The role of miRNA-424 in various cancers: Focusing on drug resistance and sensitivity

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Abstract

Background

However, advanced technologies have been developed in the treatment of various cancers, but the mortality rate from cancer is still very high. Drug resistance is a major problem for patients with cancer, which causes the treatment process to fail. In addition to inhibiting drug resistance, targeted therapy is also very important in treatment.

Main body:

Nowadays, miRNAs have gained increasing interest as they play a major role in both drug resistance and targeted therapy. MicroRNA (miRNA) is an important part of non-coding RNA that regulates gene expression at a post-transcriptional level. The prevailing studies about miRNA expression have been expanded into a variety of neoplasms. MiR-424 targets genes involved in various cellular processes and can participate in proliferation, differentiation, apoptosis, invasion, angiogenesis, and drug resistance and sensitivity.

Conclusion

In this study, we focus on the role of miR-424s in many cancer types by displaying the potential target genes associated with each cancer, as well as briefly describing the clinical uses of miR-424s as a diagnostic and predictive tool in malignancies.

1. Introduction

Cancer is the second leading cause of death in the world. There were an estimated 18.1 million cancer cases around the world in 2018, of these 9.5 million cases were in men and 8.5 million in women. The highest prevalence of cancers is related to lung cancers (11.6%), breast cancers (11.6%), prostate cancers (7.1%), and colorectal cancers (6.1%). About 50% of cancers can be treated before the onset of clinical symptoms due to rapid diagnosis. There have been many successes in the diagnosis and treatment of cancer in recent years (1). Damage to healthy cells during chemotherapy and resistance to chemotherapy drugs are major problems in the treatment of this disease. So targeted therapy and reduction of drug resistance are the most important reasons for successful cancer treatment (2). One of the factors involved in both targeted therapy and reduction of drug resistance is microRNA. MicroRNAs are small, single-stranded, untranslatable RNAs and have between 18–24 nucleotides whose function is to bind the 3' UTR region of their target gene and regulate its expression by impairing the translation. miRNAs are important regulators in diverse biological processes of cancer, such as cell proliferation, apoptosis, angiogenesis, cell differentiation, adhesion and metastasis (3, 4).

1.2 Properties and functions of miR-424

miR-424 is a member of the family of miR15/107. Members of this family have AGCAGC sequences in the Seed area and are involved in the cell division, apoptosis, stress responses, and cancer. miR-424 or its autologous miR-322 and miR-503 are encoded as a cluster by H19X on the Xq2603 chromosome. miR-424 is involved in cell cycle regulation, EMT, differentiation, hypoxia, proliferation, apoptosis, invasion, angiogenesis, and drug resistance and sensitivity. Transcription factor PU1 is one of the inducers of miR-424 (3). In this study, we looked at the role of miR-424 in a variety of cancers and described the target genes of miR-424 and we have specifically focused on its role in drug resistance and sensitivity.

2. Drug Resistance Or Sensitivity And Micrornas

Drug resistance is a major problem in patients with advanced cancer. It is the cause of 90% of deaths in patients who are resistant to chemotherapy drugs. MicroRNAs can play a role in drug resistance or sensitivity by targeting genes that are effective in responding to chemotherapy drugs. Another way that microRNAs can affect drug resistance and sensitivity is survival and

apoptosis signaling pathways and drug transport routes (5). The function of miR-424 in tumor inhibition or tumor induction as well as in drug resistance and sensitivity in a variety of cancers is listed.

3. Target Genes Of Mir-424 And Its Role In Drug Resistance And Sensitivity In Various Cancers

According to multiple studies and investigations, miR-424 plays a vital role in various cancers. (Fig. 1) and (Table 1)

Table 1
Expression of miR-424 and its target genes and its effect on malignancies

Related cancer	Expression of miR	Target gene	mechanism	Type of study	Case of study	P_{value}	References
Endometrial Carcinoma	Decrease in tissues with high differentiation	E2F6	Inhibit EMT by overexpression of E-cadherin	In vitro	Human endometrial cancer tissue And Endometrial cancer cell lines	P < 0.05	(52)
Endometrial Carcinoma	-	E2F7	Arrest S phase of cell cycle and inhibit proliferation	In vitro	Human endometrial cancer tissue And Endometrial cancer cell lines	P < 0.05	(53)
Endometrial Carcinoma	-	MMSET	Targeting of MMSET inhibit Twist1 and inhibit EMT	In vitro	Human endometrial cancer tissue And Endometrial cancer cell lines	P < 0.05	(54)
Cutaneous Melanoma	Decease	PDGRα CXCL10/IP-10	Promote mucosal defense and inhibit proliferation	In vitro	Cell lines	P < 0.05	(55)
Esophageal Squamous Cell Carcinoma	Increase due to connection of E2F1 to miR-424	PRKCD	Inhibit proliferation by reducing of P21 and inhibit transition G1/S	In vitro And In vivo	Clinical specimens And Cell lines	P < 0.05	(56)
Esophageal Squamous Cell Carcinoma	-	WEE1	Inhibit CDC2 and transition G2/M	In vitro And In vivo	Clinical specimens And Cell lines	P < 0.05	(56)
Gastric Cancer	increase	LATS1	Promote GC growth and invasion	In vivo	Gastric cancer patients	P = 0.04	(19)
Gastric Cancer	-	$circLARP_4$	Increasing LARP4 reduce miR-424 and have tumor suppression by regulation miR424/LATS1/YAP signaling	In vivo And In vitro	Gastric cancer patients And Cell line	P = 0.04	(19)

