Review Article

miR-216 Is a Key Regulator and Potential Marker in Human Cancers

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Abstract

MicroRNAs, a class of small noncoding RNAs, have been identified as promising biomarkers for cancer identification and management by regulating gene expression and other cellular biological pathways. This review gathers findings for understanding the molecular basis and clinical importance of microRNA-216 (miR-216) in several cancers. Increased or decreased expression of miR-216 has been observed in a variety of cancers, including esophageal cancer, breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, cervical cancer, brain tumor (glioma), prostate cancer, and acute myeloid leukemia, indicating its activity as an oncogene or tumor suppressor. Through this study, we proposed that miR-216 can potentially be a candidate as a prognostic marker for early detection of tumor development, progression, as well as metastasis in cancer patients.

Keywords: Biomarker, cancer, miR-216, microRNA, microRNA-216

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Introduction

There are about 20,000 protein-coding genes that constitute about 2% of the human genome. At least 70% of the sequences are transcribed into RNAs, and most of the transcripts have been identified as noncoding RNAs (ncRNAs).[1-5] The long ncRNAs with >200 nucleotides and short ncRNAs with 20 nucleotides are recognized as the fundamental regulators of the human genome based on remarkable advances in sequencing techniques and large-scale genome sequencing.[6-8] The human genome encodes about 1000 kinds of microRNAs (miRNAs), which are endogenous, noncoding, single-stranded molecules and have a regulatory role across the mammalian genome. They are present in eukaryotes, and their length ranges from 22 to 24 nucleotides.[9] MiRNAs are responsible for post-transcription regulations by interacting with messenger RNA (mRNA) and silencing the related gene. They are mostly produced by the transcription of other genes' intron regions via RNA polymerase II.[10] More studies are needed to discover new biological phenomena related to carcinogenesis, like miRNAs. MiRNA expression varies depending on different cancerous tissues and can be raised, lowered, or stay the same.[11] MicroRNA 216 (MiR-216) containing two homologous miRNAs on chromosome 2p16.1 of the human is more proper as a possible biomarker for cancer prognosis and diagnosis than a therapeutic target. Using the RNAfold (Rfold) webserver (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi), the anticipated secondary structure of miR-216 with a minimum free energy (MFE) of −40.30 kcal/mol and dot-bracket notation has been shown [Figure 1].

MiR-216 of flies, mice, humans, and other species with similar sequences and structures exhibited conservative evolution. MiR-216 regulation is important for physiological homeostasis

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in the human body. According to some studies, MiR-216 enhances cell proliferation and invasion while inducing apoptosis in certain malignancies.[12,13]

This review aims to amass the evidence to reach the molecular mechanism as well as clinical prominence of the miR-216 in different types of cancers.

Changes miR-216 in Different Tumors

Some studies have shown that miR-216 is downregulated in a variety of human tumors such as glioma,[14,15] breast cancer (BC),[12] bone metastasis,[16] cervical cancer (CC),[17,18] esophageal cancer,[19] gastric cancer,[20] pancreatic cancer (PC),[21-27] and miR-216 is upregulated in acute myeloid leukemia (AML),[13] and colorectal cancer (CRC)[28,29] [Table 1].

Brain Cancer (Glioma)

Gliomas are one of the most common and aggressive central nervous system (CNS) tumors.[30,31] In spite of advances in cancer treatment in recent years, glioma patients have a poor prognosis and survival rate.[32,33] Nowadays, glioma represents 51.4% of all primary CNS malignancies.[34] Glioblastoma (GBM) is also the most common and lethal type of glioma in adults, with a median survival period of 14 months.[35]

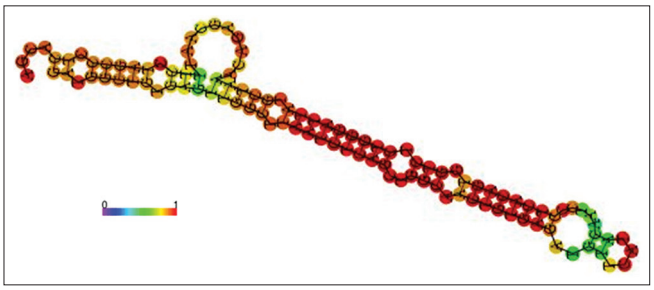

Figure 1: Prediction of Optimal Secondary structure of the has-miR-216 (EPS format) with −40.30 kcal/mol with its dot-bracket notation using the Rfold webserver. The sequence of this microRNA: TAATCTCAGCTGGCAACTGTG

