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REVIEW

miR-451: A Novel Biomarker and Potential Therapeutic Target for Cancer

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Abstract: MicroRNAs (miRNAs) are endogenous, non-coding, single-stranded small RNAs involved in a variety of cellular processes, including ontogeny, cell proliferation, differentiation, and apoptosis. They can also function as oncogenes or tumor suppressor genes. Recent studies have revealed that miRNA-451 (miR-451) is involved in the regulation of various human physiological and pathological processes. Furthermore, it has been shown that miR-451 not only directly affects the biological functions of tumor cells but also indirectly affects tumor cell invasion and metastasis upon secretion into the tumor microenvironment via exosomes. Thus, miR-451 also influences the progression of tumorigenesis and drug resistance. This review summarizes the expression of miR-451 in various cancer types and the relationship between miR-451 and the diagnosis, treatment, and drug resistance of solid tumors. In addition, we address possible mechanisms of action of miR-451 and its potential application as a biomarker in the diagnosis and treatment of human cancers.

Keywords: MicroRNA, cancer, biomarker, therapeutic target, exosomes

Introduction

Although great progress has been made in cancer treatments over the past several years,[1,2] the overall survival rates for some types of cancers are still very low owing to metastasis, recurrence, and drug resistance. Therefore, the identification of diagnostic molecular biomarkers for early cancer detection and the development of targeted treatments are crucial.

Increasing evidence has confirmed that noncoding RNAs (ncRNAs) participate in both physiological and pathological processes, including cell development, differentiation, proliferation, and apoptosis. MicroRNAs (miRNAs or miRs), a subtype of ncRNAs, are a class of small, endogenous, highly conserved, single-stranded noncoding RNAs of approximately 22 nucleotides.[3] They may function as oncogenes or tumor suppressor genes, depending on the cancer type and physiological environment.[4,5] More than 2500 mature miRNAs have been identified in the human genome and recorded in the public miRBase database. Among these, more than 1000 regulate over 50% of protein-coding human genes, and each miRNA can control up to 100 gene transcripts. A single miRNA may regulate gene expression at both the transcriptional and posttranscriptional levels by binding to the 3′ untranslated region of hundreds of target messenger RNAs (mRNAs).[6] The identification of downstream target mRNAs is a major focus of miRNA research. Epigenetic and genetic alterations of miRNAs are common events in cancer progression. Therefore, miRNAs have significant promise as diagnostic, prognostic, and therapeutic cancer biomarkers.[7–10]

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miR-451 was first identified in the human pituitary gland in 2005 by Altuvia et al[11] The gene encoding this miRNA is located in human chromosomal region 17qll.2. miR-451 participates in multiple physiological and pathological processes, including hematopoietic system differentiation,[12] embryonic development, epithelial cell polarity,[13] and nervous system development.[14] It is dysregulated in multiple cancers and participates in numerous cancer-related biological processes, including proliferation, apoptosis, angiogenesis, epithelial-mesenchymal transition (EMT), drug resistance, and metastasis. It often acts as a tumor suppressor gene in cancers and modulates multiple pathways by targeting different downstream mRNAs.

In this review, we focus on the function of miR-451 in multiple cancer types and its underlying mechanisms. More importantly, we will discuss the potential of miR-451 as a biomarker for early cancer diagnosis and as a therapeutic candidate for the treatment of metastatic or recurrent cancer and to overcome drug resistance.

miR-451 Function by Cancer Type

In recent years, researchers have begun to employ gene-chip and second-generation sequencing technologies to detect the expression of miR-451 in patient-derived tumor tissues and body fluids and cancer cell lines, which revealed that miR-451 expression differs between cancers as well as sample types (eg, blood, saliva, or urine). miR-451 acts as a tumor suppressor gene in most cancer types, whereas in appendiceal mucinous cystadenocarcinoma[15] and pancreatic cancer,[16,17] it acts as an oncogene.

miR-451 and Lung Cancers

Lung cancer is the most common cancer type and the leading cause of cancer mortality worldwide, accounting for 12% of the total cancer cases and 18% of the total cancer deaths in 2018.[18] Lung cancers are classified as small-cell lung carcinoma (SCLC) or non-small-cell lung carcinoma (NSCLC), which accounts for approximately 85% of all lung cancers. In 2011, Wang et al[19] reported that miR-451 was the most strongly downregulated miRNA in 23 matched normal and NSCLC tumor tissues and that low miR-451 expression was correlated with poor tumor differentiation, advanced pathological stage, lymph-node (LN) metastasis, and shorter overall survival. Overexpression of miR-451 by transfection with a miR-451 mimic triggered apoptosis and inhibited proliferation in NSCLC cell lines by directly targeting RAB14, a member of the RAS oncogene family of small GTPases. Mechanistically, miR-451 was reported to suppress cell proliferation and metastasis by targeting the inflammatory factors PSMB8/NOS2 in A549 cells.[20] Other investigators have verified these results in additional lung cancer tissues.[21,22] The link between low miR-451 expression and poor prognosis for NSCLC has been investigated by Goto et al,[22] who found that renewed expression of miR-451 led to suppression of macrophage migration inhibitory factor (MIF) and phosphorylated Akt expression, as well as cell proliferation and migration in NSCLC cell lines. In addition, miR-451 was found to selectively promote sensitivity to cisplatin in ERCC1-high NSCLC cells by targeting the Wnt/β-catenin and PI3K/AKT pathways.[23] These results support the role of miR-451 as a tumor suppressor in lung cancer.