Related cancer	Expression of miR	Target gene	mechanism	Type of study	Case of study	P_{value}	References
Gastric Cancer	-	NNT-AS1	Inhibition of NNT-AS1 inhibit cell cycle in G0/G1 phase due to decreasing CDK6. CyclinE1.D_1	In vivo And In vitro	Patient samples And cell line	P < 0.1	(20)
Gastric Cancer	-	SMURF1	Increasing of SMURF1 due to reduction of miR-424 result in drug resistant	In vitro	Gastric cancer microarray dataset GSE86195	P < 0.05	(21)
Hepatocellular Carcinoma	Decrease	AKT3/E2F3	Targeting AKT3/E2F3 repress cell cycle/E2f signaling	In vivo And In vitro	Mouse And Cell line	P < 0.05	(31)
Non-Small Cell Lung Cancer	Decrease	LYPLA1	LYPLA1 interact with CD95 so inhibition of that can induce apoptosis	In vitro	Cell line	P < 0.05	(27)
Non-Small Cell Lung Cancer	-	TNFAIP1	TNFAIP1 is a tumor inhibitor so inhibition of that increase migration and invasion	In vitro	Cell line	P < 0.05	(29)
Glioma	Decrease	PVT1	PVT1 connect to miR424 and suppress that can control cell growth	In vitro	Human glioma tissues And Cell line	P < 0.05	(34)
Colorectal Cancer	Decrease	AKT3 PSAT1	Reduce proliferation and induce apoptosis	In vitro And In vivo	Human CRC samples And Cell line And mouse	P < 0.05	(57)
Osteosarcoma	Decrease	FASN	Decrease activity of this enzyme limits migration and invasion	In vitro	Cell line	P < 0.05	(22)
Osteosarcoma	-	Cyclin A2 CCNA2	Inhibits cell cycle	In vitro And In vivo	Mouse And Cell line	P < 0.05	(23)

Related cancer	Expression of miR	Target gene	mechanism	Type of study	Case of study	P_{value}	References
Ovarian carcinoma	Increase	-	Increasing of miR-424 in LDH + cell line is associated with chemo resistant	In vitro In vivo	Ovarian carcinomas patients And Cell line	P = 0.05	(39)
Epithelial Ovarian Cancer	Decrease	CCAT2	CCAT2 is oncogene with poor prognosis	In vitro	Tissue Sample And Cell line	P < 0.05	(58)
Ovarian Clear Cell Carcinoma	Decrease	DCLK1	Knockdown of DCLK1 inhibits tumor growth	In vitro And In vivo	Mouse And Tissue of patient And Cell line	P < 0.05	(59)
Pancreatic cancer	Increase	SOSC6	Induce growth, invasion, migration with inhibiting SOSC6	In vitro	Cell line	P < 0.05	(60)
Papillary thyroid carcinoma	Increase	BCL2	Targeting BCL2 are associated with high-risk	In vitro	TCGA data access	-	(61)
Prostate cancer	Increase	COPI	Targeting COPI increase STAT3 and STAT3 have important role in tumor progression	In vitro And In vivo	Tissue pf patients And Mice And Cell line	P < 0.05	(51)
Prostate cancer	-	PD1-PDL1 CTALA4-B7.1/2	Increase immune response	In vivo	Radical prostatectomy specimens	P < 0.01	(62)
Tongue Squamous Cell Carcinoma	Increase	TGFß3	Promote EMT	In vivo In vitro	Tissue samples And Cell line	P < 0.05	(63)
Renal Cancer	Decrease	WEE1	Targeting WEE1 inhibit transition of G2/M	In vitro	Cell line	P < 0.05	(64)

Related cancer	Expression of miR	Target gene	mechanism	Type of study	Case of study	P_{value}	References
Bladder cancer	Increase in cells that DNMT1 inactivated	EGFR	Inhibit EMT	In vitro And In vivo	Tissue specimens And Cell line And mice	P < 0.05	(37)
Breast Cancer	Increase	CDK1 YAP ERK1/2	Control cell cycle	In vitro	Tissue of patient And Cell line	P < 0.05	(10)
Breast Cancer	-	CCND2 CDK6 CDC25A CHK1	Inhibit proliferation	In vitro And In vivo	Mice And Cell line	P < 0.05	(11)
Breast Cancer	-	SMAD7 SMURF2	SMAD7 SMURF2 are regulator of TGFß pathway	In vitro	Clinical specimens And Cell line	P < 0.05	(14)
Cervical cancer	Decrease	CUL2	CUL2 is E3 ubiquitin ligase induce proliferation by transition G1/S	In vitro	Human cervical biopsied tissue specimens And Cell line	P < 0.05	(65)
Cervical cancer	-	PVT1	Inhibiting of PVT1 inhibit proliferation	In vitro	Cell Lines And Tissues Samples	P < 0.05	(66)
Cervical cancer	-	RBBP6	Targeting RBBP6 result in not binding of P53/RB1 so inhibit proliferation	In vitro	Patient sample And Cell line	P < 0.05	(67)
Cervical intraepithelial neoplasia	Increase	APTX	Targeting APTX increase sensitivity of radiotherapy resistant cell line	In vitro	Cell line	P < 0.05	(68)
Hemangioma	Decrease	VEGFR2	Inhibit phosphorylation of AKT, ERK so inhibit cell growth	In vitro	Hemangioma specimens	P < 0.05	(69)

