



Review

MiRNA-433 and Cancers

 Jie Tang,¹  Desheng Ni,²  Song Li²

¹Department of General Surgery, The Second Affiliated Hospital of Bengbu Medical College, Bengbu, China

²Department of Hepatobiliary Pancreatic Gastrointestinal Surgery, JinHua People's Hospital, JinHua, Jinhua, China

Abstract

Being a carrier of genes encoding post-transcriptional regulatory information, miRNA-433 has a crucial regulatory role in cell growth and development in animals and plants. We found that miRNA-433 is associated with 19 cancers, with its expression significantly downregulated in 17 cancers. MiRNA-433 overexpression can inhibit the proliferation, migration, and invasion of cancer cells. These include cells of cholangiocarcinoma, liver cancer, pancreatic cancer, breast cancer, etc. MiRNA-433 suppresses the expression of this target gene by binding to the specific seed sequence of the downstream target gene. Notably, the seed sequences of different downstream target genes that miRNA-433 binds to are the same. In this article, we discuss in detail the mechanism of miRNA-433 in human diseases and provide ideas for further research on its biological functions.

Keywords: Cancer, Human diseases, MiRNAs, MiRNA-433

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In 1993, Rosalind C. Lee et al. found the first miRNA in nematodes.^[1] Thereafter, additional miRNAs have been found in plants, green algae, viruses, and deeper clade animals.^[2] MiRNAs are non-coding, conserved single-stranded sequences having an approximate length of 18–24 nucleotides.^[3] In the nucleus, miRNAs are transcribed from DNA sequences and processed to produce precursor miRNAs (pri-miRNAs). These pri-miRNAs are transported to the cytoplasm via exportin-5, where they are processed by Dicer into mature miRNAs and finally cut into miRNA/miRNA duplexes.^[4–7] As carriers of genes encoding post-transcriptional regulatory information, miRNAs have critical regulatory roles in cell growth, differentiation, development, and apoptosis in plants and animals.^[8–10]

The involvement of miRNAs in human diseases was first convincingly proven in the 2002 study by Calin Dan Du-

mitru et al. This study demonstrated that miRNA-15 and miRNA-16 are downregulated in B cell chronic lymphocytic leukemias and have major regulatory effects on this cancer.^[11] With the deepening of miRNA research in the recent decades, the role of miRNA in human diseases has become increasingly clear. For example, miR-217 inhibits the proliferation, migration, and invasion of hepatocellular carcinoma cells by targeting mitogen-activated protein kinase 1 (MAPK1) and is negatively correlated with MAPK1.^[12] MiRNA-155 possibly participates in atopic dermatitis pathogenesis by regulating Th17 cell differentiation and function.^[13] MiR-181 may be a new crucial regulator of cisplatin-resistant non-small cell lung cancer.^[14] Therefore, investigating about miRNAs is meaningful for revealing the mechanism underlying disease occurrence at a deeper level.

Address for correspondence: Song Li, MD. Department of Hepatobiliary Pancreatic Gastrointestinal Surgery, JinHua People's Hospital, JinHua, Jinhua, China

Phone: +86 18160838806 **E-mail:** Leezh0403@163.com

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MiRNA-433, located on chromosome 14, was first reported by Guisheng Song et al. in 2008. They revealed that miRNA-433 was coupled with miRNA-127, and their formation was regulated by nuclear receptors.^[15, 16] MiRNA-433 has a key regulatory role in human diseases. According to Ying Ma et al.'s study, miR-433 inhibited the growth, invasion, and migration of oral squamous carcinoma cells by targeting histone deacetylase 6(HDAC6).^[17] T. Liang et al. reported that miRNA-433 inhibited the migration and invasion of ovarian cancer cells by targeting Notch1.^[18] MiR-433 regulated myocardial ischemia reperfusion injury by targeting N-myc downstream regulated gene4(NDRG4) and modulating the Phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signal pathway.^[19] Thus, further studying the mechanism of miRNA-433 in diseases is of great significance. This paper summarizes and investigates the expression, function, target genes, and interacting molecules of miR-433 and its role in human diseases.