miR-451 and Digestive System Cancers

Hepatocellular carcinoma (HCC) is the most common aggressive carcinoma of the liver and the third-ranking contributor to tumor-associated death worldwide.[24] Li et al[25] found that miR-451 was markedly downregulated in HCC cells and tissues and functions as a tumor suppressor in HCC. They further verified that IKK-β is an important mediator of NF-κB activation in response to miR-451 inhibition in HCC. Global microarray-based miRNA expression profiling of 12 pairs of matched HCC and non-HCC tissues revealed that miR-451 is involved in hepatitis B virus-unrelated HCC.[26] miR-451 in HCC tissues is significantly correlated with advanced clinical stage, metastasis, and reduced disease-free and overall survival.[27] The same study revealed that activation of Erk1/2 signaling can mediate miR-451/c-Myc-induced EMT and metastasis in HCC cells by regulating the expression of EMT-related and MMP family proteins. In 2004, it was discovered that miR-451 can inhibit the migratory ability of hepatoma cell lines by targeting ATF2.[28] Furthermore, miR-451 is downregulated in multiple HCC cell lines and negatively regulates cell growth and invasion in a caspase-3- and MMP-9-dependent manner. Liu et al[29] further showed that miR-451 may act as a tumor suppressor in HCC by antagonizing angiogenesis through directly targeting the IL-6R-STAT3-VEGF pathway.

Colorectal cancer (CRC) is the third most common type of cancer worldwide.[30] Xu et al[31] evaluated 20 CRC tumor and adjacent non-cancerous tissues by microarray analysis. They found that miR-145, miR-451, and miR-1 were significantly downregulated in the tumor tissues. Another group found that miR-451 expression was

downregulated in CRC tissues and was negatively correlated with the Dukes stage.[32] In-vitro and *in-vivo* studies revealed that miR-451 may inhibit colon cancer growth by directly targeting Ywhaz and indirectly regulating nuclear FoxO3 accumulation.[32] In 2013, Li and colleagues reported that miR-451 inhibits CRC cell growth by downregulating the P13K/AKT pathway.[33] Others discovered that miR-451 suppresses cell growth by downregulating the expression of its target gene *IL6R* in the CRC cell line RKO.[34] In 2017, Mamoori et al[35] analyzed 70 matched cancerous and non-cancerous fresh-frozen tissues of patients with CRC (35 men and 35 women) who underwent resection of colorectal adenocarcinoma. They noticed that miR-451 was downregulated in the majority of the CRC tissues. Downregulation of miR-451 correlated significantly with the presence of coexisting adenoma and cancer persistence or recurrence after surgery. The authors further confirmed that miR-451 has a tumor-suppressing role in CRC by targeting MIF.

Gastric cancer (GC) is the second most frequently diagnosed cancer in the world, particularly in eastern Asia.[36] As early-stage GC is difficult to detect, patients often are in an advanced stage of the disease at diagnosis. The recurrence rate in patients with highly aggressive cancer subtypes at an advanced stage is as high as 70%, even after successful complete resection. Su et al[37] studied 107 paired human primary gastric tumor and adjacent normal tissues and GC cell lines. They reported low miR-451 expression in the GC tissues and cell lines and that downregulation of miR-451 tended to be positively correlated with lymphatic metastasis, TNM stage, advanced clinical stage, and shorter overall survival in patients with GC. Shen et al[38] confirmed that miR-451 is positively correlated with tumor stage, lymphatic metastasis, and shorter overall survival in patients with GC and suggested downregulation of miR-451 as a diagnostic and prognostic biomarker in GC. Similar results have also been reported based on the investigation of tumor tissues and the clinicopathological features of 180 patients with GC.[37,39]

Esophageal cancer (EC) is one of the most aggressive tumors in the gastrointestinal system and is the sixth most common cause of cancer mortality.[40] In 2012, Wang et al[41] reported that increased miR-451 expression induced apoptosis and suppressed cell proliferation, invasion, and metastasis by activating the PI3K/AKT pathway in EC9706 cells. By screening peripheral blood samples of 78 patients with esophageal cancer and 23 healthy donors, Hui et al[42] found that miR-451 and miR-129 expression levels did not increase significantly over those in normal controls in early-stage esophageal squamous cell cancer (ESCC), but significantly increased at stages III and IV. The relative expression of miR-451 alone allowed diagnosis of EC with a sensitivity of 83% and a specificity of 79%. Zang et al[43] found that decreased miR-429 and miR-451 levels were associated with the occurrence of lymph node metastases as well as the differentiation status and TNM stage in ESCC by using miRNA microarray chip analysis of 53 pairs of primary ESCC tissues and corresponding adjacent normal esophageal tissues. Zang et al[44] reported that miR-451 inhibits the proliferation of EC9706 cells by targeting CDKN2D and MAP3K1.

miR-451 and Urinary System Cancers

Bladder carcinoma is the second leading cause of death by urologic cancer among men and is characterized by multiple lesions with a high recurrence rate. In 2012, Xie et al[45] performed gene-chip screening of 14 invasive and three non-invasive bladder urothelial carcinoma tissue samples as well as four bladder cancer cell lines. They discovered that miR-451 was downregulated in the infiltrating bladder urothelial carcinoma group, suggesting that low expression is associated with infiltration and metastasis of bladder urothelial carcinoma. Another group found significantly higher downregulation of miR-451 in bladder cancer tissues than in paracancerous tissues, and miR-451expression was significantly associated with histological differentiation degree and TNM stage.[46] miR-451 expression maintains bladder tumor cells in an epithelial phenotype and inhibits EMT, thereby reducing their invasion and migration. Wang et al[47] also showed higher downregulation of miR-451 in bladder cancer tissues than in adjacent non-cancerous bladder tissues and suggested that miR-451 is a tumor suppressor that regulates the migration and invasion of bladder cancer cells by directly targeting *c-Myc.*