Li *et al*.[14] (2018) observed that miR-216b expression was dramatically decreased in glioma cell lines and tissues. miR-216b Overexpression impeded the growth and migration of glioma cells, whereas inhibition of miR-216b had the reverse effect. Their findings demonstrated that miR-216b plays a tumor-suppressive role in the development of glioma and recognized astrocyte elevated gene-1 (AEG-1) as a miR-216b target gene. This miR could be a promising target for developing novel glioma treatments. Using online databases, quantitative reverse transcription polymerase chain reaction (qRT-PCR), and the luciferase reporter assay, Li *et al*.[15] (2022) identified the F11 receptor (F11R) as the target of miR-216, and HOXC-AS3 targeted miR-216 as a sponge.

Breast Cancer

BC is a heterogeneous disorder with different subtypes, and each type has a diverse overall survival.[36,37] Age, height, reproductive variables (such as older age at first birth, nulliparity), usage of exogenous hormones, and family history are risk factors for BC. Lifestyle factors like inactivity, alcohol use, and postmenopausal obesity have also been linked with a higher risk of BC.[38] Moreover, the most prevalent cause of cancer-related mortality among women is BC.[39] Based on numerous studies, around one-eighth of women worldwide will develop this cancer over their lifetime.[40] Using RT-qPCR and fluorescence *in situ* hybridization (FISH) analysis, Liu *et al*.[12] (2021) showed that in BC tissues and cells, hexokinase 2 (HK2) was highly expressed while miR-216b was poorly represented. Functionally, miR-216b was strongly linked with BC progression by targeting HK2 and inactivating the mammalian target of rapamycin (mTOR) signaling pathway. Moreover, miR-216b overexpression or HK2 silencing reduced cell viability, migration, and invasion while inducing apoptosis, autophagy, and cell cycle arrest. Overall, their results suggested that miR-216b inactivates the mTOR signaling pathway via down-regulating HK2, thereby preventing the progression of BC therapy.

Table 1: MiR-216 in various cancers: functional properties

Cancer type	Expression	Role	Clinical characteristics	Related gene	Ref.
Brain Cancer (Glioma)	↓	TSG	Cell Proliferation, migration, invasion	AEG-1, F11R, HOXC-AS3	[14,15]
Breast Cancer	↓	TSG	Cell Proliferation, colony formation, metastasis, tumor progression, apoptosis inhibition	HK2	[12]
Bone Metastasis (Osteoblasts)	↓	TSG	Cell Proliferation, differentiation, migration, metastasis, apoptosis inhibition	WISP-1, VCAM-1	[16]
Cervical Cancer	↓	TSG	Cell Proliferation, invasion, metastasis, angiogenesis, apoptosis inhibition	SNHG16	[17,18]
Esophageal Cancer	↓	TSG	Cell Proliferation	IGF2BP2, LIPH-4	[19]
Gastric Cancer	↓	TSG	Cell Proliferation, colony formation, migration, metastasis, invasion, apoptosis inhibition	Cyclin T2	[20]
Pancreatic Cancer	↓	TSG	Cell Proliferation, metastasis	Kras, Janus kinase	[21-27]
Acute Myeloid Leukemia	↑	OG	Cell Proliferation, colony formation	U2AF1, IDH1/2, FLT3	[13]
Colorectal Cancer (CRC)	↑	OG	Cell Proliferation, colony formation, migration, metastasis, invasion, apoptosis inhibition	-	[29]

↓=downregulate, ↑=pregulate, AEG-1=astrocyte elevated gene-1, F11R=F11 receptor, FLT3=FMS-like tyrosine kinase 3 HOXC-AS3=HOXC Cluster Antisense RNA 3, HK2=hexokinase 2, IDH1/2=isocitrate dehydrogenase 1 and 2 (IDH1/2), TSG=tumor suppressor gene, OG=oncogene, SNHG16=small nucleolar RNA host gene 16, VCAM-1=vascular cell adhesion molecule 1, WISP-1=Wnt1 inducible signaling pathway protein 1

Prostate Cancer: Bone Metastasis (Osteoblasts)

