

The Prominent Role of miR-942 in Carcinogenesis of Tumors

Abstract

As a family of short noncoding RNAs, MicroRNAs have been identified as possible biomarkers for cancer discovery and assist in therapy control due to their epigenetic involvement in gene expression and other cellular biological processes. In the present review, the evidence for reaching the clinical effect and the molecular mechanism of miR-942 in various kinds of cancer is amassed. Dysregulation of miR-942 amounts in different kinds of malignancies, as bladder cancer, esophageal squamous cell carcinoma, breast cancer, cervical cancer, gastric cancer, colorectal cancer, Kaposi's sarcoma, melanoma, Hepatocellular carcinoma, nonsmall-cell lung cancer, oral squamous cell carcinoma, osteosarcoma, ovarian cancer, pancreatic ductal adenocarcinoma, renal cell carcinoma, and prostate cancer has stated a considerable increase or decrease in its level indicating its function as oncogene or tumor suppressor. MiR-942 is included in cell proliferation, migration, and invasion through cell cycle pathways, including pathways of transforming growth factor-beta signaling pathways, Wnt pathway, JAK/STAT pathway, PI3K/AKT pathway, apoptosis pathway, hippo signaling pathway, lectin pathway, interferon-gamma signaling, signaling by G-protein coupled receptor, developmental genes, nuclear factor-kappa B pathway, Mesodermal commitment pathway, and T-cell receptor signaling in cancer. An important biomarker, MiR-942 is a potential candidate for prediction in several cancers. The present investigation introduced miR-942 as a prognostic marker for early discovery of tumor progression, metastasis, and development.

Keywords: Biomarker, cancer, microRNA, microRNA-942, miR-942

Introduction

About 2% of humans' genome is comprised twenty-thousand protein-coding genes. Not <70% of the sequences are recommended for transcription into the RNAs that are often noncoding RNAs (ncRNAs).^[1-5] According to the modern advancements in sequencing approaches and large-scale genome sequencing, the long (>200 nucleotides) and short ncRNAs (<20 nucleotides) are proposed as the essential regulators in the human's genome.^[6-8] MicroRNAs are noncoding, endogenous, single-stranded, and small molecules having a regulatory effect on the mammalian genome and the human genome that are capable of encoding approximately a thousand types of them. MicroRNAs are about 22–24 nucleotides long and are located in eukaryotes.^[9] The main duty of MicroRNAs is regulating posttranscription that is conducted by the interaction with mRNA and silencing the target gene. MicroRNAs are mainly the result of the intron sections of other genes,

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and such genes are mostly transcribed via RNA polymerase II.^[10] It should be noted that further studies are to be conducted to emphasize the discovery of new biological events associated with carcinogenesis and innovative therapeutic targets including microRNAs. The expression of microRNAs differs in different tissues in different types of cancer. It could remain constant, be increased, or decreased.^[11]

MiR-942 of the human body consists of two homologous miRNAs on human chromosome 1, hsa-miR-942-5p and hsa-miR-942-3p. MiR-942-5p is the product of the 5' arm of miR-942 hairpin and is more suitable to be a potential diagnosis and prognosis biomarker in Cancer but not therapeutic targets. However, miR-942-3p is the product of the 3' arm of miR-942 and it might act as an oncogenic factor.^[12,13] The secondary structure predictions of miR-942 with a minimum free-energy-56.70 kcal/mol and dot-bracket notation have been plotted through the Rfold webserver (provided from Vienna package) available at <http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi>, as can be seen in Figure 1.

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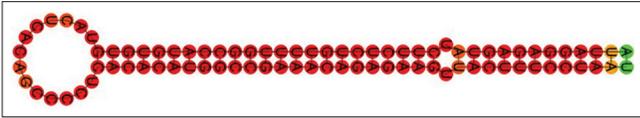


Figure 1: Prediction of Optimal Secondary structure of the has-miR-942 (EPS format) with -56.70 kcal/mol with its dot-bracket notation using the Rfold web server. The sequence of this microRNA: ATTAGGAGAG TATCTTCTCTGTTTTGGCCA TGTGTGT ACTCACAGCC CCTCACACATGGCCGAAACAGAGAAGTTACTTTCCTAAT

