Review Article

Spotlight on the Expanding Role of miR-647 in Human Cancers

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Abstract

MicroRNAs are a large group of small, non-coding ssRNAs (miRNAs) that have an epigenetically pivotal role in gene expression and other biological processes in cells and can be regarded as capable biomarkers for the early detection and management of cancer. The aim of the present review article is to summarize the evidence for recognizing the molecular mechanism, target genes, and clinical significance of miR-647 in different cancers. Multiple studies have demonstrated that aberrant expression of miR-647 could be found in a variety of malignancies, such as bladder cancer, cervical cancer, colorectal cancer, gastric cancer, glioma, hepatocellular carcinoma, non-small cell lung cancer, ovarian cancer, and prostate cancer have reported, notably, increase or decrease in expression of miR-647 so that it can function as a tumorigenic (oncomiR) or tumor suppressor gene. MiR-647 is effective in the proliferation, migration, and invasion of cancer cells by playing a function in cell cycle pathways. MiR-647 can be a valuable potential biomarker for assessing the extent of cancer, prognosis, and response to therapy and shows great therapeutic efficacy in different solid tumors. Moreover, serum concentrations of miR-647 are directly effective in decreasing overall survival and disease progression. So, an efficient therapeutic target can be the effect on miR-647 expression by antitumor drugs.

Keywords: Biomarker, cancer, microRNA, microRNA-647, miR-647

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Introduction

Up to less than 2% of the human genome consists of 20,000 protein-coding genes. It has been found that at least 70% of the genome sequences are transcribed into RNAs, and most of these transcripts have been determined as non-coding RNAs (ncRNAs).[1-5] Ongoing advances in large-scale genome sequencing revealed that long nRNAs (more than 200 nucleotides) and short ncRNAs (less than 20 nucleotides) are the major regulators of the human genome.[6-8] MicroRNAs are a large group of small, non-coding ssRNAs that are endogenous and regulated across the mammalian genome. The human genome can encode around 1000 types of microRNAs. They are found in eukaryotes and are, on average, 22–24 nucleotides in length.[9] Their primary role is to post-transcriptionally control gene expression. In this way, they interact with mRNA and silence the target gene. The majority of microRNA genes are generated in the intron regions of other genes and transcripted by RNA polymerase II.[10] More intense studies are necessary to identify new biological events concerning carcinogenesis and new therapeutic targets such as microRNAs. The microRNAs have been aberrantly expressed in different cancerous tissues so that their expression can be increased, decreased, or remain stable.[11]

In the human body, MiR-647 is made of two homologous miRNAs on human chromosome 20q13.33, hsa-miR-647-5p and hsa-miR-647-3p.[12] The Rfold web server (Vienna package) was employed to predict and plot the secondary structure of miR-647 with a minimum free-energy of -42.70 kcal/mol and dot-bracket notation (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) [Figure 1]. The MiR-647 evolved conservatively with similar structure and sequence in humans, mice, flies, and other species. MiR-647 regulation is essential in biological processes to make sure the existence of a physiological balance between human body systems. Some studies have demonstrated that miR-647 elevates cell proliferation and

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invasion and stimulates apoptosis in numerous cancers at the functional level.[15,20] Emerging evidence verified that miR-647 plays a critical role in various cancers [Table 1].

Materials and Methods

As mentioned above, researchers have selected two approaches. The first strategy was to search all articles and records released since 2000 in PubMed, Scopus, Embase, Google Scholar, and Cochrane databases utilizing MIRN647, MiRNA647, Hsa-Mir-647, MicroRNA 647, and Hsa-miR-647 keywords. Inclusion criteria comprised the expression and biological mechanisms of miR-647 in the tumorigenesis of various cancers.

