2 to synergistically inhibit the proliferation and survival of renal cancer cells, and participate in tumor-related processes.⁵⁹ In basal-like breast cancer, a study has found that miR-424-5p regulates tumor cell proliferation, migration, and invasion by targeting doublecortin like kinase 1 (DCLK1).⁶⁰ In the respiratory system, non-small cell lung cancer accounts for approximately 80% of all lung cancer cases. In the past few decades, the average survival time of patients diagnosed with non-small cell lung cancer (NSCLC) is less than 6 months.⁶¹ Another study found that miR-424 promotes the progression and metastasis of non-small cell lung cancer by regulating the tumor suppressor gene TNFAIP1.⁶² miR-424 can inhibit the proliferation and invasion of NSCLC by inhibiting the expression of E2F6.⁶³ In the motor system, a study group demonstrated that miR-424 inhibits osteosarcoma cell migration and invasion by targeting fatty acid synthase.⁶⁴

Drug Resistance and Radio-Sensitivity of Radiotherapy

Drug resistance is the main obstacle to the long-term effectiveness of cancer treatment. Drug resistance is mainly due to the generation of drug-resistant cells in the tumor tissue, which in turn leads to chemotherapeutic drugs being unable to exert a full anti-cancer effect. However, even if most of the tumor cells are killed, this small population of drug-resistant tumor cells will continue to proliferate, ultimately causing cancer relapse. In summary, following the emergence of drug resistance, the efficacy of chemotherapy will gradually decline, and eventually malignant tumors will no longer be treatable. In the reproductive system, studies have found that high expression of miR-424 and miR-503 is closely related to

chemoresistance and tumor progression of ovarian cancer.⁶⁵ miR-424-3p increases the sensitivity of the ovarian cancer cells SK-OV-3 and TOV-21G to cisplatin by reducing the expression of galectin-3 (anti-apoptotic protein); these results indicate that miR-424-3p may be an appropriate target to recover the sensitivity to chemotherapy drugs.⁶⁶

Studies have found that the sensitivity of the commonly used chemotherapy drug, docetaxel, is affected by miR-424.⁶⁷ Further research confirmed that miR-424 is involved in the regulation of PD-L1/PD-1 and CD80/CTLA-4 in chemotherapy-resistant ovarian cancer.⁶⁸ In the endocrine system, miR-424-5p inactivates Hippo signaling, thereby promoting anoikis drug resistance and lung metastasis. Therefore, miR-424-5p has the potential to become a therapeutic target for lung metastases from thyroid cancer.⁶⁹ A study in hormone receptor-positive metastatic breast cancer found that miR-424-5p can be used as a potential indicator of the sensitivity response to dovitinib.⁷⁰ Furthermore, the deletion of miR-424 (322)/503 can promote breast cancer resistance by up-regulating its two targets: BCL-2 and insulin-like growth factor-1 receptor (IGF1R).⁷¹ In the digestive system, preliminary verification based on the GEO database and human gastric cancer tissues showed that miR-424 regulates gastric cancer cisplatin resistance by targeting SMURF1.⁷² In non-small cell lung cancer, studies have confirmed that the deletion of miR-424-3p is involved in chemotherapy resistance by targeting YAP1.⁷³ In addition to chemotherapy resistance, the decline of tumor sensitivity to radiotherapy after long-term treatment has also attracted increasing attention. Studies have found that miR-424 can promote IR-induced DNA damage, apoptosis, and G2/M cell cycle arrest through APTX, thereby enhancing the radiation sensitivity of radiation-resistant cervical cancer cells.⁷⁴

Cell Cycle

The cell cycle is the time required from the end of cell division to the end of the next cell division. The cell cycle is divided into four stages: G1 phase (gap1), which refers to the gap time before DNA replication is due to complete from mitosis; S phase (synthesis phase), which refers to the period of DNA replication; G2 phase (gap2), which refers to the completion of DNA replication but before the onset of mitosis; M phase, also known as D phase (mitosis or division), begins to end cell division. Dysregulation of the cell cycle is one of the main mechanisms of tumorigenesis.