A conservative evolution was observed in MiR-942 of humans, mice, flies, and other varieties of which comparable sequence and structure exist. The regulation of MiR-942 is significant in the biological process for the physiological equilibrium between various systems in the human body. As reported in some studies, MiR-942 appears to improve cell proliferation and invasion while it can induce apoptosis in multiple cancers.^[14-18] In the present review, the evidence for reaching the molecular mechanism and clinical significance of the miR-942 is amassed in various kinds of cancers.

miR-942 variations in several tumors

According to several investigations, miR-942 has been dysregulated in diverse human tumors such as bladder cancer,^[12] breast cancer,^[15,16] cervical cancer,^[13,17] colorectal cancer (CRC),^[18-21] esophageal squamous cell carcinoma (ESCC),^[22] gastric cancer,^[23] hepatocellular carcinoma (HCC),^[24-27] Kaposi's sarcoma,^[28] melanoma,^[29] nonsmall-cell lung cancer (NSCLC),^[30-32] oral squamous cell carcinoma (OSCC),^[33] osteosarcoma,^[34] ovarian cancer (OC),^[35,36] pancreatic ductal adenocarcinoma (PDAC),^[37] renal cell carcinoma (RCC),^[38-40] as well as prostate cancer^[41,42] [Table 1].

Bladder Cancer

As a significantly popular urological malignancy, bladder cancer has been known as a prevalent universal cancer so that its occurrence is increasing. Although various treatments have been provided, a 5-year survival rate of bladder cancer cases is yet reached.^[43] Almost 33% to 75% of the BC patients are not capable of responding to therapy owing to metastasis or disease relapse. Furthermore, biomarkers are considered as the surrogate markers that are capable of enhancing or declining the clinicians' suspect of the additional clinically significant issues, such as cancer episode, recurrence, expansion, or the cases losses could or could not occur and or particular therapies can be capable of declining risks of the events.^[44] Wang *et al.*, indicated that by hindering the expression of large tumor suppressor 2, i.e., LATS2 a TAZ inhibitor, TAZ-induced miR-942-3p expression up-regulation leads to the amplification of upstream signaling. The effects on cell proliferation, angiogenesis, EMT, glycolysis and, ROS levels induced by TAZ knockdown were attenuated by MiR-942-3p. An

innovative positive feedback loop were identified between TAZ and miR-942-3p regulating biological functions in bladder cancer cells by GAS1 expression showing TAZ, miR-942-3p, and GAS1 as possible therapeutic options for bladder cancer therapy.^[12]

Breast Cancer

According to several studies, breast cancer is accounted for the most prevalent malignancy and a significant reason for universal death of women involving 23% of all new cases and 14% of all cancer deaths in 2008.^[45] Although notable progress has been achieved in the early prognosis and targeted therapies, the precise reason for such disease has been under investigation so far. Therefore, the discovery of molecular mechanism (s) of genetic tumors and the development of such diseases are of great importance. In other words, promoting reliable biomarkers for the prediction of drug responses and tumor progression are the top priorities.^[46,47] Based on an investigation conducted by Zhang *et al.*, although miR-942 had great expression in breast cancer, the cell viability, proliferation, migration, and invasion of breast cancer were considerably suppressed by its low expression. However, such low expression led to an increase in cell apoptosis. The induction of down-regulation of N-cadherin and Snail and up-regulation of E-cadherin was associated with the low-expression of miR-942. FOXA2, which was verified as the direct target gene for miR-942 and was low-expressed in breast cancer, partially reversed the impact of overexpressed miR-942 on promoting cell viability, migration, proliferation, invasion, proliferation, and suppressed cell apoptosis. Lower expression of FOXA2 and higher expression of miR-942 resulted in a less survival rate in breast cancer cases. The progression of breast cancer was promoted by MiR-942 via downregulating the expression of FOXA2.^[15] Li *et al.* demonstrated that sponging miR-942, hsa_circ_0001785 can regulate the SOCS3 in breast cancer cells.^[16]