Prostate cancer (PCa) is the most prevalent type of cancer diagnosed in the US and other Western countries.[41] Surgery is the most common treatment option in the first stages. However, in later stages, systemic intervention is needed to suppress tumor progress and avoid secondary metastases. One of the prevalent complications related to progressed Pca is bone metastasis, which results in bone breakage and severe pain. In PCa, bone metastasis has predictive importance because the severity of the disease in the bone has a significant impact on survival.[42-44] Bone lesions caused by metastasis involve the osteoclasts and osteoblasts.[45] The major cellular components of bones, osteoblasts, are important in osteogenesis.[46,47] Cancer cells release soluble factors in the tumor microenvironment that enhance osteoblast activation, proliferation, and maturation. They also stimulate osteoblastic bone metastasis by secreting bone matrix and growth factors.[48,49] As a result, osteoblast-derived factors play an important role in bone metastasis. Tai *et al*.[16] (2014) found that osteoblast-derived Wnt1 inducible signaling pathway protein 1 (WISP-1) hindered miR-126 expression. In addition, the miR-216 mimic inhibited the expression and migration of vascular cell adhesion molecule 1 (VCAM-1) induced by WISP-1. According to this research, osteoblast-derived WISP-1 down-regulates the expression of miR-126 by the focal adhesion kinase (FAK), mitogen-activated protein kinase (p38), and alpha v beta 1 ($\alpha v\beta 1$) integrin pathways and stimulates migration and the production of VCAM-1 in human PCa cells.

Cervical Cancer

CC is the fourth most widespread malignancy in women and the fourth main reason for cancer-related death in them, accounting for around 275,000 deaths annually.[50] Furthermore, cervical intraepithelial neoplasia (CIN) is regarded as a precursor to CC. However, CC develops via various precancerous stages, from low-grade CIN (CIN I) and high-grade CIN (CINII/III) to CC.[51] This complicated cancer involves a series of epigenetic or genetic modifications.[52,53] Thus, investigating the molecular and pathogenic pathways of CC is crucial and could be helpful for the diagnosis and therapy of human CC. Yang *et al*.[17] (2016) demonstrated that one of the top hub nodes was miR-216. In a study conducted by Zhu *et al*.[18] (2018), a negative correlation between miR-216-5p and small nucleolar RNA host gene 16 (SNHG16) expression levels in CC specimens was observed.

Esophageal Cancer

In 2020, esophageal cancer (EC) was known as the seventh most frequently diagnosed cancer (604,100 new cases) and the sixth most deadly cancer (544,076 fatalities) around the world.[54] There are two forms of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma, which have different etiology and epidemiology.[55] The most common form of EC is ESCC, happening mainly in the upper and mid-esophagus and originating from the lining of the esophageal squamous epithelium. ESCCs account for more than 90% of EC cases, and EC is the fourth most common cause of death from cancer in China.[56] ESCC has a 5-year survival rate below 20% due to late detection, frequent metastasis, and rapid tumor growth.[57,58] Furthermore, the exact genetic and molecular processes of ESCC are unknown.[59] Xiao *et al*.[19] (2022) showed that to stimulate the expression of insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), miR-216's target gene, LIPH-4 could bind to miR-216b and function as a competitive endogenous RNA (ceRNA). LIPH-4 operated as an oncogene via the miR-216b/IGF2BP2 axis in ESCC.

Gastric Cancer

Gastric cancer is a malignant digestive tract cancer that emanates from gastric mucosal epithelial cells. According to a study in the field, it has the third-highest fatality rate and the fifth-highest incidence rate in the world. It has been at the frontline of malignancies in the world.[60,61] According to several statistical studies, <25% of patients with early gastric cancer diagnosis and therapy had a poor 5-year survival rate.[62,63] Occult occultation, recurrence, and easy metastasis are the leading causes of poor prognosis and death in gastric cancer. Determining the molecular mechanism underlying the development of gastric cancer is crucial for gastric cancer treatment and prognosis improvement. Chen *et al*.[20] (2020) stated that miR-216 was significantly downregulated in cancer tissues relative to normal tissues. MiR-216b was also reduced in different gastric cancer cell lines. In this study, miR-216b overexpression prevents gastric cancer cell proliferation, migration, and apoptosis. They confirmed that the inhibition of the invasion and proliferation of gastric cancer cells by miR-216b is mediated by cyclin T2. Cyclin T2 overexpression can counteract the anticancer effect of miR-216b mimics.