Renal-cell carcinoma (RCC) is the most common cancer of the adult kidney, the incidence and mortality rates of which have increased by 2–3% per decade over the past 20 years. In 2010, Heinzelmann et al[48] performed RT-PCR analysis of miRNA expression in 30 human RCC tissues, including 10 non-metastatic tumors, four tumors of patients with metastasis three years after diagnosis or later, and four tumors of patients with primary metastasis. They identified 12 miRNAs that were strongly downregulated in metastatic RCC, including miR-451. These findings prompted further research on the role of miR-451 in

metastatic RCC. It was found to be downregulated in RCC tissues and cell lines, and miR-451 downregulation was correlated with a lower survival rate of patients with RCC.[49] Upregulation of miR-451 expression inhibited the growth of RCC cells and induced apoptosis by targeting its downstream gene, *PSMB8*.[49]

miR-451 and Female Reproductive System Cancers

Ovarian cancer (OC) is the most lethal gynecologic malignancy in the world.[50] In 2014, Ling et al[51] analyzed 115 epithelial OC and 34 normal ovarian tissues and showed that miR-451 was downregulated in epithelial OC. Low levels of miR-451 were associated with advanced FIGO stage, high serum CA-125 levels, and LN metastasis, and miR-451 independently predicted poor prognosis for patients with epithelial OC. A study of nineteen paired cases of OC and endometriosis foci revealed that the expression levels of miR-1, miR-133a, and miR-451 were significantly reduced in ovarian tumors.[52]

Cervical cancer is the fourth-leading cause of cancer deaths in women worldwide. In 2008, Martinez et al[53] reported that miR-451 expression was lower in cell lines containing human papilloma virus-16 and/or −18 DNA than in normal cervical cells. miR-451 expression was higher in the multidrug resistant (MDR) human cervical cancer cell line KB-3-1 than in its parental cell line KB-V1, and miR-451 antagomirs decreased P-glycoprotein expression and increased doxorubicin sensitivity in MDR cancer cells.[54] In 2018, Yang et al[55] reported that miR-451 is differentially expressed in different stages of cervical squamous cell carcinoma.

miR-451 and Endocrine Cancers

Breast cancer (BC) is one of the most common malignancies among women, and its incidence is increasing.[56] Early detection is essential for effective treatment and survival. Despite recent advances in early diagnostic methods, metastasis remains the leading cause of death in patients with BC. The current treatment regimen for BC is multimodal, including surgery, chemotherapy, radiotherapy, hormonal treatment, and targeted therapy. Wang et al[57] analyzed 73 invasive, ductal BC tissue samples with or without LN metastasis and found that miR-451 was upregulated in the LN metastasis group. Al-Khanbashi et al[58] analyzed 72 tissue samples and 108 serum samples from 9 and 27 patients with BC, respectively, and showed that tissue miR-451 was upregulated and significantly associated with the pathological stage. They also found that serum miR-451 levels significantly decreased during treatment, and higher serum levels were associated with improved clinical and pathological responses and disease-free survival. In 2019, Shao et al[59] analyzed plasma samples from 143 patients with BC receiving solo or combination docetaxel chemotherapy and found that miR-451 expression was significantly higher in the sensitive group (partial response and stable disease) than in the resistant group.

Thyroid cancer is the most common human endocrine malignancy, accounting for 95% of all endocrine tumors. In 2013, Wang et al[60] conducted a miRNA microarray analysis of samples from patients with papillary thyroid cancer with/without LN metastasis and showed that miR-451 was upregulated in the LN group. In addition, miR-2861 and miR-451 levels were significantly greater in lateral than in central LN metastases. They also revealed that miR-2861 and miR-451 are unique miRNAs associated with the prognosis and progression of thyroid cancer.

Pancreatic carcinoma is typically asymptomatic at early stages, and the disease becomes apparent only at an advanced stage, with extensive local tumor invasion to surrounding tissues or distant organs. In 2012, Ali et al[16] found that miR-451 was significantly elevated in pancreatic carcinoma tissues. A study by Guo et al[17] indicated that miR-451 was significantly overexpressed in pancreatic cancer tissues and cell lines, and elevated miR-451 expression was associated with improved cell viability both in vitro and in vivo. Further, these authors showed that in pancreatic cancer, a high level of miR-451 is closely linked to poor prognosis and lymphatic metastasis, and miR-451 acts by directly targeting CAB39.

miR-451 and Head and Neck Cancer

Nasopharyngeal carcinoma is a common head and neck cancer derived from the epithelium of the nasopharynx. Liu et al[61] found that miR-451 was significantly downregulated in nasopharyngeal carcinoma cell lines and clinical tissues. Patients with low miR-451 expression had poorer overall survival and disease-free survival than patients with high expression, indicating that miR-451 is an independent prognostic factor in nasopharyngeal carcinoma. In 2010, Hui et al[62] first identified miR-451 as the only significantly overexpressed miRNA (by 4.7-fold) in non-relapsed compared with relapsed patients with locally advanced head and neck squamous cell carcinoma.