Cervical Cancer

In 2018, with an expected 570,000 patients and 311,000 mortalities around the world, cervical cancer has been accounted for the fourth-most prevalent cancer and the fourth major cause of death by cancer in females.^[48] However, nearly 85% of cervical cancer mortalities happen in developing or underdeveloped countries, and with an 18-fold higher death rate in low-income and middle-income countries in comparison to wealthier countries.^[49] Furthermore, the infection caused by the human papillomavirus is known as one of the major reasons for such a disease. Nevertheless, most of such infections have been known to be self-evident.^[50,51] Ou *et al.*, demonstrated that by sponging miR-942-5p, circ-AKT1 up-regulates AKT1. CircRNA-AKT1's sequestration of miR-942-5p to up-regulate AKT1 and promote cervical cancer progression can be a new molecular target to improve cervical

Table 1: Functional characterization of miR-942 in cancers

Cancer type	Expression	Related gene	Clinical features	Role	Ref.
Bladder cancer	↑	GAS1, LATS2	Cell proliferation; migration; invasion; metastasis; inhibition of apoptosis	OG	[12]
Breast cancer	↑	FOXA2, SOCS3	Cell viability; proliferation; migration; invasion; inhibition of apoptosis; shorter survival rate	OG	[15,16]
Cervical cancer	↓	AKT1, GFI1	Cell proliferation; invasion; EMT	TSG	[13,17]
Colorectal cancer	↑	APC, DLG2, BATF2, CCBE1	Cell proliferation; metastasis	OG	[18-21,104]
Esophageal squamous cell carcinoma	↑	sFRP4, GSK3 β , TLE1	Cell proliferation; differentiation; migration	OG	[22]
Gastric cancer	↑	NFKBIA	Cell proliferation; invasion	OG	[23]
Hepatocellular carcinoma	↑	RRM2B, MBL2, ALX4, ISG12a, PPAR γ , BAMBI, GFI1	Proliferation; inhibition of apoptosis; colony formation; migration, invasion; metastasis	OG	[24-27]
Kaposi's sarcoma	↑	I κ B α	Tumor development	OG	[28]
Melanoma	↑	DKK3	Cell proliferation; migration; invasion; inhibition of apoptosis; cell viability	OG	[29]
Nonsmall-cell lung cancer	↑	BARX2, ZNF471	Cell migration; invasion; angiogenesis; metastasis	OG	[30-32]
Oral squamous cell carcinoma	↓	LTBP2	Cell proliferation; migration; invasion; high T stage; advanced TNM stage	TSG	[33]
Osteosarcoma	↑	STAT	Cell proliferation; induce apoptosis	OG	[34]
Ovary cancer	↓	CUL4B, EPSTI1	Cell proliferation; apoptosis; migration; invasion	TSG	[35,36]
Pancreatic cancer	↓	ANK1, GDNF, PAX6	Cell growth; clonogenic ability; migration, invasion; liver metastasis; apoptosis resistance	TSG	[37]
Renal cell carcinoma	↑	FOXO3, SALL1, METAP1, DCAF11	Metastasis	OG	[38-40]
Prostate cancer	↓	-	High grade tumor	TSG	[41,42]

↓: Downregulate, ↑: Upregulate, TSG: Tumor suppressor gene, OG: Oncogene, EMT: Epithelial-mesenchymal transition

cancer treatment.^[13] Zhang *et al.*, confirmed that lncRNA HCG11 can be capable of binding to miR-942-5p directly. Furthermore, the invasion and growth of cervical cancer cells were suppressed through inhibition of miR-942-5p with the growth factor-independent transcription repressor 1 (GFI1) gene as the target gene of miR-942-5p.^[17]

Colorectal Cancer

CRC is accounted for the third most prevalent variety of cancer in humans around the world with more than 1.2 million new subjects per annum^[52] Although researchers have achieved significant progress in acquiring awareness of the precise molecular mechanism and advances in CRC therapy in radiation therapy, chemotherapy, surgical resection, diagnosis of CRC, there has yet been poor overall survival and no significant improvement has not yet been obtained.^[45,53] Shan *et al.*, found that there is a negative relation between miR-942 and Linc00675 and that miR-942 is highly expressed in clinical CRC tissues. Furthermore, they stated the prevention of Wnt/ β -catenin signaling in the Linc00675/miR-942-regulated pathway in CRC cells.^[18] The function of the Wnt signaling pathway in carcinogenesis and embryonic development has been identified. It has been considered to have a major impact on the initiation and progression of CRC. Another study demonstrated that miR-942 up-regulated the Wnt signaling by directly targeting APC, a tumor suppressor in the same pathway.^[19]