Related cancer	Expression of miR	Target gene	mechanism	Type of study	Case of study	P_{value}	References
Senile Hemangioma	Decrease	MEK1 Cyclin E1	Limit cell growth	In vitro	Skin specimens	P < 0.05	(70)
Infantile Hemangioma	Decrease	MALAT1	Restrain c-MYC, cyclin D1,BCL2 and increase apoptosis	In vitro And In vivo	Tissue Specimens And mice	P < 0.05 And P < 0.01	(71)
Infantile Hemangioma	-	FGF/FGFR1	Inhibit phosphorylation of ERK1/2 and stop migration and invasion	In vitro	Tissue specimen	P < 0.05	(72)
Acute myeloid leukemia	Decrease	PLAG1	Sensitize cell into TRAIL-induce apoptosis	In vitro	Patients' blood	P < 0.02	(46)
Acute myeloid leukemia	-	miR-9	Induce differentiation in THP1 cell lines	In vitro	Cell line	P < 0.05	(47)
Chronic myeloid leukemia	Decrease	ABL/BCR	Induce apoptosis and inhibit proliferation and sensitize cells to imatinib	In vitro	CML cell lines And Patient samples	P < 0.02	(48)
Chronic lymphocytic leukemia	Decrease	PLAG1	PLAG1 has important role in pathogenesis of CLL	In vitro	Patients' blood And Cell line	P < 0.02	(73)
Diffuse large B-cell lymphoma	Increase	SIAH1	SIAH1 is a E3-ubiquitous ligase located down-stream of P53 and it has anti-tumor function	In vitro	Patients tissue And Cell line	P = 0.0430	(74)
Non-Small Cell Lung Cancer	Decrease	YAP1	YAP1 sensitize cisplatin resistant	In vitro	Clinical Tissue Samples And Cell line	P < 0.01	(26)
Head and Neck Squamous Cell Carcinoma	Increase	-	Increase response as a biomarker	In vitro	Data acquisition	P < 0.05	(75)
Endometrial Endometrioid Adenocarcinoma	Decrease by methylation of its promotor	CDC14A CDC25A CDK6	Inhibit proliferation	In vitro	Patient tissue	P < 0.05	(76)

Related cancer	Expression of miR	Target gene	mechanism	Type of study	Case of study	P_{value}	References
Cervical Cancer	Decrease	KDM5B	Blocking KDM5B stop Notch pathway so stop growth and induce apoptosis	In vitro	Tissues sample And Cell line	P < 0.05	(77)

3.1 The effect of miR-424 in drug resistance and sensitivity of breast cancer

The most common cancer diagnosed among women around the world is breast cancer. After lung cancer, breast cancer is the second leading cause of death among women. Epigenetic events as well as miRNA expression are the master regulators of tumorigenesis and add a further layer to the complexity of breast cancer pathogenesis. Studies show that miR-424 is highly expressed in breast cancer patients compared to healthy people and can discriminate early-stage breast cancer patients from healthy controls. This study was performed on humans with $P < 0.0001$ (6, 7). Even the presence of miR-424 in urine helps to differentiate between patients and healthy individuals. This study has 98.6% sensitivity and 100% specificity (8, 9). Regarding the role of miR-424 in cell proliferation, it has been shown that miR-424 has an inhibitory role in cell proliferation by inhibiting CDK1 and YAP from the Hippo pathway and inhibiting p-ERK1/2 from the ERK pathway (10). MiR-424 levels in breast cancer cells that express TRb (thyroid receptor) are increased by the T3 hormone and targets of that like CCND2, CDK6, Cdc25, E2F3, c-Myb and CHK1 that all of them involved in proliferation are declining (11). However, in breast cancer patients with a negative lymph node that constitutes 60% of all breast cancer cases, it has been shown that there is no association between proliferation and miR-424(12). Hyperglycemic conditions reduce miR-424 and the inhibitory effect of miR-424 is removed from cdc42 in this way, STAT5 is activated and causes the expression of Prdm14 gene. Increased Prdm14 expression is associated with invasion and poor prognosis (13). MiR-424 increases metastasis by targeting Smad7 and Smurf2 because these are two negative regulators of the TGFß pathway. Binding of TGFß to its receptors is one of the signaling pathways involved in metastasis ($P < 0.05$) (14). Another role of miR-424 is inhibition of CDC25A, BCL2, IGF1R genes. Increased expression of these three genes is associated with a poor prognosis (15). Some chemotherapy drugs, such as paclitaxel (PTX), 5-fluorouracil (5-FU), doxorubicin/adriamycin (DOX), fulvestrant, taxol and cisplatin are used to treat breast cancer, but most of them may eventually lead to chemoresistance and treatment failure (5). Mir-424 sensitizes cells to a variety of anticancer drugs by targeting Bcl2 and IGF1R and sensitize cell to cisplatin by targeting WEE1 and Chk1 (11, 15). Studies have shown that in Fulvestrant-resistant cell lines miR-424 level is reduced therefore, it may be possible to reduce the resistance by increasing the level of miR-424 (16). Also, miR-424 sensitizes breast cancer cells to taxol by targeting P53, caspase 3 and Bcl2 (17). All of this resistance is to chemotherapy drugs.

3.2 The effect of miR-424 in drug resistance and sensitivity of gastric cancer

Gastric Cancer is one of the most common and lethal malignancies worldwide (18). The survival time in these patients is 5 years. Because of the high rates of postsurgical recurrence and metastasis, the prognosis of GC patients diagnosed as advanced-stage is pessimistically bad (19, 20) There are many signaling pathways that play a role in the onset and progression of cancers. The Hippo pathway plays an important role in cell growth and metastasis and LATS1 (Large tumor suppressor kinase 1) is one of the main members of this pathway. CircRNAs are a type of ncRNAs that controls gene expression. CircLARP4 is a type of circRNAs that in normal cells LARP4 is high and decreases miR-424. Finally, LATS1 increases and YAP pathway decreases. But in gastric cancer, the opposite happens. CircLARP4 may function as a tumor suppressive factor in GC via regulation of miR-424/LATS1/YAP signaling pathway ($P = 0.04$) (19). LncRNANNT-AS1 is a type of lncRNA (Long- non-coding RNA) that has a high expression in GC and this high expression is accompanied by a bad prognosis. LncRNAs are involved in regulating gene expression and can activate or suppress gene expression through a variety of mechanisms (20). NNT-AS1 has been found to act as oncogene in human cancer and is a powerful cell cycle regulator through the miR-424/E2F1. LncRNANNT-AS1 inhibition inhibits the cell cycle in the G0/G1 phase and also inhibits tumor proliferation and invasion. NNT-AS1 connects to the miR-424