Glioblastoma multiforme is the most common primary neoplasm of the central nervous system diagnosed at WHO grade IV and has the highest malignancy and mortality rates even with the current standard treatment. Multiple studies have supported the role of miR-451 in the regulation of glioblastoma multiforme via different pathways. Nan et al[63] reported that miR-451 was downregulated in the human glioblastoma cells A172, LN229, and U251 and that renewed expression of miR-451 had dramatic effects on the three cell lines, inhibiting cell growth, inducing G0/G1 phase arrest, and increasing cell apoptosis, perhaps via regulation of the PI3K/AKT signaling pathway. Godlewski et al[64] found that the miR-451 level decreased in low glucose conditions, slowing proliferation, but enhancing migration and survival in glioblastoma cell lines by regulating its downstream target CAB39, which can bind LKB1, a marker in the LKB1/AMPK pathway. In glioblastoma patients, elevated miR-451 is associated with shorter survival. As a regulator of the LKB1/AMPK pathway, it may crucially contribute to cellular adaptation in response to altered energy availability.[64] In 2017, Zhao et al[65] also noted that miR-451 expression was lower in glioma than in control brain tissues, especially in the central parts of the tumor. They found that decreased miR-451 expression suppressed tumor cell proliferation but enhanced migration, which was accompanied by low-level CAB39/AMPK/mTOR pathway activation and strong Rac1/cofilin pathway activation, in glioma cell lines.

miR-451 and Osteosarcoma

Osteosarcoma (OS) is the most common primary bone tumor in adolescents and young adults and is associated with a poor prognosis owing to its high malignant and metastatic potential. In 2012, Namløs et al[66] reported that miR-451 was downregulated in OS tissues and cell lines. In 2013, Yuan et al[67] found that miR-451 was commonly downregulated in OS tissues at advanced clinical stages with distant metastasis or showing a poor response to neoadjuvant chemotherapy. The authors identified low miR-451 expression as an unfavorable prognostic marker for overall and disease-free survival. Re-expression of miR-451 significantly inhibited cell proliferation, migration, and tumorigenesis, thereby increasing cell apoptosis in OS cell lines. Zhang et al[68] analyzed primary human OS tissues and found that decreased miR-451 expression was correlated with metastasis and recurrence. Forced expression of miR-451 suppressed cell proliferation and invasion by targeting CXCL16 in vitro. Liu et al[69] also reported that miR-451 expression decreased in OS tissues and cell lines, and overexpression of miR-451 inhibited cell proliferation and migration by directly targeting IL-6R. Liu et al[70] transfected cells with miR-451 mimics and showed that miR-451 can inhibit cell proliferation, migration, and angiogenesis and promote apoptosis of human OS cells by inhibiting the expression of its downstream target, MIF. Another study[71] showed that high expression of miR-451 and miR-15b in pretreatment OS samples correlated with a positive response to chemotherapy. Li et al[72] found that *LRH-1* is a direct target gene of miR-451 in OS. Xu et al[73] explored the mechanism of miR-451 in human OS cell lines U2OS, SAOS, and MG63 and found that miR-451 may act as a tumor suppressor by modulating the levels of COX2, PGE2, and CCND1.

In addition to the above-mentioned cancers, miR-451 has been reported to be dysregulated in other cancer types. miR-451 expression in solid tumors and the pathways it is involved in are summarized in Table 1 and Figure 1.

miR-451 in Cancer Diagnosis

Biomarkers are biological indicators that can be used for early detection, to define tumor subtypes, or to predict disease outcome. A desirable biomarker requires a certain sensitivity and specificity. It should be easily accessible, so that it can be easily detected in samples obtained noninvasively, such as blood, saliva, and/or urine.[74] The abnormal miR-451 expression observed in various cancer types indicates its potential as a novel cancer biomarker (Table 2).

Zhu et al[75] identified five miRNAs (miR-16, miR-25, miR-92a, miR-451, and miR-486-5p) that showed consistently elevated levels in the plasma of patients with GC and provided high diagnostic accuracy for early-stage noncardia gastric adenocarcinoma. In 2012, Konishi et al[76] screened the plasma of pre- and post-operative patients with GC and found that nine miRNAs were significantly reduced in post-operative patients. In validation experiments, miR-451 and miR-486 were found to be decreased in post-operative plasma in 90% and 93% of patients, respectively, suggesting that they could be useful as blood-based biomarkers to screen for GC. Brenner et al[77] identified miR-451, miR-199a-3p, and miR-195 as predictive biomarkers for GC recurrence; miR-451 had the strongest prognostic effect. Redova et al[78] analyzed 667 miRNAs in the sera of 15 patients with RCC and 12 matched healthy controls using TaqMan Low-Density Arrays. They showed that the combination of miR-378 and miR-451 enabled the identification of RCC with a sensitivity of 81%,