MiRNA-433 and Cancers

MiRNA-433-3p and miRNA-433-5p as miRNA-433 mature bodies, they are similar in many biological functions. After summarizing miRNA-433- and cancer-related literature, we found that miRNA-433 is associated with 19 cancers, with its expression significantly downregulated in 17 cancers (highlighted in black font) (Fig. 1). At the same time, we downloaded the expression data of miRNA-433 in pan cancer and further analyzed and visualized it through R Language version 4.2.1 (Fig. 2). We divided the main miRNA-433 functions in cancer as follows:

Inhibit the Proliferation, Invasion, and Migration of Cancer Cells and Promote Apoptosis

LiHua Guo et al. found that miR-433 inhibited cell prolifer-

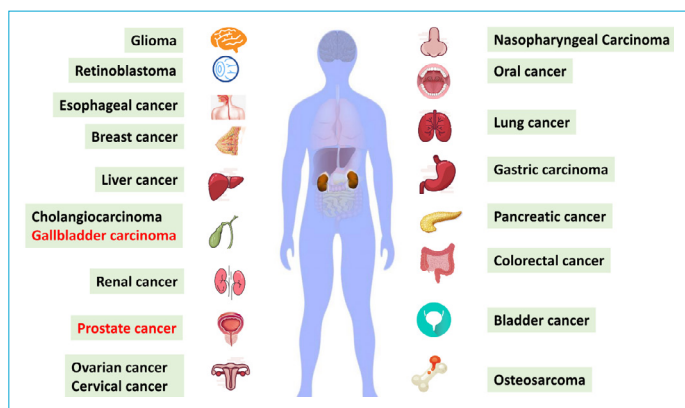


Figure 1. MiRNA-433 and related cancers (The black font indicates that the expression of miRNA is down-regulated in this cancer, and the red font indicates that the expression of miRNA in this cancer is unknown).

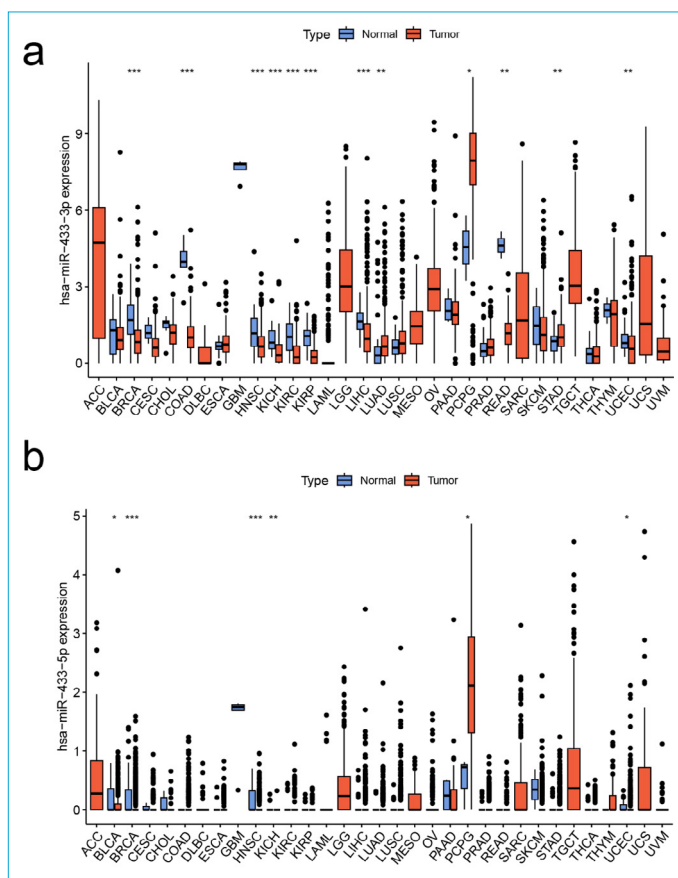


Figure 2. The expression of miRNA-433 in pan cancer. (a: miRNA-433-3p, b: miRNA-433-5p).

eration, migration, and invasion, and cell cycle progression by directly targeting Kirsten rat sarcoma viral oncogene homologue(KRAS) in gastric cancer.^[20] They thus opened the prelude for investigating the tumor suppressor role of miRNA-433. Since then, studies have found the anti-tumor effects of miRNA-433 in many cancers, including inhibition of cell proliferation, migration, and invasion and promotion of apoptosis. For example, ChangYan Liang et al. revealed that miRNA-433 inhibits cell proliferation and invasion and increases apoptosis in cervical cancer by directly targeting metadherin (MTDH).^[21] In 2018, Qizhong Shi et al. found that miR-433 overexpression inhibits the proliferation, migration, and invasion of esophageal cancer cells by preventing growth factor receptor-bound protein 2(GRB2) expression, thereby suggesting that miR-433 can be targeted for esophageal cancer treatment.^[22] Jing Zhang et al. found that miR-433 could inhibit the proliferation, migration, and invasion of glioma cells by targeting ajuba LIM protein(AJUBA) expression.^[23] Of course, the antitumor effect of miRNA-433 is not reflected only in the aforementioned cancers. Cancers in which miRNA-433 acts as a tumor suppressor are listed in Table 1.