Besides, the second strategy aimed to detect the targeted genes of miR-647 and dependent pathways engaged in carcinogenesis following prediction in relevant databases specific to microRNAs, like Software available in DIANA-miRPath v3. 0 (http://snf-515788.vm.okeanos.grnet.gr/), Tarbase V.8 (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=tarbasev8/index), and ultimately KEGG database (available at www.genome.jp/kegg/pathway.html).

Changes miR-647 in Different Tumors

Bladder cancer

One widespread urological malignancy is bladder cancer, the 10th most common cancer in the world. The availability of several treatments has resulted in a high five-year survival rate for bladder cancer (BC) patients.[13] Almost 33–75% of cases with bladder cancer are treatment-resistant because of metastasis or relapse of the disease. Furthermore, biomarkers such as microRNAs are considered important factors that improve or decrease the risk of clinically important events such as cancer episodes, expansion, recurrence, or patient deaths.[14] In one study, Du *et al*. (2021) extracted three differentially expressed circRNAs (has_circ_0023642, has_circ_0047322, has_circ_0041151) from the microarray dataset (GSE92675) in bladder cancer. They also detected four miRNAs (miR-616, miR-515-5p, miR-647, and miR-1178) that have potential binding sites with these three circRNAs.[15]

Cervical cancer

Globally, cervical cancer is the fourth common leading cause of cancer death in women, with an estimated 604,000 women distinguished with this condition and about 342,000 of them dying in 2020.[16] However, ~85% of the global deaths from cervical cancer occur in developing or underdeveloped countries, with the rate 18 times greater than in middle- and low-income countries compared to developed countries.[17] In addition, a vast majority of this type of cancer is due to the human papillomavirus infection. However, an important portion of this condition is self-evidence.[18,19] In functional experiments, Yang *et al*. (2020) demonstrated that ZFAS1 facilitated CC tumor growth and metastasis *in vivo*, as well

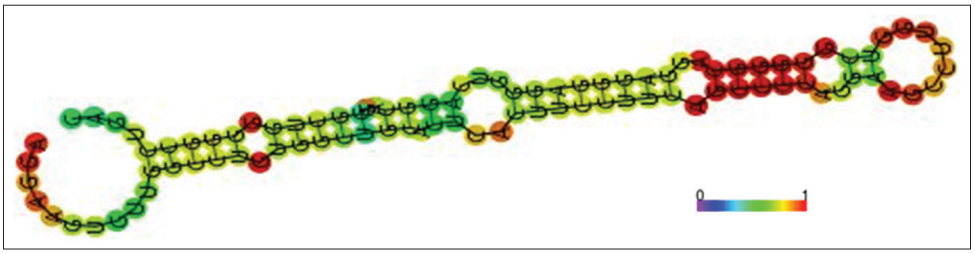

Figure 1: Prediction of Optimal Secondary structure of the has-miR-647 (EPS format) with -42.70 kcal/mol with its dot-bracket notation using the Rfold web server. The sequence of this microRNA: AGGAAGTGTTGGCCTGTGGCTGCACTCACTTC CTTCAGCCCCAGGAAGCCTTGGTCGGGGGCAG GAGGGAGGGTCAGGCAGGGCTGGGGGCCTGAC

Table 1: Functional characterization of miR-647 in cancers

9Cancer type	Expression	Related gene	Clinical features	Role	Ref.
Bladder cancer	↓	has_circ_0023642, has_circ_0047322, has_circ_0041151	metastasis	TSG	15
Cervical cancer	↓	ZAFS1	Cell proliferation; differentiation; migration; metastasis; invasion	TSG	20
Colorectal cancer	↑	NFIX	Cell proliferation; migration	OG	24
Gastric cancer	↓↑	SRF/MYH9, TP73 STX6, STX7, PRKCA	Cell proliferation; invasion; metastasis; migration; inhibition of apoptosis	TSG/OG	26-28
Glioma	↓	HOXA9	Cell proliferation; colony formation; invasion; increase in apoptosis	TSG	31
Hepatocellular carcinoma	↑	PTPRF	Cell proliferation; migration; invasion	OG	35
Non-small-cell lung cancer	↓	TRAF2, NF-κB pathway, IGF2	Cell proliferation; invasion; increase in apoptosis	TSG	39,40
Ovarian cancer	↓	VAMP2, MDM2	Cell proliferation; migration; increase in apoptosis	TSG	45
Prostate Cancer	↓	PAQR4	Cell proliferation; migration	TSG	49