Table 1 Expression and Pathways Affected by miR-451

Cancer Type	Sample	Expression	Target Gene	Pathway	Reference
Glioblastoma multiforme	Cell lines	Down		PI3K/AKT	63
	Tissues/Cell lines	Down	*CAB39*	LKB1/AMPK	64
	Tissues	Down	*CAB39*	AMPK/mTOR & Rac1/cofilin	65
Nasopharyngeal carcinoma	Tissues	Down	*RAB14*		101
	Tissues/Cell lines	Down	*MIF*		61
Esophageal cancer	Cell lines	Down		PI3K/AKT	41
	Cell lines	Down	*CDKN2D, MAP3K1*		44
Breast cancer	Tissues/Cell lines	Down	*Ywhaz*		109
HCC	Tissues/Cell lines	Down	*IKK-β*	NF-κB	25
	Cell lines	Down	*IL6R*	IL6R-STAT3-VEGF	29
	Tissues/Cell lines	Down	*ATF2*		28
	Cell lines	Down	*c-Myc*	EMT & miR-451/c-Myc/Erk1/2	27
Lung cancer	Tissue	Down	*RAB14*		19
	Tissue	Down	*MIF*	p-AKT	22
	Cell lines	Down	*PSMB8/NOS2*		20
	Cell lines	Down	*MCL-1*		91
	Cell lines	Down	*c-Myc*	miR-451/c-Myc/rad-51	99
	Cell lines	Down	*c-Myc*	miR-451/c-Myc/ERK/GSK-3K	103
	Cell lines	Down	*MDR1*	Notch-1/AP-1/miR-451/MDR-1	92
	Cell lines	Down	*TRIM66*	TATDN1/miR-451/TRIM66	93
	Cell lines	Down		PTEN	100
Gastrointestinal cancer	Cell lines	Down	*MIF*		102
Pancreatic cancer	Tissues/Cell lines	Down	*CAB39*		17
Renal cell carcinoma	Cell lines	Down	*PSMB8*		49
	Cell lines	Down	*ATF2*		96
Bladder carcinoma	Tissues/Cell lines	Down	*c-Myc*		47
Colorectal cancer	Tissues/Cell lines	Down	*Ywhaz/Fox3*		32
	Cell lines	Down	*CAB39*	PI3K/AKT	33
	Cell lines	Down	*IL-6R*		34
	Cell lines	Down	*MIF*		35,97
Osteosarcoma	Cell lines	Down	*IL6R*		69
	Tissues/Cell lines	Down	*CXCL16*		68
	Tissues/Cell lines	Down	*MIF*		70
	Cell lines	Down	*LRH-1*		72
Mucinous Cystadenocarcinoma	Tissues	Up			
Cervical cancer	Cell lines	Down	*MDR1*/P-glycoprotein		54
Prostate cancer	Cell lines	Down	*NEDD9*	HDAC3/Sp1/miR-451/NEDD9	98

a specificity of 83%, and an area under the receiver operating characteristic curve of 0.86.

Xie et al[79] detected significant upregulation of miR-451 in both the whole saliva and saliva supernatants of patients with EC, suggesting its utility as a noninvasive biomarker for the early detection of EC. Du et al[80] screened miRNAs in saliva samples from seven patients with EC and three healthy controls, and found that miR-10b, miR-144, and miR-451 have potential as biomarkers for EC. Zhang et al[81] acknowledged that miR-451 was