Table 1. Functions of miRNA-433 in cancers and molecules that interact with miRNA-433

| Type of cancers | Upstream factors | 3p/5p | Target genes | Functions | References |
|--------------------------|--|-------|---|--|------------------|
| Ovarian cancer | / | / | Notch1 | Migration , Invasion | [18] |
| Cervical cancer | /Circ-ATP8A2 | / | AKT/ β -catenin, EGFR | Proliferation, Invasion, Apoptosis | [21, 33] |
| Renal cancer | LncRNAPCGEM1 | 3p | FGF2 | Proliferation, Invasion, Apoptosis | [34] |
| Breast cancer | LncRNAGNAS-AS1 | 3p | AKT3,Rap1a/MAPK, GATA3 | Proliferation, Migration, Viability, Apoptosis Clinical staging and degree of differentiation | [32, 35-37] |
| Lung cancer | Hsa_circ_0010235, LncRNAPCGEM1, CircMED13L_012, Circ_0011292 | 3p/5p | TIPRL,WTAP,MAPK8, TMED5,Smad2,CHEK1 | Proliferation, Autophagy, Invasion, Apoptosis | [28, 38-42] |
| Liver cancer | KDM5A,LINC01006 | 3p | FXYD3-PI3K/AKT, CBX3,CREB1,PAK4 | Diagnosis, Proliferation, Migration, Invasion, Tumor foci formation | [43-47] |
| Gastric carcinoma | / | 3p | KRAS | Proliferation, Migration, Invasion, Apoptosis, Prognosis, Tumor site, Pathological grade, Chemotherapy | [20, 26, 30, 31] |
| Nasopharyngeal carcinoma | / | / | SCD1 | Proliferation, Migration, lipid accumulation | [48] |
| Pancreatic cancer | LINC00657 | / | PAK4 | Proliferation, Apoptosis | [49] |
| Retinoblastoma | / | / | Notch1/PAX6 | Proliferation, Migration, Invasion, Apoptosis | [50] |
| Osteosarcoma | Circ_0002137, SNHG14 | 3p | IGF1R ,FBXO22 | Proliferation, Invasion, Apoptosis | [51, 52] |
| Colorectal cancer | LINC00460 | 3p | HOXA1,CyclinD1/CDK4 CREB1/CCAR1/JNK1, MACC1,ANXA2 | Proliferation, Invasion, viability, Apoptosis | [53-57] |
| Cholangiocarcinoma | / | / | HDAC6 | Proliferation, Migration, Cilia formation | [58] |
| Esophageal cancer | CircLPAR3, Circ_0023984 | 3p | HMGB1,REV3L,GRB2 | Proliferation, Migration, Invasion | [22, 59, 60] |
| Bladder cancer | CircRIMS1, CircMBOAT2 | 3p | CREB1/c-Met,CCAR1 | EMT, Proliferation, Migration, Invasion, Tumor growth and metastasis | [61-63] |
| Glioma | CircMMP1 | 3p | SMC4,HMGB3 ,AJUBA | Proliferation, Migration, Invasion, Apoptosis | [23, 64, 65] |
| Oral cancer | Linc01234 | 3p | HDAC6,PAK4,GRB2 | Proliferation, Migration, Invasion, Apoptosis | [17, 66, 67] |
| Prostate cancer | / | / | / | Distinguishing the degree of malignancy | [68, 69] |
| Gallbladder carcinoma | / | / | cyclin M | Chemoresistance | [25] |

Chemotherapy

In 2014, Karolina Weiner Gorzel et al. demonstrated for the first time that the chemosensitivity of paclitaxel is related to the miR-433 expression level. MiR-433 confers drug resistance to paclitaxel in ovarian cancer cells. At the same time, it can functionally inactivate Rb protein, thereby disrupting cell cycle progression and inducing cellular senescence.^[24] In 2018, Jianhua Yu et al. showed that miR-433 expression enhanced the resistance of gallbladder cancer cells to gem-

citabine.^[25] Researchers have confirmed the same chemoresistance in gastric cancer^[26, 27] and lung cancer.^[28] These findings provide a basis for the potential use of miR-433 as a biomarker for chemosensitivity evaluation.