↓: down-regulate, ↑: up-regulate, TSG=Tumor suppressor gene, OG=Oncogene

as cell proliferation, migration, and invasion *in vitro*. These results indicated that METLL3-mediated m6A modification arranged the sequestration of miR-647 by ZAFS1.[20]

Colorectal cancer

Following the GLOBOCAN 2020 information, colorectal cancer (CRC) has been introduced as the third leading cause of carcinogenic death in both genders and fourth-most typically diagnosed cancer occurring worldwide. About two million new CRC cases and nearly one million fatalities were estimated in 2020. Based on the studies, a global rise in CRC occurrence was also seen, generally in developing countries adopting the "western" lifestyle.[21] Even though the remarkable advancements in the molecular mechanism recognition and treatment of CRC through surgical resection, radiation therapy, chemotherapy, prognosis, and general survival, this cancer still requires further progress.[22,23] One study by Liu *et al*. (2017) revealed that miR-647 and miR-1914 promote the proliferation and migration of CRC cells by targeting NFIX in straight. Moreover, targeted delivery of siRNAs can turn off miR-647/1914, causing overexpression of NFIX, a practicable approach for CRC treatment.[24]

Gastric cancer

It has been reported that the second top reason for cancer death worldwide is gastric cancer. Although there are many advances in treating Gastric cancer (GC), patients have poor prognoses. Because of lacking appropriate biomarkers to determine GC initially, the five-year survival rate is low. It is fascinating to note that the sensitivity and specificity of CA125 and CEA (carcinoembryonic antigen) are limited in clinical settings, even with combined utilization, because they are not unique for GC diagnosis. Therefore, new methods based on molecular techniques are necessary to distinguish this disorder as soon as possible.[25] The study has been done by Ye *et al*., (2017) who indicated that miR-647 could function as a tumor suppressor in gastric cancer by targeting the SRF/MYH9 axis to inhibit metastasis.[26] In another study, Zhang *et al*. (2018) stated that TP73 had noticeably declined subsequent miR-647 overexpression and substantially increased subsequent miR-647 suppression. Overexpression of miR-647 causes increasing proliferation, migration, and invasion of MGC-803 cells and decreasing percentage of apoptotic cells. Totally, miR-647 plays the role of a tumor enhancer in gastric cancer by repressing TP73.[27] Ma *et al*., in their study, showed that the expression of serum miR-647 was significantly downregulated in patients with gastric cancer. Receiver-operating characteristic curve analyses revealed that serum miR-647 had a high efficiency for differentiating patients with GC from healthy controls. Additionally, low expression of miR-647 in serum was related to aggressive clinical characteristics and poor survival in GC. Mechanistically, since miR-647 downregulates in GC cell lines, it induces an increase in the expression levels of STX6, STX7, and PRKCA. Finally, their results clearly illustrated that serum miR-647 might act as a novel serum biomarker to follow up the GC progression.[28]

Glioma

Gliomas are the most prevalent kind of primary adult intracranial tumors. Some glioma subtypes result in morbidity and, in some cases, mortality incommensurate to their partially rare incidence.[29] Albeit Gliomas are more prevalent in aged adults, as they contain 8% of all pediatric brain tumors. In spite of multidisciplinary approaches to therapy, such as aggressive surgery, chemotherapy, and radiation, the median survival among some patients with this condition is just 12–15 months.[30] In one study, the results of Qin *et al*. (2020) showed that miR-647 expression was considerably downregulated in Glioblastoma Multiforme (GBM) cell lines in contrast to healthy cells. This overexpression of miR-647 prevents glioma cell proliferation, colony formation, and cell invasion but elevates apoptosis *in vitro*. HOXA9 was confirmed to be a direct target of miR-647, and the HOXA9 overexpression inverted the impacts of miR-647 on glioma cell behavior.[31]