A study identified that miR-424 in the digestive system regulates the cell cycle of esophageal squamous cell carcinoma (ESCC) to promote proliferation, and can be used as a new prognostic marker and an effective therapeutic target.⁷⁵ In gastric cancer, miR-424-5p regulates the TGF- β signaling pathway and cyclin (c-Myc, CDK2, CDK4, CDK6) through SMAD3, where it has roles in regulating the cell cycle.⁷⁶ Meanwhile, in the motion system, miR-424 suppressed the development of osteosarcoma by targeting the expression of cyclin cell A2.⁷⁷ In epithelial ovarian cancer, miR-424-5p suppresses the expression of CCNE1, and blocks cells in the G1/G0 phase through the E2F1-pRb pathway.⁴¹ In conclusion, some studies have shown that miR-424 plays an important role in regulating the cell cycle, and can regulate the expression of miR-424 to inhibit the occurrence and development of tumors.

Stem Cell Properties

Cancer stem cells (CSCs) represent a subset of the cancer cell population that possess self-renewal ability and account for cancer initiation, progression, metastasis, and recurrence. It has been shown that in breast cancer cells, hyperglycemia can excessively activate tumor stem cells through the miR-424/cdc42/prdm14 axis, and enhance tumor invasion.⁷⁸ Similarly, in another common endocrine-related tumor, prostate cancer, miR-424 targets E3 ubiquitin ligase COP1 and recognizes STAT3 as a key substrate of COP1, promoting prostate epithelial cell tumorigenicity and cancer stem cell-like properties.⁷⁹

Relationship with Viruses

Various viruses have been shown to be closely related to the occurrence of tumors. EBV was the first human virus to be shown to be directly related to canceration, which has been shown to be closely related to various malignant tumors.⁸⁰ The causal relationship between human papillomavirus (HPV) and cervical cancer is well established in biology and epidemiology. HPV-16 and -18 infections account for approximately 70% of cervical cancer cases.⁸¹ A previous study reported that miR-424 plays a key role in the regulation of HPV replication. Furthermore, HPV E6 and E7 proteins inhibit miR-424 levels, control CHK1, and have been shown to play a central role in viral replication.³⁷ Furthermore, the interaction between HPV16 and E7CUL2 recruits CUL2 and activates the regulatory loops between CUL2, E2F1, and miR-424, which results in persistent CUL2

overexpression, and subsequent promotion of HPV16-induced cervical cancer development.⁸²

In conclusion, existing evidence indicates that miR-424 plays an important role in various stages of tumorigenesis. Moreover, analysis of miR-424 expression can help to diagnose diseases, and has the potential to become an important molecule in tumor diagnosis and prognosis. In addition, in the future, the expression of miR-424 may be adjusted to regulate the occurrence and development of tumors and limit tumor progression. Taken together, these studies have suggested that miR-424 performs different functions in various cancers (Table 1).

Molecules That Regulate the Expression of miR-424 in Tumors

LncRNA

Accumulating evidence has shown that a variety of lncRNAs and circRNAs are involved in the occurrence and development of tumors by regulating miR-424. For example, in the reproductive system, estrogen receptor 1 (ESR1) plays an important role in the pathological process of ovarian cancer. ESR1-induced upregulation of LINC00511 may be caused by sponged miR-424-5p and miR-370-5p, which in turn promotes the proliferation and invasion of ovarian cancer CAOV3 cells.⁸³ Moreover, it has been shown that Lnc-SNHG12 negatively regulates miR-424-5p to promote cancer.⁸⁴ Another study found that Lnc-CCAT2 negatively targets miR-424 as a competitive endogenous RNA (ceRNA) or sponge for ovarian cancer, and represents a new diagnostic marker and therapeutic target.⁸⁵ Tumor promoting effects of Lnc-PVT1 were found in cervical cancer, as competitive endogenous RNA (ceRNA) or molecular sponge negatively regulates miR-424.⁸⁶ Furthermore, LncRNA BLACAT1 expression is increased in cervical cancer (CSCC), while BLACAT1 overexpression may promote tumor progression by down-regulating miR-424.⁸⁷ Another study found that the tumor-promoting Small nucleolar RNA host gene 12 (SNHG12) acts as a molecular sponge of miR-424-5p and has a negative regulatory effect.⁸⁴ With regards to the digestive system, Lnc-RNA NNT-AS1 can affect the tumorigenesis and cell cycle of gastric cancer cells by binding to miR-424/E2F1.⁸⁸ Moreover, in hepatocellular carcinoma, LncRNA-LINC00511 plays an important role in the malignant progression of HCC by regulating miR-424.⁸⁹ Another study has found that Lnc-RNA DLX6-AS1 increases the expression of WEE1 by targeting miR-424-