Foci Site, Pathological Grade, and Prognosis are Correlated

Hongchun Luo et al. first proposed that miRNA-433 is downregulated in gastric cancer and regulates GRB2, which

is involved in the molecular pathogenesis of this cancer.^[29] In the same year, Tetsuya Ueda et al. reverified that miRNA-433 expression is downregulated in gastric cancer, The miRNA-433 expression level was closely correlated with gastric cancer prognosis, and the survival rate was lower in patients with low miRNA-433 expression than in those with high miRNA-433 expression.^[30] In 2014, Ou Yangyang et al. reported that miRNA-433 expression correlates with the foci site and pathological grade of gastric cancer. The pathological grade of patients with high miRNA-433 expression was significantly better than that of those with low miRNA-433 expression.^[31] MiR-433 expression in breast cancer was positively related to the differentiation degree and negatively correlated with the clinical stage.^[32] These studies have suggested that miRNA-433 is an important player in the pathogenesis of some cancers. These findings possibly offer a new direction for cancer treatment.

MiRNA-433 and Other Diseases

With increase in in-depth research, the role of miRNA-433 in human diseases is gradually clear. In addition to cancer, miRNA-433 has a crucial role in non-cancer (Table 2). By summarizing the published relevant literature, we found that miRNA-433 is also a crucial player in the regulation of fibrosis, osteoblast differentiation, and inflammatory responses.

Fibrosis Promotion

In 2013, Rong Li et al. proposed that miR-433 is involved in renal fibrosis. Overexpression of miR-433 promotes transforming growth factor- β 1-induced fibrosis and may be a potential target for tissue fibrosis treatment.^[70] A study reported that miR-433 could directly target ganglion cell layer (GCL) and promote fibrosis by reducing the glutathione(GSH) level.^[71] Clarifying the role of miRNAs

Table 2. MiRNA-433 and other diseases (except cancers)

| Disease classification | Upstream factors | Target genes | MiRNA-433 functions |
|-----------------------------|------------------|---------------------|---|
| Nervous system | | | |
| Alzheimer disease | / | JAK2 | Restores A β inhibition of human neuroblastoma cell viability ^[79] |
| | CIRC-HUWE1 | Fgf7 | Mitigates cellular neuronal damage by Fgf7 ^[80] |
| Parkinson disease | / | FGF20 | Affects α -synuclein expression by inhibiting FGF20 ^[81] |
| / | / | Cdk12 | Regulates neuronal growth by promoting autophagy and inhibiting cell proliferation ^[82] |
| / | / | HIF-1 α | Inhibition of proliferation and migration of vascular endothelial cells and neurons by HIF-1 α ^[83] |
| Spinal cord injury | / | MAPK1 | Protects motor dysfunction and inflammatory responses after spinal cord injury ^[77] |
| Endocrine system | | | |
| Diabetes mellitus | / | COX2 | Protective effect on pancreatic beta cells cultured with high glucose ^[84] |
| Cardiovascular system | | | |
| Myocardial damage | Nobiletin | SIRT1 | Inhibits SIRT1 expression and affects cardiomyocyte hypoxia/reoxygenation injury ^[85] |
| | / | NDRG4 | Regulates myocardial ischemia-reperfusion injury by inhibiting NDRG4 ^[19] |
| Cardiac fibrosis | / | AZIN1/JNK1 | Promotes the proliferative effect of cardiac fibroblasts ^[72] |
| Digestive system | | | |
| Liver fibrosis | LncRNAGAS5 | TLR10 | Downregulation of miR-433 ameliorates liver fibrosis by targeting TLR10 ^[86] |
| Inflammatory bowel disease | / | MAPK8 | Acts as a protective agent for inflammatory bowel disease ^[78] |
| Skeletal system | | | |
| | / | Runx2 | Inhibition of BMP2-induced osteoblast differentiation by Runx2 ^[75] |
| | / | Igf1/ Hif1 α | Regulates circadian clocks and osteoblastic genes in vivo ^[87] |
| | / | / | Negative regulators of osteoblast maturation in vitro ^[76] |
| | / | MAPK/ Wnt | Negative regulators of bone formation in vivo ^[88] |
| | / | Dkk1 | Promotes osteoblast differentiation by inhibiting Dkk1 expression ^[89] |
| Others | | | |
| Polycystic ovarian syndrome | HOTAIRM1 | PIK3CD | Increases the proliferative capacity of granulosa cells and reduces apoptosis ^[90] |
| Depressive symptoms | / | FGF20 | Regulates FGF20 gene expression ^[91] |
| Acute vertigo | / | / | As a marker for differentiating posterior circulation stroke from peripheral vertigo ^[92] |

in renal fibrosis may allow the early diagnosis and treatment of renal diseases. The presence of cardiac fibrosis was strongly related to increased miR-433 expression. Antizyme Inhibitor 1 (AZIN1) is a miR-433-mediated target gene in cardiac fibrosis.^[72] In conclusion, miR-433 may represent a new treatment approach for fibrosis.^[73]