and NNT-AS1/miR-424 targeted E2F1 in the cycle progression regulation of GC cells. E2F1 is an important transcription factor in regulating cell cycle and apoptosis ($P < 0.1$) (20). MiR-424 is involved in the drug resistance of GC patients who are being treated based on platinum chemotherapy drugs. One of the target genes of miR-424 is SMURF1, which belongs to the NEDD4 family and is involved in ubiquitinase activity. In patients who resistance to cisplatin, the reduction of miR-424 increased the SMURF1, and it also stimulated the RhoA. RhoA belongs to the Rho GTPase family and many studies have shown that it plays a role in drug resistance (21). Another study showed that a decrease in miR-424-3p prevents an increase in ABCC2 and leads to drug resistance and tumor progression and the opposite of privous results was obtained by Yon gyuan et al. who showed that both *in vivo* and *in vitro* overexpression of miR-424-3p play an important role in the resistance of gastric cancer cells to cisplatin ($P < 0.01$) Cisplatin is a chemotherapy drug (18).

3.3 The effect of miR-424 in drug resistance and sensitivity of osteosarcoma

Osteosarcoma (OS) is one of the most common bone cancers in childhood and adolescence. Despite advancements in aggressive OS treatment, the prognosis has not significantly improved, and thus there is a need for alternative molecular therapies (22, 23). In OS, members of the miR-16 family, including miR-424, are declining and one of the most important goals of mir-424 in this malignancy is FASN (Fatty Acid Synthase) enzyme. This enzyme is involved in the catalysis of long-chain fatty acids and is expressed in many cancers. Decreased activity of this enzyme limits the growth of cancer cells and invasion and migration. FASN is one of the targets of miR-424 so maybe miR-424 stops the growth of cancer cells by inhibiting this enzyme. Other targets of this miRNA, such as CDC25A, CCNA2, CCNE1, are decreased but overexpression of miR-424 significantly decreased cyclinA2 expression (22, 23). In creating resistance in OS an lncRNA called LINC01116 has major role. LINC01116 inhibits the miR-424-5p expression by connecting to EZH2; thereby enhancing doxorubicin resistance osteosarcoma cells (24). TFAP2C (Transcription factor activating protein 2 gamma) increases the expression of lincRNA (Long intergenic non-coding RNAs) LINC00922 in doxorubicin-resistant osteosarcoma. LincRNAs have emerged as tumor promoters and suppressors. LINC00922 also acts as a sponge of miR-424-5p. The formation of a reinforcing loop TFAP2C/LINC00922/miR-424-5p reduces the resistance to doxorubicin (25). Doxorubicin is a chemotherapeutic drug used to treat a variety of cancers.

3.4 The effect of miR-424 in drug resistance and sensitivity of non-small cell lung cancer (NSCLC)

The first common cancer in the world is lung cancer. Non-small Cell Lung Cancer (NSCLC) is a type of lung cancer whose survival time is only 15%. NSCLC accounts for approximately 85% of lung cancer cases (26, 27). One of the chemotherapy treatments is based on cisplatin drugs (28). But drug resistance has limited this method. miR-424-3p and miR-424-5p decrease in lung cancer. Both of them can control the cell growth, migration and invasion. miR-424-3p targets YAP1 (Yes-associated protein 1) protein. YAP1 was pronouncedly up-regulated in NSCLC tissues. High expression of YAP1 was significantly associated with poor overall prognosis. miR-424-3p sensitizes chemotherapy-resistant cells to paclitaxel by targeting YAP1. miR-424-5p does not have this capability. MiR-424-3p increases the level of Bax but reduces the Bcl2 level so it can increase apoptosis ($P < 0.01$) (26). Acyl Protein Thioesterase 1 that also called lysophospholipase 1 (LYPLA1) is a cytosolic enzyme that is capable of catalyzing depalmitoylation targeted by miR-424. LYPLAs can interact with CD95 to stimulate depalmitoylation, thereby regulating apoptosis through CD95. So inhibition of LYPLA1 inhibits growth of cells, invasion and migration (27). Zhanga and his colleagues achieved the opposite result other target genes of miR-424 include TNFAIP1 (Tumor Necrosis Factor alpha-induced protein 1). TNFAIP1 is a tumor inhibitor in lung cancer through involvement in DNA synthesis and apoptosis. By inhibiting TNFAIP1, miR-424 increases migration and invasion and cell growth (29).

3.5 The effect of miR-424 in drug resistance and sensitivity of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the second most common cancer in males and the sixth most common cancer in females. It has a poor prognosis due to its high cell migration and invasion, resulting in more than 695,000 deaths per year. Hepatocellular carcinoma had lower levels of miR-424 ($P < 0.05$), as well as its expression is negatively associated to Ki-67 (30). Ki-67 protein is widely used as a biomarker for cell proliferation and is closely linked to cell proliferation. MiR-424 suppresses HCC development

by repressing cell cycle/E2F signaling by directly targeting Akt3 and E2F3. Akt3 was found to control cyclin D and GSK3, whereas miR-424 and E2F3 were found to regulate cyclin E, c-Myc, and Cdc-2 ($P < 0.05$) (31). Recurrent tumors in patients following liver transplantation (LT) have been shown to reduce the expression of miR-424. MiR424 expression is a useful biomarker for predicting tumor recurrence in patients with HCC after LT, according to the gathered data ($P = 0.029$) (32). MiR-424 levels in HCC cells that express TRb (thyroid receptor) are increased by the T3 hormone and targets of miR-424 like E2F3, CHK1, Cdc25, CDK6, c-Myb, and CCND2 that are all involved in proliferation are declining (11). The first line of treatment for HCC patients, is chemotherapy with Sorafenib. Resistance to sorafenib is one of the problems facing these patients. The protein associated with drug resistance in this patient is CBX4 (choromobox homolog 4). CBX4 is a polycomb protein and has high expression and poor prognosis in HCC patients but miR424 reduces CBX4 expression and causes drug sensitivity. Surafenib is an immunotherapy treatment (33).