5p, which in turn promotes hepatocellular carcinoma.⁹⁰ In the respiratory system, non-small cell lung cancer accounts for approximately 80% of lung cancer subclasses, and is the disease with the highest cancer-related mortality in both men and women. A research team found that the miR-424-5p/lncRNA PVT1/CARM1 axis can influence non-small cell lung cancer. Furthermore, radiotherapy sensitivity of small cell lung carcinoma, overexpression of miR-424-5p, or inhibition of lncRNA PVT1 can increase the radiotherapy sensitivity of NSCLC.⁹¹ Lnc-RNA LINC00641 was found to inhibit the progression of non-small cell lung cancer by sponging miR-424-5p and up-regulating PLSCR4. Further rescue experiments showed that miR-424-5p and PLSCR4 can reverse the cell process mediated by LINC00641. In conclusion, LINC00641 exerts a tumor suppressive effect in NSCLC through miR-424-5p.⁹²

In the central nervous system, a previous study demonstrated that lncRNA-CCAT2 enhances the chemoresistance of glioma cells through the lncRNA-CCAT2/miR-424/Chk1 axis, and promotes the migration of glioma cells. As such, the curative effect of chemotherapy for glioma can be improved by inhibiting this axis.⁹³ Recent studies have found that lncRNA-CCAT2 also can down-regulate miR-424 to promote VEGFA expression, induce PI3K/AKT signaling, and promote cell proliferation and endothelial angiogenesis.⁹⁴ It was also found that down-regulation of lncRNA-PVT1 inhibits the progression of glioma by up-regulating the expression of miR-424.⁹⁵ In addition, in invasive pituitary neuroendocrine tumors, LncRNA-XIST competitively combines with miR-424-5p to increase the expression of bFGF to promote cell proliferation, migration, invasion, and inhibit cell cycle arrest and apoptosis.⁹⁶ In the circulatory system, a research group used tumor xenograft experiments to show that LncRNA-MALAT1 inhibits miR-424 and activates the MEKK3-mediated IKK/NF-kappaB pathway to promote the development of hemangioma. This suggests that LncRNA-MALAT1, miR-424, and MEKK3 can be used as potential targets for the improvement of IH treatment efficiency.⁹⁷

CircRNA

In addition to lncRNA, part of circRNA is also involved in the regulation of microRNA. Circ-LARP4 inhibits the proliferation and invasion of gastric cancer cells by sponging miR-424-5p and regulating the expression of LATS1. The increased expression of miR-424 or the decreased