Pancreatic Cancer

PC is the fourth most frequent reason for cancer-related mortality in the US and sixth in China; 90–95% of pancreatic malignancies are exocrine tumors classified as pancreatic ductal adenocarcinomas (PDAC).[64,65] PC is the fourth leading reason of cancer death globally.[66,67] Exocrine ductal adenocarcinomas (PDAC) account for 96% of pancreatic malignancies.[66] Periampullary carcinomas are another type of pancreatic tumor; 12% of them are adenocarcinomas of the Vater ampulla (AMP). In comparison to PDAC, patients with AMP have improved prognosis (5-year survival of >45%) primarily because of early disease identification.[68,69] By 2030, pancreatic ductal adenocarcinoma (PDAC) is projected to be the second most deadly cancer in the US.[70,71] PDAC is a deadly cancer with a 5-year survival rate of about 5% after diagnosis.[72,73] After curative resection, more than half of patients experience distant metastasis or local recurrence due to the severe aggressivity of PDAC cells.[74,75] Patients with PDAC can now benefit from molecularly targeted effects.[76,77] Szafranska *et al*.[21] (2007) showed that pancreas tissue is distinguished by the expression of miR-217 and -216 and the absence of miR-133a. Greither *et al*.[22] (2010) demonstrated

that patients with PDACs expressing elevated levels of miR-222, miR-210, miR-203, or miR-155, but not miR-217 or miR 216, will have shorter overall survival. Also, the overexpression of all four miRNAs raises the relative risk of mortality from 2.20–2.50 fold to 5.24 fold. Yang *et al*.[23] (2014) displayed that stool miR-216, miR-155, and miR-21 significantly differentiate PDAC patients from chronic pancreatitis (CP) and normal persons. This proof-of-concept study assessed the potential of stool-based miRNAs as prospective biomarkers for screening PDAC. Furthermore, it was discovered that miR-155 and miR-21 were overexpressed in PDAC tissues, pancreatic juice, and stool specimens, while miR-216 was down-expressed. According to Rachagani *et al*.[24] (2015) study, as pancreatic intraepithelial neoplasia (PanIN) lesions developed into PDAC, the expression of the tumor suppressors miR-217 and miR-216 in the pancreas were unchanged at 10 weeks of age but gradually declined from 25–50 weeks of age. In addition to KC mice, human PC tissue showed substantial down-regulation of miR-217 and miR-216. By targeting downstream genes, mainly the Kras oncogene and Janus kinase, miR-217 and miR-216 may act as tumor suppressors in PC. It was also discovered that miR-216 and miR-217 could target many essential genes involved in the pathogenesis of PC. Azevedo-Pouly *et al*.[25] (2017) showed that in these mice, the expression of three miRNAs, miR-217, miR-216a, and miR-216b, placed in a 30-kbp area on 11qA3.3, reduced with age and phenotypic intensity. Also, miR-217 and 216 expression was examined in other acinar- special elastase promoter (Ela)-KrasG12D mouse strain and shown to be downregulated. They hypothesized that miR-216/-217 might preserve acinar differentiation or serve as tumor-suppressive miRNAs because they are enriched in acinars, decreased in human PDAC, and target Kirsten rat sarcoma (Kras). To assess this idea, a 27.9-kbp area of 11qA3.3, including the miR-216/217 host gene, was deleted in the germ line of mice. Yonemori *et al*.[26] (2017) reported that the miR-216 cluster was remarkably diminished in PDAC samples. The aggressiveness of cancer cells was inhibited by ectopic expression of these miRNAs, indicating that the miR-216 cluster is an anti-tumor miRNA in PDAC cells. It is still unclear how miR-216b-3p (the passenger strand of pre-miR-216b) affects cancer cells. Felix *et al*.[27] (2019) expressed that in PDAC the miR-216 family, including miR-216a-3p, miR-216b-3p, miR-216a-5p, and miR-216b-5p was consistently downregulated.

Acute myeloid leukemia (AML)