Hepatocellular carcinoma

Yearly, 600,000 people die because of Hepatocellular carcinoma (HCC), so the disease is the third most cause of mortality due to cancer on the global scale. Besides, chronic infection with the hepatitis B and C viruses can be involved in developing HCC. In addition, intracerebral and bone metastasis causes a poor prognosis and a higher recurrence rate in early HCC,[32] regardless of the extraordinary therapeutic progress in the treatment of HCC, such as hepatic resection and chemotherapy, the prognosis outcomes of the patients are still inefficacious due to the growth of disseminated tumor metastases.[33] Theoretically, hepatocarcinogenesis depends on two prime principles: the activation of oncogenes or the inactivation of tumor suppressor genes.[34] In this way, focusing on differentiating the causes of HCC can provide a correct understanding of its initial diagnosis and treatment. Ye *et al*. (2022) reported that, opposite to the Protein Tyrosine Phosphatase Receptor Type F (PTPRF) effect, miR-647 could elevate the proliferation, migration, and invasion of HCV-huh7.5 cells. Besides, the functional testing results indicated that miR-647 overexpression or PTPFRF inhibition significantly affected the signaling of the Erk pathway, which could modulate cell growth, migration, and invasion. Moreover, using a dual luciferase reporter assay, they recognized PTPRF as a direct target of miR-647. Their results provided evidence of the role of miR-647 in promoting the biology of HCV-huh7.5 cells by preventing PTPRF expression.[35]

Non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the highest recurring lung cancer and the most-deadly malignant tumor in the world, responsible for about 1.5 million deaths in 2012.[36] In Europe, out of 353,000 die annually because of the disease, about 20% of them occur due to cancer.[37] Nearly, 70% of patients with lung cancer are because of NSCLC, a significant type with a poor prognosis after chemotherapy. So, predicting molecular targets and biomarkers for lung cancer is essential.[38] Zhang

et al., in one study that was conducted in 2018, claimed that overexpressing TRAF2 somewhat causes rescuing of the suppressive function of miR-647 in A549 and H1299 cells. Also, their results show that miR-647, by attenuating the NF-κB pathway, induces repression of lung carcinogenesis; in other words, they demonstrated that miR-647 as a tumor suppressor impacts NSCLC by the downregulation in expression of TRAF2 and the NF-κB signaling pathway.[39] Jiang *et al*. (2021) announced that miR-647 inhibits proliferation and improves cisplatin-induced cell apoptosis in NSCLC by downregulation in IGF2 expression.[40]

Ovarian cancer

According to the research, OC has been found to be one of the most malignant tumors of the women's reproductive system that has the first rank of mortality rates among gynecological cancers.[41] Treatment for OC principally involves platinum-based chemotherapy and surgical removal of the tumor.[42] As the population age gradually rises, the incidence of ovarian cancer (OC) has increased annually.[43] OC is usually diagnosed in advanced stages due to the absence of specific early clinical symptoms.[44] Therefore, investigating the molecular mechanism involved in the development of OC is necessary to identify effective tumor markers in diagnosing and treating OC. Sun *et al*. (2019) evidenced that circ-FAM53B, as a competing endogenous RNA (ceRNA) competitively sponged miR-646 and miR-647, provoking upregulation of VAMP2 and MDM2 expression at the post-transcriptional level. This mechanism mediates the OC cells' behaviors.[45]