Li *et al.*, revealed that miR-942-5p was notably upregulated in human CRC tissues and cell lines. Furthermore, miR-942-5p could directly target DLG2 mRNA leading to the enhancement of CRC cells malignancy phenotypes. They also found that DLG2 overexpression enhanced YAP phosphorylation, a critical downstream effector of DLG2. The tumor-suppressive capacity of YAP in CRC cell lines was demonstrated.^[20] Yu *et al.* stated that miR-942-5p expression was clearly up-regulated in CRC tissues or cells in comparison to the control groups. Furthermore, they demonstrated that circ_0005927 was a sponge of miR-942-5p, and miR-942-5p bound to BATF2.^[21] Zhou *et al.*, confirmed that miR-942-5p exerts oncogenic actions in CRC by targeting CCBE1 and identified miR-942-5p as a potential clinical biomarker for CRC diagnosis and therapy.^[54]

Esophageal Squamous Cell Carcinoma

Very often, esophageal cancer does not respond to the current therapeutic approaches and therefore, has poor outcomes. The annual rate of new esophageal cancer is around 400,000 cases worldwide, being the eighth most prevalent cancer and the sixth most prevalent cause of cancer-associated deaths. For most of the 20th century, squamous cell cancer (SCC) comprised the vast majority of esophageal cancers globally.^[55] Ge *et al.*, reported that in ESCC, miR-942 is significantly up-regulated and that

higher miR-942 levels are correlated with weak diagnosis in ESCC cases. MiR-942 directly targeting sFRP4, GSK3 β and, TLE1, multiple level negative regulators of Wnt/ β -catenin signaling cascade, miR-942 upregulate the Wnt/ β -catenin signaling activity. Furthermore, their findings revealed that by directly binding to the miR-942 promoter, c-myc promotes its expression. Taken together, the oncogenic effect of miR-942 in ESCC established in this study suggests miR-942 as an efficient therapeutic option for ESCC.^[22]

Gastric Cancer

Based on several studies, gastric cancer accounts for the second principal cause of cancer-associated deaths. Despite the efficacy of the initial treatment of Gastric cancer, the prolonged survival rate of such cancer is yet limited since there have not been appropriate biomarkers for initial gastric cancer (GC) determination. Although CA125 and carcinoembryonic antigen (CEA) have been recognized as markers in clinical studies, they lack enough sensitivity and specificity even in the case of integrated use. Therefore, there is an urgent need for novel molecular diagnoses for the initial discovery of GC.^[56] Lu *et al.*, stated circ-CEP85 L can be capable of binding to miR-942-5p directly. Furthermore, rescue trials demonstrated that the invasion and proliferation of gastric cancer cells may be inhibited by circ-CEP85 L through sponging miR-942-5p. Conclusively, they verified the effective reversal of NFKBIA-induced circ-CEP85 L overexpression inhibition by down-regulation of miR-942-5p.^[23]

Hepatocellular Carcinoma

HCC, known as the 3rd major reason for world cancer-associated mortality leading to nearly 600,000 deaths per annum. Furthermore, HCC has been associated with the infections caused by hepatitis B and C virus. Moreover, weaker diagnosis and recurrence rates have been largely associated with intracerebral and bone metastasis in the initial HCC.^[57] Despite successful progress in the HCC therapeutic approaches, including chemotherapy, ablation, and hepatectomy, due to the unlimited proliferation and distant metastasis of HCC, patients' outcomes are still unfavorable.^[58] The association between the initiation and progression of HCC with multiple genetic mutations, activation of oncogenes, or inactivation of antioncogenes is well understood.^[59] Therefore, identifying promising new therapeutic options can facilitate the early diagnosis and therapy of HCC. Zhang *et al.*, showed the significant upregulation in HCC. The high expression of miR-942 was significantly correlated with lymphatic metastasis, serum alanine transaminase level, tumor size, and T stage. Furthermore, the high expression of miR-942 was related to shorter disease-free survival time and overall survival in HCC patients. RRM2B was proven to be a target gene of miR-942. The malignant phenotypes