Table 1 The Function of the Target Gene of miR-424 in Difference Cancers

Cancer Type	Target Genes	Related Function	References
Bladder cancer	<i>EGFR</i>	EMT	[24]
HCC	<i>TRIM29</i>	proliferation and invasion	[28]
Glioma	<i>KIF23</i>	migration, invasion and EMT	[34]
Cervical cancer	<i>CHEK1</i>	HPV replication	[35]
Cervical cancer	<i>KDM5B</i>	growth proliferation apoptosis	[36]
Cervical cancer	<i>Chk1</i>	proliferation,apoptosis,suppressed cell-cycle progression	[37]
Endometrial cancer	<i>E2F7</i>	proliferation, apoptosis and cell arrest	[38]
Endometrial cancer	<i>NSD2</i>	invasion and sphere formation	[39]
Ovarian cancer	<i>CCNE1</i>	cell cycle	[41]
Ovarian cancer	<i>DCLK1</i>	proliferation, migration, invasion and EMT	[42]
Colorectal cancer	<i>CCNE1</i>	malignant behavior	[45]
Colorectal cancer	<i>AKT3 PSAT1</i>	tumor-suppressive apoptosis	[46]
Colorectal cancer	<i>SCN4B</i>	proliferation and metastasis	[47]
Prostate and colon cancer	<i>RICTOR</i>	tumorigenicity and invasive	[48]
Intrahepatic cholangiocarcinoma	<i>ARK5</i>	metastasis and invasion	[49]
HCC	<i>YAP1</i>	proliferation and apoptosis	[50]
HCC	<i>MYB</i>	proliferation,migration and invasion	[52]
HCC	<i>AKT3</i>	proliferation and apoptosis	[53]
Tongue squamous cell carcinoma	<i>TGFBR3</i>	EMT and migration	[55]
Esophageal squamous cell carcinoma	<i>SAMD7</i>	EMT	[56]
Pancreatic cancer	<i>SOCS6</i>	proliferation, migration,invasion and apoptosis	[57]
Renal cancer	<i>WEE1</i>	mitotic entry and apoptosis	[59]
Breast cancer	<i>DCLK1</i>	proliferation, migration and invasion	[60]
NSCLC	<i>TNFAIP1</i>	progression and metastasis	[62]
NSCLC	<i>E2F6</i>	proliferation and migration Abilities	[63]
Osteosarcoma	<i>FASN</i>	migration and invasion	[64]
Ovarian cancer	<i>LGALS3</i>	chemoresistance and apoptosis	[66]
Ovarian cancer	<i>PD-L1</i>	chemoresistance	[68]
Ovarian cancer	<i>PD-L1 PD-1 CD80</i>	chemoresistance	[68]
	<i>CTLA-4</i>		
Thyroid cancer	<i>WWC1 SAV1 LATS2</i>	chemoresistance and metastasis	[69]
Breast cancer	<i>IGF1R BCL-2</i>	epithelial involution, tumorigenesis, and the phenomenon of chemoresistance	[71]
Gastric cancer	<i>SMURF1</i>	chemoresistance	[72]
NSCLC	<i>YAP1</i>	chemoresistance	[73]
Cervical cancer	<i>APTX</i>	radiosensitize	[74]
Esophageal squamous cell carcinoma	<i>PRKCD WEE1</i>	cell cycle	[75]
Osteosarcoma	<i>PCNA</i>	cell cycle and proliferation	[77]
Breast cancer	<i>CDC42</i>	distant metastasis and mortality	[78]
Prostate cancer	<i>STAT3</i>	EMT and stem cell-like features	[79]
Cervical carcinogenesis	<i>CLU2</i>	proliferation	[82]
Ovarian cancer	<i>ESR1</i>	proliferation and invasion	[83]
Gastric cancer	<i>E2F1</i>	tumorigenesis and cell cycle	[88]
NSCLC	<i>CARM1</i>	proliferation,invasion,apoptosis and proliferation	[91]
NSCLC	<i>PLSCR4</i>	proliferation and apoptosis	[92]
Glioma	<i>CHEK1</i>	chemosensitivity	[93]
Glioma	<i>VEGFA</i>	angiogenesis	[94]
Invasive neuroendocrine tumor	<i>FGF2</i>	proliferation, migration, invasion and apoptosis	[96]
Gastric cancer	<i>LATS1</i>	proliferation and invasion	[98]

expression of LATS1, is closely related to the pathological stage and poor prognosis of GC patients.⁹⁸ Studies have also found that the high expression of Circ-LARP4 is related to a shorted perioperative period and prolonged survival of osteosarcoma, as well as increased chemical sensitivity to cisplatin and doxorubicin through cavernous miR-424.⁹⁹ In short, an increasing number of circ-RNAs have been shown to be involved in the regulation of miR-424, and their function needs to be explored further.

Taken together, these studies have suggested that miR-424 regulated by different non-coding RNA in various cancers (Table 2).

Bioinformatics Analysis of miR-424

We performed KEGG pathway analysis of miR-424 using Webgestalt (<http://bioinfo.vanderbilt.edu/webgestalt/>) to predict the possible downstream pathway of miR-424 target genes, screening is performed with $P < 0.05$ as the critical value. After KEGG analysis, the 20 most relevant routes were selected, 15 of which were found to have significant P-values. The 20 KEGG pathways with the highest concentration are shown in Figure 1A. miR-424 target genes were mainly enriched in the Hippo signaling pathway, pancreatic cancer, EGFR tyrosine kinase inhibitor resistance, AGE-RAGE signaling pathways in diabetic complications, Hepatitis B, proteoglycans in cancer, cell cycle, and several cancer-related pathways. These data indicated that miR-424-5p might play important roles in the malignant behavior of cancer. Among them, Hippo