3.6 The effect of miR-424 in drug resistance and sensitivity of glioma

One of the most common cancers of the central nervous system is glioma. Approximately 15% of patients die within a year after being diagnosed. (34, 35). One of the genes involved in the molecular mechanism of glioma is PVT1 (Plasma-cytoma variability translocation 1). The expression of PVT1 is increased in glioma and the expression of miR-424 is decreased in glioma tissue. In glioma cells, Han et al. discovered a significant negative relationship between PVT1 and miR-424 expression. The expression of miR-424 is increased when PVT1 is inhibited. PVT1 knockdown, in brief, might alter the development of human glioma cells in vivo via the PVT1–miR-424 axis. (34). Jin etal. found miR-424 expression was significantly down-regulated in glioma tissues. miR-424 methylation eliminates the anti-tumor effects of that but, azacitidine therapy induces the expression of miR-424 and it controls cell growth by increasing apoptosis (35). CCAT2, a type of lncRNA, causes glioma cells to become resistant to chemotherapy drugs it does this by destroying the normal function of miR-424 (36).

3.7 The effect of miR-424 in drug resistance and sensitivity of bladder cancer

One of the most serious health problems is bladder cancer. About 70% of patients with non-muscle-invasive tumors had a satisfactory prognosis, whereas the remaining 30% of the total of patients having muscle-invasive tumors had a poor five-year survival rate. MiR-424 inhibits EGFR and inhibition of EGFR inhibits proliferation and EMT through AKT and MDM2 / P53 pathway. MiR-424 is increased in bladder cancer that DNMT1(DNA methyltransferases) have inactivated. Thus, DNMT1 has a regulatory role on miR-424 ($P < 0.05$) (37). One of the important drugs used in bladder cancer treatment is cisplatin, but miR-424 causes resistance by targeting UNC5B and SIRT4 (38).

3.8 The effect of miR-424 in drug resistance and sensitivity of ovarian carcinoma

Ovarian carcinoma (OC) is one of the cancers that eventually leads to death about 70% of patients. Many patients with advanced stages of this cancer are resistant to standard chemotherapy drugs, and as a result, not only will the treatment be ineffective, but the disease will return and finally kill them. MiR-424 expression is increased in cell lines that are ALDH (+) and resistant cell lines. This indicates that miR-424 and ALDH are associated with resistance (39). In another study, the opposite of the previous result was proven. In ovarian cancer, galectin 3 inhibits the apoptosis of cancer cells and causes drug resistance but miR-424-3p reduces its expression by targeting galectin 3. So reduces resistance and increases sensitivity to cisplatin (40).

3.9 The effect of miR-424 in drug resistance and sensitivity of cholangiocarcinoma

Cholangiocarcinoma (CCA), or bile duct cancer, begins when healthy bile duct cells change and grow out of control and form a tumor. This malignancy is diagnosed in approximately 8,000 new cases each year in the United States, mostly in people over 70 years of age (American Cancer Society). 5-year survival rate of cholangiocarcinoma is between 2–30% (41). Cholangiocarcinoma can be classified into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) subtypes according to the anatomical location. Among them, pCCA (50%) and dCCA (40%) represent the majority of cholangiocarcinoma cases, while iCCA is less than 10% of total. In iCCA, ARK5 expression is high, which causes metastasis in these patients. But miR-424-5p prevents EMT and metastasis

by targeting ARK5 ($P < 0.0001$) (42). Chemotherapy with cisplatin and gemcitabine is the first line of treatment for CCA patients. But it has been found that a lncRNA called LIN00665 makes these cells resistant to gemcitabine. LIN00665 does this by regulating miR-424-5p / BCL9L eventually the Wnt/ß-catenin pathway is activated and the EMT is upgraded ($P < 0.05$) (43).

4. Blood Malignancy

4.1 Role of miR-424 in drug resistance and sensitivity of acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) is a clonal and heterogeneous malignancy characterized by deregulated proliferation and inhibited differentiation of hematopoietic progenitors ($P < 0.05$) (44). NPM1 (Nucleophosmin 1) mutation is seen in 60% of CN-AML (Cytogenetics normal) cases and miR-424 levels are reduced in CN-AMLs that have the NPM1 mutation. This reduction indicates the role of miR-424 in leukemogenesis ($P < 0.05$) (45). Resistance to treatment is one of the most important factors in the failure of treatment of patients. TRAIL (TNF-related apoptosis-inducing ligand) belongs to the TNF family and is able to kill cancer cells. Cancer cells sometimes become resistant to TRAIL-induced apoptosis. MiR-424 levels decrease in TRAIL-resistant cells. It has been shown that an increase in miR424 level by targeting PLAG1 and inhibiting Bcl2 sensitizes cells into TRAIL-induced apoptosis (46). THP1 cell line with MLL-MLLT3 gene fusion has monoblastic phenotype and in this cell line maturation has stopped so inducing differentiation in this cell line can be helpful. MiR424 induces differentiation towards the monocyte by targeting miR-9. MiR-9 is a differentiation suppressor (47).