of Huh7 and MHCC97H cell lines were markedly promoted by miR-942 mimickers, while the opposite effect was observed with its inhibitor. Egr-1 and PTEN, markers of epithelial-mesenchymal transition and matrix metalloproteinases are among downstream genes of RRM2B that can be regulated by miR-942. Finally, these researchers proposed miR-942 as a potential biomarker for HCC, making its inhibitor a possible therapeutic option for treating such a fatal disease.^[24] Xu *et al.*, found that compared to normal tissues, the level is elevated in HCC cell lines and tissues. They also showed that miR-942-3p expression is related to the pathological step and tumor node metastasis step, making it an independent predictor of weak survival in HCC cases. Furthermore, mannose-binding lectin 2 (MBL2) has been known as a direct target of miR-942-3p, having an inverse correlation with miR-942-3p expression and improper survival in HCC cases. Naturally, MBL2 restoration inhibited HCC progression and attenuated the miR-942-3p-induced tumor-promoting effects. In conclusion, by targeting MBL2 and acting as an oncogenic factor in HCC, miR-942-3p can be a possible marker for HCC cases.^[25] Xu *et al.* demonstrated that an increased miR-942-5p was evident in HCC cells and tissues. Moreover, the cell growth of HCC was hindered by the up-regulation of miR-942-5p via targeting ALX4.^[26] Lu *et al.*, reported the promoted progression of HCC with miR-942-5p overexpression, which was reversed by the upregulation of GFI1.^[27] In liver cancer cells and tissues, there is a negative relation between miR-942 and the expression of interferon-stimulated gene 12a (ISG12a). Forced expression of miR-942 in TRAIL-sensitive cells turns the TRAIL-sensitive phenotype into a resistant one by significantly reducing endogenous ISG12a levels. Downregulation of ISG12a by miR-942 is required for maintaining the TRAIL-resistant phenotype of cancer cells in favor of cancer cell survival. Thus, miR-942 could be an innovative potential marker of response to medications with serious implications in designing novel therapeutic agents targeting TRAIL-resistant tumors.^[60] Further investigations revealed the effect of miR-942 on the diagnosis and prognosis of liver diseases and infections that may develop to HCC in the future. MiR-942 expression was decreased by HCV infection in HLCZ01 cells and miR-942 was negatively associated with ISG12a expression in both liver biopsies and HCV-infected cells.^[61] Tao *et al.*, stated that miR-942 expression was up-regulated inactivated, hepatic stellate cells (HSCs) and correlated inversely with activin membrane-bound inhibitor (BAMBI) expression in liver fibrosis progression. MiR-942 expression is induced in HSCs by two significant drivers of liver fibrosis and inflammation, namely transforming growth factor-beta (TGF- β) and lipopolysaccharide (LPS), via Smad2/3 respective NF- κ B/p50 binding to the miR-942 promoter. In conclusion, in human liver fibrosis, HSC activation is mediated by the TGF- β and LPS-induced miR-942

via down-regulation of BAMBI. Their study provided new insights into the molecular mechanisms of HSC activation and their role in liver fibrosis.^[62] By targeting the peroxisome proliferator-activated receptor-gamma (PPAR γ) 3'UTR, miR-942 negatively regulates PPAR γ expression. TGF β 1-induced HSC activation is promoted by PPAR γ inhibition, and this effect is blocked after inhibiting the miR-942. Furthermore, chiefly represented in fibrous septa, there is a negative correlation between miR-942 and PPAR γ in liver fibrosis. PPAR γ targeted by miR-942 decreases HSC activation in human hepatic fibrosis.^[63]