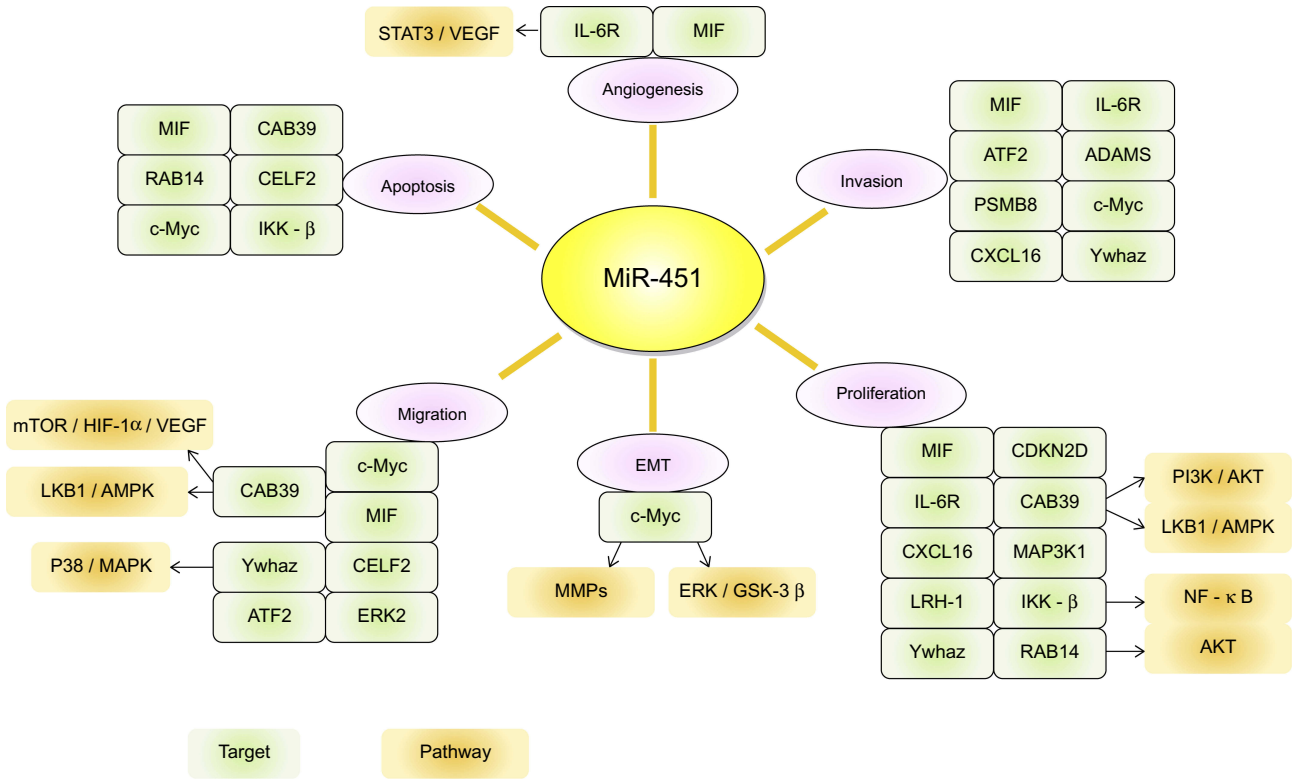

Figure 1 Experimentally confirmed cellular targets and pathways of miR-451. Numerous genes have been confirmed as targets for miR-451, which covers multiple biological signaling pathways, including cell proliferation, apoptosis, invasion, migration, EMT and angiogenesis.

a modest blood-based biomarker for papillary thyroid carcinoma malignancies and LN metastasis. Solomides et al[82] found that miR-451 levels could be used as a biomarker to distinguish normal lung tissues from malignant tissues. In BC, Hamdi et al[83] observed that miR-451 was significantly downregulated in the sera of patients with inflammatory BC (IBC) when compared to those of patients with non-IBC and healthy controls, with adequate specificity and sensitivity to serve as a serological marker for early diagnosis. De Leeneer and Claes[84] observed that the combination of plasma miR-145 and miR-451 levels provided high sensitivity (90%) and specificity (92%) for discriminating BC from CRC, EC, GC, HCC, and lung cancer in their study. Erbes et al[85] found that miR-155, miR-21, miR-125b, and miR-451 were dysregulated in midstream urine from patients with BC when compared to that of healthy controls, supporting their utility as non-invasive innovative urine-based biomarkers for BC detection. Zhu et al[7] screened circulating miRNAs in blood samples and found that miR-222, miR-20a, and miR-451 were predictive for the response to neoadjuvant chemotherapy in HR+/HER2– BC.

Shivapurkar et al[86] analyzed the expression of circulating miRNAs in the sera of patients with CRC diagnosed at an early stage before surgery. Six miRNAs (miR-15a, miR-103, miR-148a, miR-320a, miR-451, and miR-596) could be used to predict the risk of recurrence in early CRC. Phua et al[87] found that fecal miR-451 had a sensitivity of 88% and specificity of 100% in detecting CRC.

Ji et al[88] used RT-PCR to analyze the serum samples of 31 patients with OC, 23 patients with benign ovarian tumors, and eight control subjects and identified four miRNAs (miR-22, miR-93, miR-106b, and miR-451) that could be used to distinguish between samples from patients with OC and those from healthy controls.

These data indicate that the abnormal expression of miR-451 is associated with the cancer disease state and that miR-451 has great clinical potential as a noninvasive diagnostic biomarker for numerous human cancers.

miR-451 in Cancer Therapy

Adjuvant therapy such as chemotherapy or radiotherapy is used before, after, or along with the primary surgery to increase its efficiency and improve disease management. Therapy resistance currently is a major obstacle in oncology.

Table 2 miR-451 as a Diagnostic Biomarker in Human Solid Tumors

Cancer Type	Sample	MicroRNAs	Function	Reference
Gastric cancer	Plasma	miR-16, miR-25, miR-92a, miR-451, miR-486-5p	Early detection	75
	Plasma	miR-451 and miR-486	Early detection	76
	Tissue	miR-16 and miR-451	evaluate prognosis	39
	Tissues	miR-451, miR-199a-3p, miR-195	Predict recurrence	77
Esophageal cancer	Saliva	miR-10b, miR-144, miR-451	Early detection	80
	Saliva	miR-451	Early detection	79
Papillary thyroid cancer	Plasma	miR-451	lymph node metastasis	81
Lung cancer	Tissues	miR-451	Early detection	82
Breast cancer	Plasma	miR-24, miR-342-3p, miR-337-5p, miR-451	Classify IBC and non-IBC	83
	Plasma	miR-451 and miR-145	Early detection	84
	Urinary	miR-155, miR-21, miR-125b, miR-451	Early detection	85
	Plasma	miR-222, miR-20a, miR-451	Predict HR+/HER2-	7
Renal cell carcinoma	Plasma	miR-451 and miR-378	Early detection	78
Ovarian cancer	Plasma	miR-22, miR-93, miR-106b, miR-451	Early detection	88
Colorectal cancer	Plasma	miR-15a, miR-103, miR-148a, miR-320a, miR-451, miR-596	Predict recurrence	86
	Fecal	miR-223 and miR-451	Early detection	87

Recent research has suggested that abnormal miRNA expression is associated with therapy resistance.[89] Numerous preclinical trials have shown that miRNAs can influence the sensitivity of tumors to traditional antitumor therapies by using effective delivery strategies such as chemical modification, viral-based carriers, non-viral carriers, and exosomes.[2] Increasing evidence has demonstrated an important role for miR-451 in the regulation of therapy resistance (Figure 2).