signaling pathway affected the genesis and development of tumors by regulating cell proliferation, apoptosis and stem cell self-renewal ability.^{100,101} In addition, miR-424 regulates tumor proliferation and invasion processes by regulating EGFR. A research has revealed a wide range of role of EGFR via adding EGF to cultured HeLa cells to activate EGFR resulting in phosphorylation of 6600 sites in 2244 proteins.¹⁰² After ligand binding, the intracellular tyrosine sites of EGFR are phosphorylated, which consequently match to different signal transduction proteins to initiate different signal pathways.¹⁰³ The intricate signal transduction network play roles in tumor cell proliferation, metastasis and anti-apoptosis.¹⁰⁴ Therefore, overexpression or mutation of EGFR is closely related to the pathogenesis of cancer and the poor prognosis of patients.

In sum, miR-424 participates in downstream target genes through regulation, and then plays an important role in the malignant behavior of cancer. If we can further clarify the relationship between miR-424 and downstream pathways and the mechanism of action between pathways, we will clarify the potential molecular mechanism of miR-424 involved in regulating the occurrence and development of malignant tumors. It will be beneficial to tumor diagnosis and treatment. Next, we carried out the construction of ce-network (Figure 1B), combined with the above review and network diagram, we clearly found that miRNAs in organisms not only play a regulatory role on downstream target genes at the post-transcriptional level, but also their expression and function are affected by

Table 2 The Function of the Upstream Genes of miR-424 in Difference Cancers

Cancer	Upstream Genes	Function	Reference
Ovarian cancer	<i>Long Non-Coding RNA LINC00511</i>	proliferation and invasion	[83]
Cervical cancer	<i>Small nucleolar RNA host gene 12 (SNHG12)</i>	proliferation, apoptosis, migration and invasion	[84]
Ovarian cancer	<i>Long Noncoding RNA CCAT2</i>	proliferation and apoptosis	[85]
Cervical cancer	<i>lncRNA PVT1</i>	proliferation, colony formation, migration and invasion	[86]
CSCC	<i>lncRNA BLACAT1</i>	migration and invasion	[87]
Gastric cancer	<i>Long non-coding RNA NNTAS1</i>	tumorigenesis and cell cycle	[88]
HCC	<i>Long Non-Coding RNA LINC00511</i>	nodal metastasis, vascular invasion and clinical stage	[89]
HCC	<i>Long noncoding RNA DLX6-AS1</i>	proliferation, migration and invasion	[90]
NSCLC	<i>Long Non-coding RNA PVT1</i>	proliferation, invasion, apoptosis and proliferation	[91]
NSCL	<i>Long non-coding RNA LINC00641</i>	proliferation and apoptosis	[92]
Glioma	<i>lncRNA CCAT2</i>	chemoresistance	[93]
Glioma	<i>lncRNA CCAT2</i>	angiogenesis	[94]
Glioma	<i>lncRNA PVT1</i>	migration and invasion	[95]
Neuroendocrine tumor	<i>lncRNA XIST</i>	proliferation, migration, invasion and apoptosis	[96]
Infantile hemangioma	<i>lncRNA-MALAT1</i>	proliferation, apoptosis, migration and invasion	[97]
Gastric cancer	<i>Circular RNA LARP4</i>	proliferation and invasion	[98]
Osteosarcoma	<i>Circular RNA LARP4</i>	chemoresistance	[99]