4.2 Role of miR-424 in drug resistance and sensitivity of chronic myeloid leukemia (CML)

Chronic myeloid leukemia (CML) is a biphasic hematopoietic stem cell (HSC) myeloproliferative disorder. Its main feature is ABL/BCR oncogene. The ABL-BCR gene fusion produces a protein that is an active tyrosine kinase that causes proliferation and reduction of apoptosis. Therefore, by inhibiting the activity of this tyrosine kinase, proliferation can be prevented and apoptosis can be induced. miR-424 targets ABL and induces apoptosis and inhibits proliferation. And also in this way it sensitizes cells to imatinib (48). Imatinib is an immunotherapy treatment. Another factor related to drug resistance CML patients is Cobll1, which increases in blast crisis. MiR-424 destroys drug resistance by targeting this agent (49).

5. Mir-424 And Stem Cell Properties

Increase in prdm14 due to decrease in cdc42 by miR-424 increases the activity of cancer stem cells in breast cancer (13). Reduction of miR-424 in cancer stem cells causes the migration of these stem cells in ovarian cancer (50). Targeting COPI by miR-424 increase STAT3 and STAT3 promotes cancer stem cell-like properties (51).

6. Future Perspective

As stated above miR-424 has been studied more in solid tumors. One of our hypotheses is the use of this microRNA in the treatment of leukemia patients. The most important mechanisms that can be used are to induce apoptosis and inhibit cancer cell proliferation. Forrest et al. Showed that increased expression of miR-424 induces cycle arrest in the G1 phase in THP1 cell line. Also, Oshrat Hershkovitz-Rokah and colleagues showed that miR-424 inhibits proliferation in the K562 cell line. MiR-424 induces these effects by acting on cell cycle regulators. Other effects of miR-424 in the treatment of leukemia include inhibition of expressed oncogenes. For example, LYPLAs increase expression in CLL and inhibit apoptosis by binding to CD95 so miR424 induces apoptosis by inhibiting LYPLAs. WEE1 is one of the genes that increase in AML and it is one of the miR-424 targets Therefore, by increasing the expression of miR-424, WEE can be inhibited and its effects can be prevented. We know that miR-424 has 4 methylated CpG sites and methylation reduces gene expression. Therefore, one of the ways to increase the expression of miR-424 is the use of hypomethylation drugs such as 5-Azacitidine. Has been shown using of azacitidine increase the expression of miR-127 and 149 in breast cancer it also increases the expression of miR-130 in ovarian cancer. AZA is monophosphated by the uridine cytidine kinase and then diphosphate and trisphosphates by pyrimidine monophosphate kinase and pyrimidine

diphosphate kinase, respectively. 3-phosphate AZA (5-aza-CTP) enters RNA. The introduction of 5-aza-CTP into RNA disrupts protein synthesis, which promotes apoptosis. A minority of this drug is converted to 5-aza-dCTP, the 3-phosphate form of decitabine, by the enzyme ribonucleotide reductase, and enters DNA during replication, binds to DNMT1, and inhibits this enzyme. Chun-Te Wu et al. Showed that expression of miR-424 increased in cancer cells that had DNMT inactivated. Therefore, the use of 5-AZA strongly increases the expression of miR-424 with the effect of hypomethylation and with inhibition of DNMT1. Therefore, azitidine and its analogue, decitabine, increase the expression of miR0424424 in the clinic. Another factor to increase the expression of miR-424 is the transcription factor PU1. PU1 is a transcription factor for Stem cell commitment to the monocyte lineage. This factor increases the expression of miR-424 by connecting to the miR- 424s promoter both in vitro and in vivo. Induction of hypoxia increases the expression of HIF1α. This factor binds to the GCGTC sequence of miR-424424 and increases its expression. These strategies are used clinically to increase miR-424 expression. To reduce the expression of miR-424, strategies such as inhibition of DNMT enzyme, inhibition of transcription factor PU1 by using siRNA and mutation at the binding site of miR424 to HIF1α can be used. In order to use miR-424 in the clinic according to the type of cancer and according to the selected treatment route. We can use the various features of miR-424 that described in detail above. For example, the properties of inhibiting proliferation, increasing apoptosis, inhibiting tumor migration, and decreasing drug resistance can be used. Due to the role of miR-424 in drug resistance or sensitivity in various cancers drug resistance can be eliminated by increasing or decreasing its expression.

7. Conclusion

microRNAs play a major role in tumorigenesis, proliferation, cell differentiation, apoptosis and metastasis. miR-424 plays a major role in important processes such as cell cycle, EMT, hypoxia, tissue differentiation, tumor onset and progression, and tumor inhibition. In this study, we showed that miR-424 exhibits different functions in different cancers by targeting different genes. Due to the fact that miR-424 has 4 CpG sites and is a hypermethylated microRNA it can be used to increase its expression and increase its function by using hypomethylating drugs such as 5-AZA or decitabine …And by targeting genes that play an oncogenic role in leukemia, it can play an important role in inhibiting cancer.

According to the above, miR-424 can inhibit proliferation in cancer cells by targeting cell cycle regulators such as cyclin E1, cyclin D2, cyclin D, cyclin A2, CDK1, CDK6, and CDC25A. Each of these plays an important role in cell cycle. E2F1 gene is also a regulator of cell cycle, which can be one of the important goals of miR-424 in reducing cell growth. on the other hand, could play an important role in increasing cancer cell death by targeting genes involved in apoptosis these genes include Bcl2 and Akt3. In relation to the role of miR424 in the treatment of cancers, we can mention the suppression of oncogenes. WEE1 and PLAG1 are genes that are overexpressed in blood cancers miR-424 by targeting these can play a role in cancer control. One of the important recent findings is the targeting of ABL-BCR in CML patients, which makes patients sensitive to imatinib. miR424 disrupts the junction between PD1-PDL1 and CTLA4-CD80 Eventually, the cells of the immune system will be able to fight the cancer cells more efficiently. MiR-424 is also involved in drug resistance, which can be eliminated by increasing or decreasing its expression according to the type of cancer. (Fig. 2)