Chemoresistance

In lung cancer, Bian et al[90] found that miR-451 could sensitize A549 cells to cisplatin, possibly by increasing cisplatin-induced apoptosis that might be associated with the inactivation of Akt signaling. Cheng et al[91] showed that, in lung cancer cells, tumor suppressor miR-451 enhanced cisplatin sensitivity via the regulation of Mcl-1 expression. Huang et al[92] demonstrated the role of the Notch-1/AP-1/miR-451/MDR-1 signaling axis in DTX resistance of lung adenocarcinoma (LAD). They found that Notch-1 negatively regulates miR-451 via the transcription factor AP-1, and MDR-1 is a direct target of miR-451 that induces DTX resistance in LAD cells. In 2018, Wang et al[93] reported that knockdown of long ncRNA TATDN1 increased the expression of miR-451 and improved cisplatin sensitivity of NSCLC in vitro and in vivo by targeting TRIM66.

Gu et al[94] first investigated the potential influence of miR-451 in drug resistance in BC by using a paclitaxel-resistant BC cell line. They then measured the expression of circulating miR-451 in patients with BC undergoing neoadjuvant chemotherapy and found that the relative expression levels were significantly lower in the neoadjuvant chemotherapy-resistant group than in the sensitive group, and miR-451 expression in these two groups was significantly lower than that in the healthy control group. These results indicate the potential application of circulating miR-451 in predicting resistance to neoadjuvant chemotherapy in BC. Wang et al[62] showed in vitro and in vivo that miR-451 may be an important potential target in paclitaxel-resistant BC and acts through targeting Ywhaz. Pigati and his team[95] found that increased miR-451 and miR-1246 levels in the blood, milk, and ductal fluids indicate the presence of abnormal cells in the mammary gland that render MCF7 cells more sensitive to doxorubicin.

In 2008, Zhu et al[54] first reported that miR-451 can regulate drug resistance mediated by MDR-1/P-glycoprotein in OC and cervical cancer cell lines. In RCC, Sun et al[96] explored

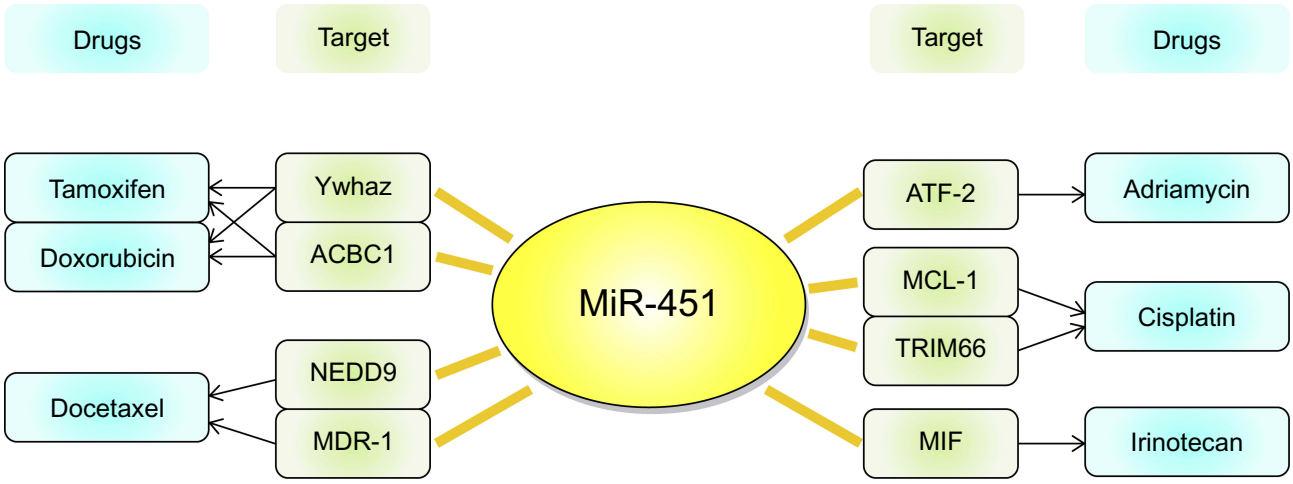

Figure 2 Mir-451 acts as an anti-oncomir gene in drug resistance by targeting its downstream targets.

how miR-451 regulates adriamycin resistance by regulating ATF-2 expression both in vitro and in vivo. Bitarte et al[97] found lower miR-451 expression in patients with CRC who did not respond to irinotecan-based first-line therapy than in patients who did, indicating the potential of miR-451 for predicting patient responses to irinotecan in the treatment of CRC. In 2018, Chen et al[98] revealed a new HDAC3/Sp1/miR-451/NEDD9 signaling axis that regulates the chemosensitivity of prostate cancer cells to docetaxel.

Radioresistance

Wang et al[99] established two DTX-resistant LAD cell models (SPC-A1/DTX and H1299/DTX) and showed that miR-451 was significantly downregulated in DTX-resistant cells. Re-expression of miR-451 could reverse radioresistance in DTX-resistant LAD cells both in vitro and in vivo by promoting cell apoptosis and DNA double-strand breaks. In addition, they showed that dysregulation of miR-451/c-Myc-survivin/rad-51 signaling is responsible for radioresistance in DTX-resistant LAD cells. Tian et al[100] reported that upregulation of miR-451 sensitized radioresistant NSCLC A549 cells to irradiation through the enhancement of apoptosis by activating PTEN. Zhang et al[101] found that high miR-451 expression enhanced radiosensitivity in nasopharyngeal carcinoma cells by inhibiting the repair of irradiation-induced double-strand breaks and increasing cell apoptosis. Bandres et al[102] demonstrated that miR-451 expression was decreased in GC versus non-tumoral tissues. miR-451 overexpression reduced cell proliferation and increased sensitivity to radiotherapy by targeting MIF. Ogawa et al[1] showed that miR-451 sensitizes glioma cells to conventional chemo- and radiotherapy by regulating the AMPK pathway.