Prostate cancer

Prostate cancer (PCa) is the commonest male malignancy and the second leading cause of mortality among men, responsible for approximately 21% of all new cancer cases and 10% of all deaths in men.[46] Despite the fact that androgen deprivation therapy can be used as primary therapy for patients with non-metastatic PCa,[47] many patients displayed poor prognoses because of tumor metastasis.[48] Thereby, it is an urgent need to examine novel diagnostic and therapeutic biomarkers as well as underlying molecular mechanisms in PCa progression. Chen *et al*. (2021) reported that CircNOLC1, raised by the transcription factor NF-κB, creates PCa progression through the miR-647/PAQR4 axis. This procedure causes PI3K/Akt pathway activation, so circNOLC1 is a potential biomarker and therapeutic target for PCa.[49]

MiR-647 Regulatory Mechanisms

The emerging evidence mentioned above manifests that miR-647 plays a key role in various cancers and leads to cancer progression through known pathways, comprising PI3K, JAK/STAT, MAPK signaling, apoptosis pathways, Chromatin organization, and signaling by GPCR. Also, all of these pathways associate mutually and have a central function in tumor cell growth, differentiation, and proliferation, as well as migration and invasion in various kinds of tumors.

MiR-647 takes part in different pathways, which are referred to in Table 2. The outcomes of bioinformatics work employing DIANA-miRPath, Tarbase, and KEGG pathways illustrate that miR-647 is closely related to other additional pathways, including steroid biosynthesis, adherence junction, thyroid hormone signaling pathway, transcriptional misregulation in cancer, endometrial cancer, hippo signaling pathway, and Wnt signaling.

Conclusion

MicroRNAs play fundamental regulatory functions in gene expression, and their dysregulation is observed in many human malignancies. Studies highlighted that miR-647 is a ncRNAs that performs a crucial role in cancer development with acceleration in invasion, migration, rapid growth, and proliferation of malignant cells. The evidence hypothesizes that miR-647 is a tumor suppressor in some cancers, while in others, it has played a tumorigenic role (oncomiR). The mechanism through which miR-647, by rising or declining in its gene target, acts a function in carcinogenesis and metastasis. Notably, some studies argue that abnormal miR-647 expression leads to increased tumor growth. Accordingly, as for the functional impact of miR-647 in the cellular pathways, it acts as a marker for assessing the extent of cancer, prognosis, and response to therapy and shows great therapeutic efficacy in different solid tumors. Moreover, serum concentrations of miR-647 are directly effective in decreasing overall survival and disease progression. So, an efficient therapeutic target can be the effect on miR-647 expression by antitumor drugs. Considering the roles of this microRNA in the diagnosis, prognosis, and treatment of the aforementioned cancers, it can probably be employed in cancer gene panels for clinical practice. Therefore, further studies and bioinformatic works on miR-647 dysregulation may provide novel sensitive diagnostic and prognostic markers, as well as therapeutic options for some cancers.

Future Prospect

An accurate examination of the upstream and downstream mechanisms of miR-647 is still needed to study and review it better. The miR-647 might be clinically suggested as a

Table 2: DIANA-miRPath v3. 0 and Tarbase v8. experimentally supported interactions for hsa-miR-647

KEGG pathway	Related genes
Steroid biosynthesis	DHCR24
Adherence junction	CDH1, PVRL4, CTNNA1
Thyroid hormone signaling pathway	THRA, NOTCH2, PIK3R3, HIF1A
Transcriptional misregulation in cancer	EWSR1
Endometrial cancer	AXIN1, CDH1, PIK3R3, CTNNA1
Hippo signaling pathway	AXIN1, CDH1, CTNNA1, WWTR1
Wnt signaling	WNT2B

multipurpose biomarker for the diagnosis and prognosis, cancer progression, and even assessing the efficacy of treatment. The miR-647 may, therefore, be employed as a novel therapeutic target in cancer treatment, and it can eventually become a crucial clinical treatment approach.

Ethical approval

This study was performed without any human or animal model experiments by the authors.

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Conflicts of interest

There are no conflicts of interest.

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