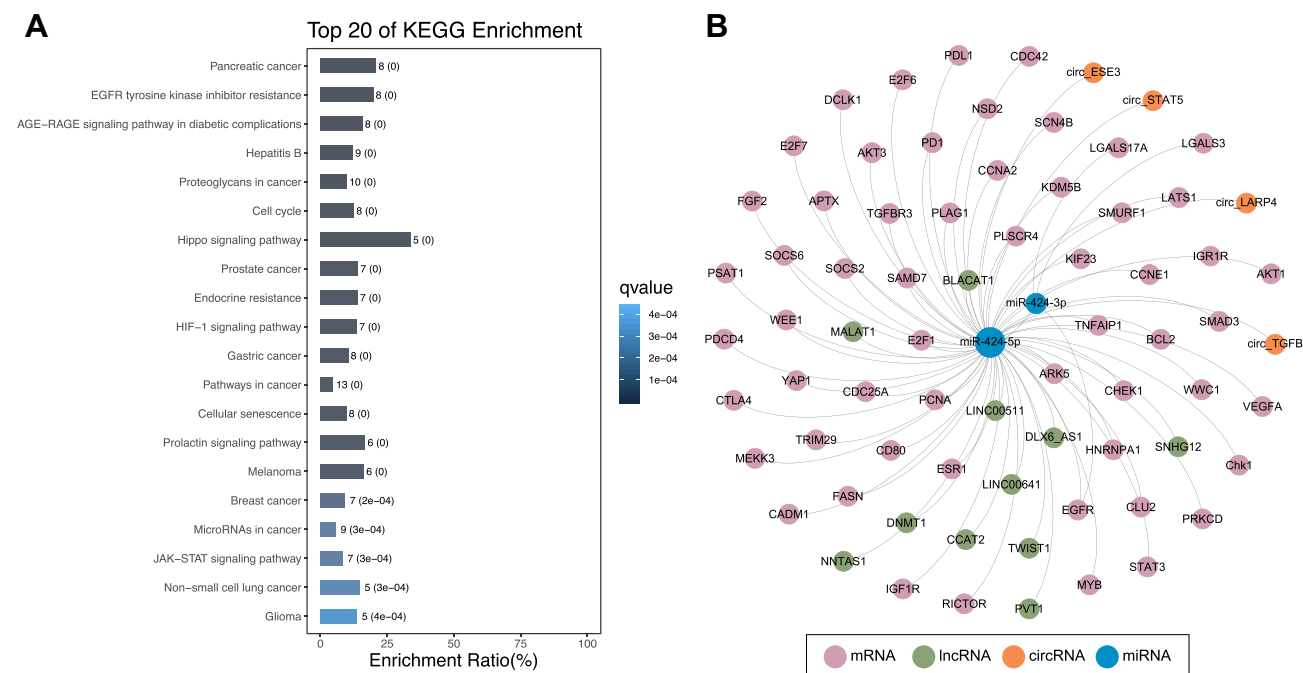


Figure 1 (A) KEGG analysis showing the number of transcripts mapped to the function involved in the target genes of miR-424. The 20 KEGG pathways most strongly enriched by functional-related gene groups. (B) The competing endogenous RNA network of cirRNA/lncRNA-microRNA-mRNA. The pink dots represent target genes of miR-424. The green dots represents lncRNA, while the orange dots diamonds represent cirRNA. The blue dots represents the miR-424-5p or miR-424-3p.

multiple signal transduction pathways and transcription factors. The regulatory relationship between them is related to each other through a complex linear relationship of point-to-multipoint divergence or multipoint-to-point convergence. The body constitutes a network-type deployment control to play its corresponding physiological or pathological role.

Discussion

In recent years, the role of miRNA in the occurrence, development, and diagnosis of diseases has attracted considerable attention, and evidence for the association between miRNA and the occurrence and development of tumors is only increasing. In line with this, miR-424 has been a hotspot in the field of cancer research, and evidence shows that it is closely related to the biological processes of tumor cell proliferation, migration, invasion, and apoptosis, as well as tumor occurrence, development, diagnosis and treatment, chemosensitivity and recurrence monitoring, prognosis assessment, and viral infections. We employed the use of bioinformatics to show the KEGG pathway of miR-424 based on the reported mRNA reported in the literature, as well as the competing endogenous RNA network of cirRNA/lncRNA-microRNA-mRNA. miR-424 can act as either a cancer-promoting factor or a tumor

suppressor. miR-424 regulates multiple mRNAs and affects multiple signal transduction pathways, while the target genes regulated by miRNA in different microenvironments are also different. The multiple target gene pathways are related to each other, and the relationship is extremely complex. Therefore, further studies are needed to clarify the precise function of miR-424 in tumors. In order to reduce the side effects of miRNA binding to other targets during cancer treatment, it is necessary to develop highly specific miRNA. In addition, to ensure that the drug can function safely and effectively after reaching the body, the design of the drug carrier needs to be continuously improved and perfected. In view of the potential value of miR-424 in the clinical application of cancer, future applied research needs to further explore the application value of miR-424 in the prevention, diagnosis, prognosis, and targeted therapy of malignant tumors. This will ultimately lead to more promising treatment opportunities for accurate diagnosis and safe and effective options for the long-term treatment of patients with tumors.

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Disclosure

The authors report no conflicts of interest in this work.

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