Abbreviations

ABCC2, ATP binding cassette subfamily C member 2

ABL, Abelson proto-oncogene

AGO, Argonaut; AKT3

AKT serine/threonine kinase 3

ALDH, Aldehyde dehydrogenase

AML, Acute myeloid leukemia

APTX, Aprataxin; Bcl2, B-cell lymphoma 2

Bcl9l, B-cell CLL/lymphoma 9-like protein

BCR, Breakpoint cluster region

CCAT2, Colon cancer associated transcript 2

CCNA2, Cyclin A2

CCNE1, Cyclin E1

CCND2, cyclin D2

CDC25A, Cell division cycle

CDK, Cycle-dependent kinase

CHK, Checkpoint kinase

CML, Chronic myeloid leukemia

COP1, Constitutive photomorphogenic-1

CTAL4, cytotoxic T lymphocyte associated protein 4

CUL2, Cullin 2

DCLK1, Doublecortin like kinase 1

DGRC8, Digeorge syndrome critical region gene 8

EGFR, Epidermal growth factor receptor

EMT, Epithelial-mesenchymal transition

ERK, Extracellular signal-regulated kinases

EZH2, Enhancer of zeste 2 Polycomb repressive complex 2 subunits

FGF, Fibroblast growth factors

GSK3, Glycogen synthase kinase-3

IGF1R, Insulin-like growth factor 1 receptor

KDM5B, Lysine demethylase 5B

MALAT1, Metastasis associated lung adenocarcinoma transcript 1

MEK1, MAP (mitogen-activated protein) kinase/ERK (extracellular signal-regulated kinase) kinase 1

MMSET, multiple myeloma SET domain

MYB, Myeloblastosis

NEDD4, Neuronal precursor cell-expressed developmentally downregulated 4

PD1, Programmed cell death protein 1

PDGF-R, Platelet-derived growth factor receptors

PLAG1, Pleomorphic adenoma gene

Pre-miRNA, Precursor miRNA

Pri-miRNA, Primary RNA

PRKCD, Protein kinase C delta

PSAT1, Phosphoserine aminotransferase 1

RBBP6, Retinoblastoma binding protein 6

RISC, RNA-induced silencing complex

SIAH1, Siah E3 ubiquitin protein ligase 1

SIRT4, Sirtuin 4

Smad, Small worm phenotype, mothers against decapentaplegic

Smurf, Smad ubiquitination regulatory factor

STAT5, Signal transducer and activator of transcription 5

TGF-B, Transforming growth factor beta

TRBP, TAR RNA binding protein

TWIST1, Twist family BHLH transcription factor 1

UNC5B, Unc-5 netrin receptor B

VEGFR2, Vascular endothelial growth factor receptor 2

WEE, Western equine encephalitis

Wnt, Wingless and int-1

YAP, Yes-associated protein

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran

Consent for publication: Not Applicable

Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing Interests: The authors declare no conflict of interest.

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Author's contribution: Mohammad Reza Alivand and Saeed Solali designed the study. Fatemeh Najafı wrote the first draft of the manuscript. Shohreh Karimi, Bahareh Kazemi, Mahdi Derakhshani, Farahnaz Allahverdizadeh, and Sajjad Vakili gathered the

data. Saeed Solali and Mohammad Reza Alivand supervised the study. Zahra Foruzandeh and Farhad Seif revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