Kaposi's Sarcoma

Kaposi sarcoma has been identified as a soft tissue tumor that is prevalent among humans of different races and ages with several types and presentations. In its most popular type, Kaposi sarcoma is experienced in subjects with immunosuppression, including acquired immunodeficiency syndrome (AIDs) or immunosuppression owing to organ transplantation.^[64] Kaposi's sarcoma (KS) is caused by its related herpesvirus, known as Kaposi's sarcoma-associated herpesvirus (KSHV), or human herpesvirus 8. AIDS-associated KS (AIDS-KS) is still clinically challenging in patients from the United States and sub-Saharan Africa, such as a subset of AIDS cases on highly active antiretroviral therapy (HAART).^[65-68] There is also a link between KSHV infection and two AIDS-associated B-cell lymphoproliferative diseases, including a subset of multicentric Castleman's disease (MCD) and primary effusion lymphoma (PEL).^[69,70] Yan *et al.*, found that miR-942-5p suppression relieves I κ B α expression and reduces Vpr inhibition of Kaposi's sarcoma-associated herpesvirus (KSHV) lytic replication, while miR-942-5p overexpression enhances Vpr inhibition of KSHV lytic replication. Collectively, their findings demonstrate that, via activating NF- κ B signaling through up-regulation of a cellular miRNA to target I κ B α , internalized HIV-1 Vpr inhibits KSHV lytic replication. Based on these findings, the significant impact of Vpr on KSHV's life cycle is evident.^[28]

Melanoma

Melanoma is a kind of aggressive skin cancer, which accounted for nearly 73% of skin cancer-related death and is usually resulted from direct exposure to the Sun's ultraviolet radiation.^[71,72] The incidence of melanoma is gradually increasing worldwide in the past years.^[73] Current therapies of melanoma are surgery, chemotherapy, and target therapy.^[74] However, the prognosis of melanoma is still poor with only 10%–15% of the 10-year survival rate in metastatic melanoma.^[75] Therefore, a better understanding of melanoma pathogenesis needs to be investigated to improve the prognosis. Zhang *et al.*, studies the upregulation of miR-942-5p in melanoma cells and tissues which was considerably related to a weak

diagnosis. The Wnt/ β -catenin pathway can be activated via MiR-942-5p by targeting 3'-UTR of DKK3, leading to melanoma cell proliferation, invasion, and migration, which promotes the progression of melanoma. Based on their findings, miR-942-5p can be a biomarker for the prognosis and diagnosis of melanoma.^[29]

Non-small-Cell Lung Cancer

NSCLC is regarded as the most prevalent lung cancer and the most fatal malignancy worldwide. Based on several investigations, lung cancer is accounted for the most prevalent reason for global fatality and considered approximately 1.5 million losses in 2012.^[76] The disease accounts for yearly death of 353,000 in Europe, showing about 20% of total cancer deaths.^[77] The principal kind of lung cancer is known as NSCLC involving almost 80% of lung cancer patients. NSCLC is accounted for a weak prognosis following chemotherapy. Therefore, prognostic biomarkers and molecular targets are of great importance for lung cancer.^[78] Yang *et al.* showed the relatively high expression of miR-942 in human NSCLC tissues and cells. *In vitro* assays expressed the promotion of cell migration, invasion, and angiogenesis by miR-942 overexpression. By inhibiting BARX2, miR-942 increases EMT-associated proteins, N-cadherin, and vimentin, while reduces the expression of E-cadherin. According to their investigation, directly targeting BARX2, miR-942 induces EMT-related metastasis providing a possible therapeutic approach for NSCLC.^[30] Wang *et al.* showed that LIFR-AS1 is a pivotal miR-942-5p-interacting lncRNA. MiR-942-5p overexpression reduces LIFR-AS1 in NSCLC cells. LIFR-AS1 can sponge miR-942-5p, leading to the repression of ZNF471.^[31] Zhou *et al.*, revealed that serum miR-942 expression amounts were notably up-regulated in NSCLC. In addition, serum miR-942 was superior to CEA, CYFRA21-1, and SCCA for the initial prognosis of NSCLC. The integration of serum miR-601 and miR-942 improved the effectiveness of identifying early-stage NSCLC. Taken together, serum miR-942 can be capable of acting as a hopeful molecular marker for the early prognosis of NSCLC and its diagnosis prediction.^[32]