miR-451 and EMT

The transdifferentiation of epithelial cells into motile mesenchymal cells is termed "EMT." EMT has important roles in development and stem-cell behavior, but it also contributes to cancer progression. Recent research has demonstrated a relationship between EMT and chemotherapeutic resistance in cancer cells. Chen's team[103] first reported the involvement of the miR-451/c-Myc/ERK/GSK-3b signaling axis in EMT in DTX-resistant LAD cells. They established two DTX-resistant LAD cell models and found that these cell models displayed EMT-like properties and gained increased invasion or migration activity. Re-expression of miR-451 could reverse EMT to a mesenchymal–epithelial transition in vitro and in vivo and could inhibit invasion and metastasis of the two DTX-resistant LAD cells. Huang et al[27] found that miR-451 downregulation-induced c-Myc overexpression leads to the activation of Erk1/2 signaling, which induces EMT and loss of mesenchymal–epithelial transition through the regulation of GSK-3β/snail/E-cadherin and increased expression of MMP family members in HCC cells. Zeng et al[46] found that EMT-related proteins were increased in miR-451 mimic-treated compared with control bladder tumor cells, suggesting that miR-451 could maintain the bladder tumor cells in an epithelial phenotype and inhibit EMT, thereby reducing the invasion and migration of bladder tumors. In 2019, Mamoori et al[104] evaluated immunomarkers and EMT markers to examine the regulatory roles of miR-451 in CRC stemness and found that EMT markers showed significantly reduced expression followed by miR-451 overexpression, suggesting a significant role for miR-451 in CRC initiation, maintenance, and progression.

miR-451 and the Tumor Microenvironment

The tumor microenvironment includes tumor cells and their adjacent stroma, which mainly contains extracellular matrix components, including fibroblasts, macrophages, cytokines, and signaling molecules. Tumor initiation and progression are complex processes involving consecutive gene mutations and changes in the fundamental biological behavior of cells caused by changes in their neighboring stroma. Recent research has highlighted the significant roles of miRNAs in the interplay between tumor cells and their microenvironments in favor of tumor formation, angiogenesis, metastasis, and resistance to chemo- and radiotherapy. Studies have shown that miR-451 not only directly affects tumor cell proliferation but also indirectly affects tumor cell invasion and metastasis upon secretion into the microenvironment via exosomes. miR-451 is the only reported miRNA that is not processed by Dicer but instead matures via an Ago2-mediated pathway. This unique processing pathway might relate to the high secretion of miR-451. Gu et al[105] reported that the breast microenvironment, including the milk, may contribute to BC initiation and development, as miR-451 was significantly upregulated in the milk of patients with milk stasis plus neoplasm. Khazaei et al[106] evaluated miR-451 expression in esophageal SCC patient serum samples and found that it is mainly secreted into the serum through exosomal compartments. Exosomal miR-451 is overexpressed in the conditioned medium of cocultured KYSE-30 cells and normal fibroblasts, and miR-451-enriched conditioned medium in turn promotes the migration ability of KYSE-30 cells. These data support a signaling role for miR-451 in extracellular matrix cross-talk in the esophageal tumor microenvironment.

Surprisingly, miR-451 is also related to cell metabolism and can mediate cell energy-consuming models via several targets. Ansari et al[107] found that miR-451 levels in glioblastoma multiforme cancer cells were high in a glucose-rich environment and low in conditions of glucose depletion, and that miR-451 is a potent inhibitor of the AMPK signaling pathway. Zhao et al[65] demonstrated that miR-451 is downregulated in glioma tissues compared to normal brain tissues, especially in the central portions of tumors, indicating that the microenvironment inside the tumor is heterogeneous. Central glioma cells are in a hypoxic–hypoglycemic microenvironment with low miR-451 expression; therefore, tumor cell growth inhibited and necrosis is apparent. In the peripheral parts of the tumor, the survival of tumor cells is enhanced, and they actively proliferate and infiltrate into the surrounding parenchyma. In glioma cell lines, decreased miR-451 expression suppressed tumor cell proliferation but enhanced migration, concomitant with low level CAB39/AMPK/mTOR pathway activation and strong Rac1/cofilin pathway activation, respectively. Korabecna et al[108] identified five miRNAs derived from cancer cells, including miR-451, that may together regulate 2304 target genes in macrophages, including those involved in cell apoptosis, gene expression, and protein transportation, that may contribute to carcinogenesis. In 2018, Panigrahi et al[2] showed that miR-451 levels were significantly higher in exosomes from human prostate cancer cells under hypoxic conditions than in those under normoxic conditions. These results suggest the potential of miR-451 as a biomarker that influences the tumor microenvironment in patients with prostate cancer.

Conclusion

In this review, we focused on the functions of miR-451 in the progression of multiple cancer types. miR-451 functions as a tumor suppressor and is downregulated in most cancer types. It can be detected in different sample types, such as cancer tissues, blood, saliva, and urine. miR-451 has been associated with multiple target genes and pathways. It functions in both direct and indirect ways. The indirect way via secretion into the tumor microenvironment through exosomes overcomes miRNA degradation by RNase in the serum and endocytic compartments. miR-451 has potential as a biomarker for cancer diagnosis and prognosis or as a treatment target in combination with established drugs to reduce drug resistance. However, its clinical application has a long way to go.

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Disclosure

The authors report no conflicts of interest in this work.

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