AML is a disease with unsatisfactory clinical outcomes that is cytogenetically and molecularly heterogeneous.[78] Cytogenetic changes (i.e., t[16;16]/inv[16], +8, −7/7q-, −5/5q-, t[9;11], t[15;17], t[8;21], and complex) and molecular changes, like mutations nucleophosmin 1 (NPM1), v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (C-KIT), FMS-like tyrosine kinase 3 - internal tandem duplication (FLT3-ITD), and CCAAT/enhancer-binding protein alpha (CEBPA), also abnormal expression in Wilms' tumor 1 (WT1), brain and acute leukemia cytoplasmic (BAALC), meningioma 1 (MN1), and ETS-related gene (ERG), are critical in leukemogenesis and give the best prognostic data for AML.[79,80] The expression and clinical importance of MiR-216b in acute myeloid leukemia patients were reported by Zhang *et al*.[13] (2018).They examined bone marrow miR-216b expression in 115 patients with de novo AML by real-time quantitative polymerase chain reaction (PCR). Remarkably, bone marrow (BM) miR-216b expression was increased in these patients, suggesting that it could be a biomarker to differentiate AML from controls. There were no significant associations between the expression of miR-216 with gender, age, hemoglobin, white blood cells, platelets, BM blasts, karyotypes, and French-American-British categories. Patients with elevated miR-216b expression had a reduced incidence of FLT3-ITD mutations and a greater occurrence of U2 small nuclear ribonucleoprotein auxiliary factor 1 (U2AF1) and isocitrate dehydrogenase 1 and 2 (IDH1/2) mutations. Furthermore, overexpression of miR-216b in cytogenetically normal AML patients negatively affected the overall survival and complete remission (CR) rate. The level of BM miR-216b in the follow-up patients was notably diminished in the CR phase compared to the detection time and returned in the relapse phase. Overall, their results showed that miR-216b overexpression was common in *de novo* AML and predicted a poor outcome in CN-AML. Furthermore, miR-216b expression in AML was a useful indicator of disease recurrence.

Colorectal Cancer (CRC)

Colorectal cancer (CRC) has one of the world's highest rates of mortality and morbidity. About half a million people died from CRC in 2012.[81] Furthermore, colorectal cancer (CRC) is the third most prevalent malignant tumor and the second cause of cancer-related death.[82] According to the global 2018 estimates, there were 1,800,977 diagnosed cases and 861,663 deaths.[83] Until 2035, the death rate from colon and rectal cancer is anticipated to increase by 60 and 71.5%, respectively.[84] A profile of miR-216 (one of the five serum miRNAs) was recognized by Zhang *et al*.[28] (2014) as a biomarker for forecasting chemosensitivity in CRC Cai *et al*.[29] (2021) reported up-regulation of miR-216 in colorectal cancer cells.

Conclusion

MiRNAs play an important role in gene regulation, and their dysregulation is considered a hallmark of cancer. Several studies have shown that miR-216 belongs to a class of noncoding RNAs that are mainly involved in cancer cell invasion, migration, and proliferation. According to most studies, miR-216 acts almost like a tumor suppressor, while it also plays an oncogenic role in some cancers. The mechanism by which up- or down-regulation of miR-216 contributes to tumor growth and carcinogenesis is complicated.

miR-216 mostly correlated with carcinogenesis and related with cancer progression through known pathways, including cell cycle pathway, Ras/mitogen-activated protein kinase (RAS/MAPK) pathway, isocitrate dehydrogenases pathway,

IGF signaling, metastasis adhesion protein, Junctional Adhesion Molecule and vascular cell adhesion molecule, glycerophospholipid biosynthesis pathway in cancer, which all these pathways have a correlation with each other also and has a main function in growth, proliferation or rapid growth, cell differentiation, as well as in invading and migrating the cancer cells in a variety of tumors. Furthermore, despite its unknown properties, it contains different levels that mostly affect cell proliferation and, thus, tumor growth. Variations in miR-216 expression are strongly related to the severity of malignant tumor development, according to the findings of previous studies. Thus, they may be candidates for evaluating cancer severity, prognosis, response to treatment, and even as a potential therapeutic approach for solid tumors. Serum miR-216 levels are directly associated with disease progression and a decreased survival rate. MiR-216 has promising potential for diagnosing disease progression, stage, prognosis, and measuring therapy effectiveness due to its functional mechanisms in cellular pathways. Increasing expression of miR-216 has therapeutic potential as effective as anti-tumor drugs. Based on the findings, miR-216 is suggested as a predictive marker for the early detection of tumor growth, progression, and metastasis.

Future Prospect

A detailed investigation of the upstream and downstream mechanisms of miR-216 is stillrequired to ponder way better and confirm it. MiR-216 could be used clinically as a multipurpose biomarker for diagnosis and prognosis, cancer progression, and even treatment efficacy evaluation. The miR-216 could, therefore, be used as a novel therapeutic target in cancer treatment and eventually become a key clinical treatment approach.

Method

In this study, two approaches were employed by the authors. Using the keywords MIRN216, MiRNA216, Hsa-Mir-216, MicroRNA 216, and Hsa-miR-216, the databases PubMed, Scopus, Embase, Cochrane, and Google Scholar were searched for all articles published after the year 2000. the relationship between the expression of miR-216 and the molecular mechanism(s) in growing tumors of any type of cancer was chosen as inclusion criteria.

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Conflicts of interest

There are no conflicts of interest.

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