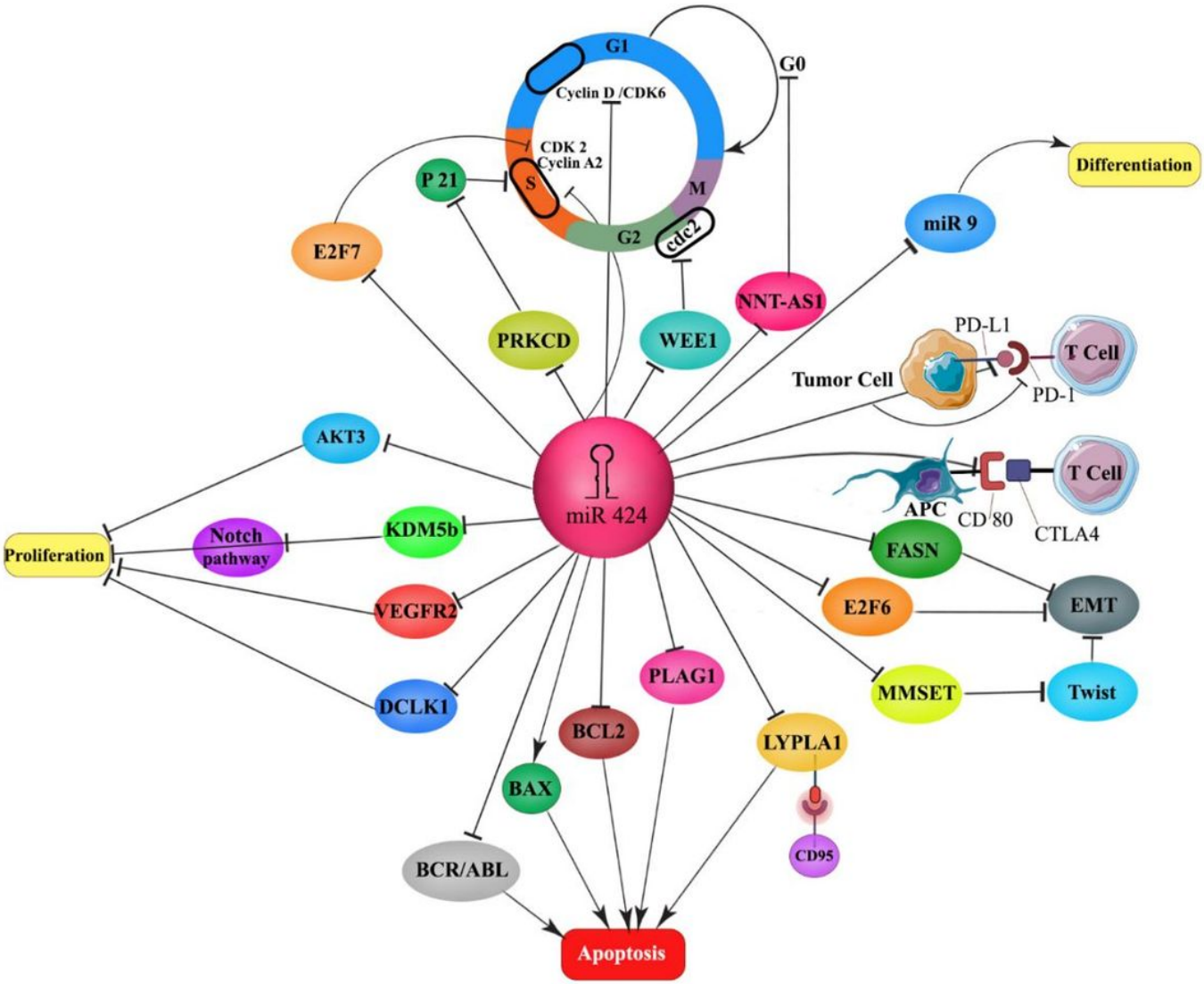

Figure 1

The role of miR-424 through inhibition or induction of various genes in inhibition of proliferation, cell cycle, EMT and induction of apoptosis and differentiation

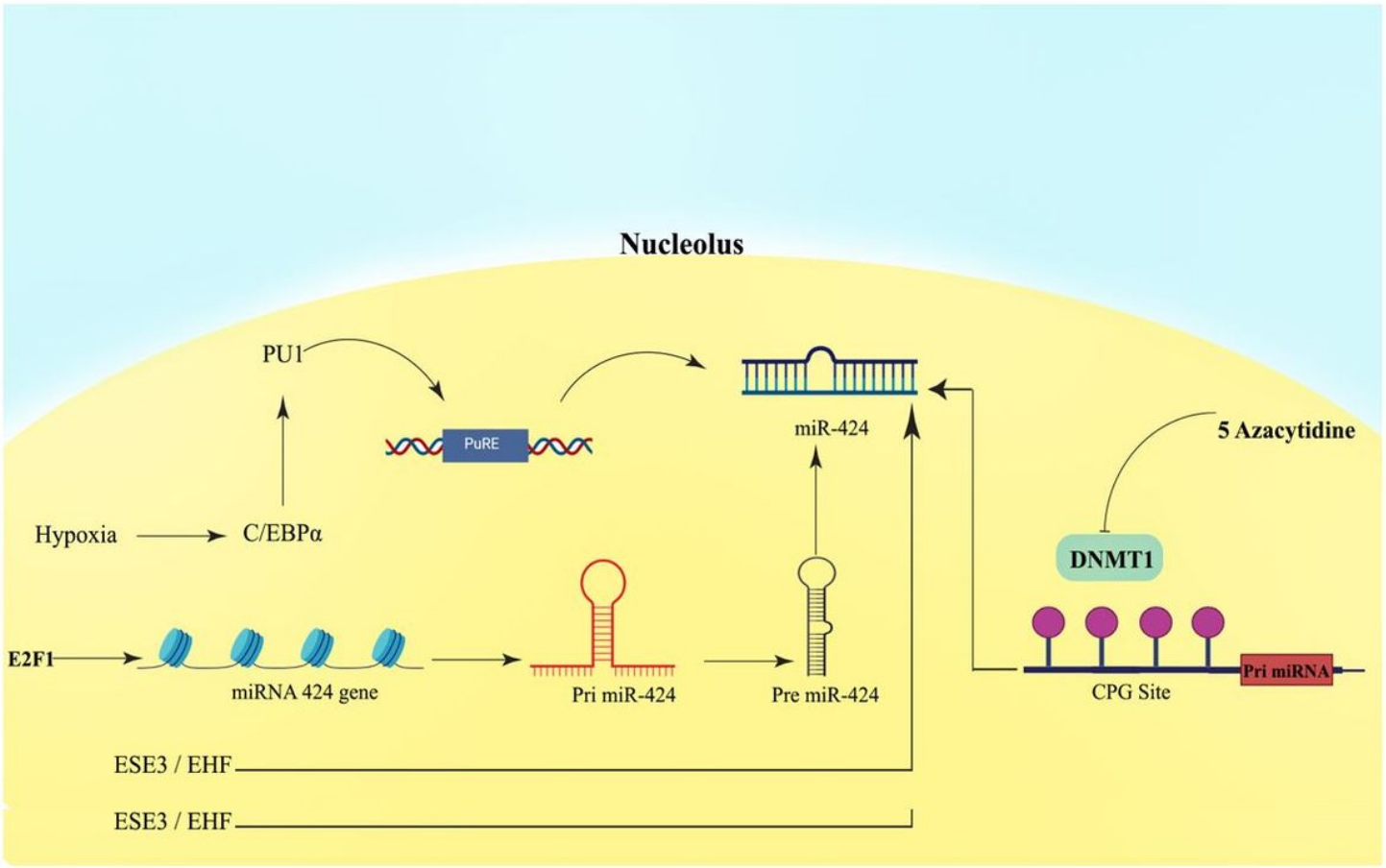

Figure 2

Internal and external factors that increase miR-424 expression.