Osteoblast Differentiation

Delphine Simon et al. first proposed the role of miRNA-433 in bone diseases in 2010. Their study revealed that miRNA-433 is related to X-linked chondrodysplasia and inhibits HDAC6 expression. MiRNA-433 is probably the molecular cause of X-linked chondrodysplasia.^[74] A study showed that miR-433 inhibits BMP2-induced osteoblast differentiation by reducing the Runt-related transcription factor 2 (Runx2) transcription level. MiR-433 is suggested to be crucial for osteoblast differentiation.^[75] Neha S. Dole, M.S et al. confirmed that miR-433 expression was negatively correlated with osteoblast differentiation, and the miR-433 level was the lowest when osteoblast differentiation level was the highest.^[76] These studies have sufficiently proved that miRNA-433 has a crucial role in bone diseases, which is worthy of further exploration.

Inflammation

MiRNA-433 expression was significantly downregulated in the serum of patients and mice with spinal cord injury. By targeting MAPK1, miRNA-433 protected motor dysfunction and inflammatory responses after spinal cord injury.^[77] MiR-433-3p is delivered to lipopolysaccharide-induced macrophages and targets MAPK8, leading to the inhibition of the MAPK signaling pathway and decreased production of inflammatory cytokines. MiRNA-433 restores the dynamic balance of the intestinal microenvironment by regulating inflammatory factor aggregation.^[78] These findings may provide a theoretical basis for inflammation treatment.

Conclusion

Through literature summary, we realized that the downstream target is the key for miRNA-433's major regulatory role in diseases. MiRNA-433 inhibits the expression of downstream target genes by combining with specific seed sequences of these genes. Notably, the seed sequences of miRNA-433 binding to different downstream target genes are the same. A seed sequence of miRNA-433 was 3'... UAGUACU... 5'. Current research shows that all downstream targets of miRNA-433 are combined with this seed sequence. The downstream target genes only act as mediators during miRNA-433 biological function. Figure 3 depicts the reported targets of miRNA-433 involved in injury, inflammation, proliferation, apoptosis, metastasis, fibrosis, bone differentiation, angiogenesis and chemical resistance.

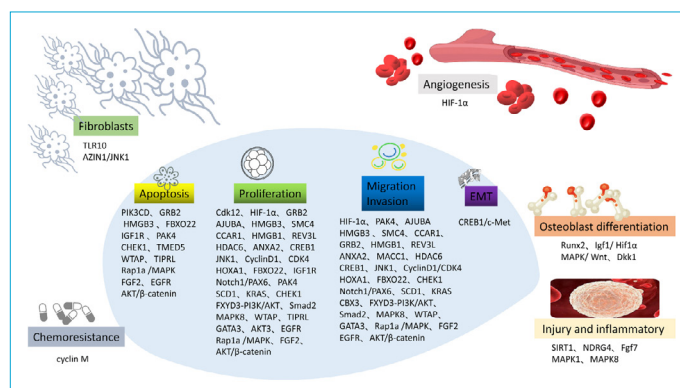


Figure 3. The reported targets of miRNA-433 involved in injury, inflammation, proliferation, apoptosis, metastasis, fibrosis, bone differentiation, angiogenesis and chemical resistance.

bone differentiation, angiogenesis, and chemoresistance. As shown in Figure 3, we can clearly see that a target gene can have multiple functions, and a function can also have multiple targets. Although the specific action mechanism remains unclear, we provided evidence for disease treatment and diagnosis by studying the miRNA-433 and target gene relationship, especially in cancer.

The ability of miRNAs to target multiple genes is highly worthy of in-depth research. However, a specific miRNA target may include both oncogenes and tumor suppressor genes, as well as some targets unrelated to cancer, which makes the development of selective miRNA targeted gene therapy possible. Although great progress has been made in this field, further improvement is still required. If these miRNAs targets have crucial regulatory effects on cancer cell proliferation, migration, and invasion, we can target inhibition or promotion of these miRNAs to promote tumor regression. The use of this type of therapy represents a new approach to addressing some of the medically more challenging diseases. Although many basic research involving miRNA therapies have been conducted over the years, only a small proportion of miRNA therapies have entered into clinical development so far. One of the biggest challenges in developing miRNA-based therapies is determining the best matched miRNAs for each disease, as only the best matched miRNAs can minimize potential toxicity and target effects.

Disclosures

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