Oral Squamous Cell Carcinoma

OSCC represents the most malignant neoplasm in oral cancer with a mortality rate of more than 50%. The OSCC is multistep neoplasia initially developed from mild oral epithelial hyperplasia to dysplasia followed by carcinoma *in situ*.^[79] OSCC is rated among the 6th most frequent oral malignancies, with a yearly prevalence of more than 500,000 cases.^[80] OSCC alone is considered responsible for more than 90% of oral cancers cases and has the highest rate of mortality globally.^[81-83] Wang *et al.*, indicated that by accelerating EMT and phosphorylation of PI3K/Akt/mTOR signaling pathway components,

the circEPSTI1/miR-942-5p/LTBP2 axis influences oral squamous, cell carcinoma, cell invasion, and proliferation.^[33]

Osteosarcoma

Osteosarcoma is known as the most prevalent bone cancer in infants, adolescents, and young adults^[84] and mostly around the remodeling and bone growth regions. Based on new studies, the possible cause of osteosarcoma is the genetic and epigenetic alterations disrupting mesenchymal stem cells for modifying into osteoblasts.^[85] Therapy outcomes have recently been updated considerably for osteosarcoma,^[86] leading to a notable advancement in osteosarcoma cases with a 5-year survival rate (60%–70%). Nevertheless, outcomes have yet been unknown, and recurrence of the pulmonary metastasis after chemotherapy and surgery is the reason for the mortality in most subjects.^[87,88] Sun *et al.*, stated that circ_0001649 acts as a sponge absorbing miR-942 to suppress osteosarcoma cell proliferation, induce apoptosis, and hinder the STAT pathway.^[34]

Ovarian Cancer

OC is a malignant tumor of the female reproductive system, with epithelial OC ranking first with respect to mortality among gynecological cancers.^[89] The main treatment strategies for OC are platinum-based chemotherapy and surgery.^[90] The occurrence of OC increases by gradual aging.^[91] The diagnosis of OC is mostly made at advanced stages owing to the shortage of specific early clinical symptoms.^[92] Hence, investigating the molecular mechanisms of OC progression can contribute to the discovery of efficient tumor markers for OC diagnosis and therapy monitoring. Du *et al.* revealed that miR-942-5p level was reduced in OC cells and tissues. Moreover, up-regulation of miR-942-5p impeded OC cell growth via targeting CUL4B.^[35] Xie *et al.* found that by sponging miR-942, circEPSTI1 regulates EPSTI1 expression and OC development.^[36]

Pancreatic Ductal Adenocarcinoma

PDAC, the most prevalent neoplastic disorder of the pancreas, accounts for more than 90% of the whole pancreatic malignancies.^[93] Currently, the 5-year overall survival of PDAC is lower than 8% making it the fourth most prevalent reason for cancer-related mortalities around the world.^[94] Although numerous investigations have recently been conducted on PDAC, not enough effectiveness has been achieved by chemotherapy, radiation, and therapeutic regimens.^[95] Therefore, the only therapy remains surgery which only 15–20 percent of PDAC cases could be eligible for effective surgery at the presentation time.^[96] Wong *et al.* identified 169 circRNAs in PDAC cells differentially expressed in comparison to nontumor human pancreatic ductal epithelial cells. Compared with the others,

circFOXK2 was identified as significantly upregulated in PDAC cells and 63% of primary tumors (53 of 84). Multiple miRNA binding sites were found in circFOXK2, functioning as a sponge for miR-942 and promoting ANK1, GDNF, and PAX6 expression.^[37]

Renal Cell Carcinoma

RCC is accounted for the most prevalent malignant solid tumor in adults. A total of 63,920 new kidney and renal pelvis cancer cases and 13,860 associated deaths were expected to happen in the US in 2014.^[97] With surgical resection remaining the best curative therapeutic strategy for RCC, nearly 20%–30% of cases undergo local and/or distant disease recurrence.^[98] Furthermore, at the time of the initial prognosis, metastases are found in up to 30%.^[99] MiR-942 has been one of the most reliable predictors of effectiveness. In this innovative paracrine mechanism, MMP-9 and VEGF secretion are up-regulated by high levels of miR-942 in MRCC cells for enhancing endothelial migration and sunitinib resistance.^[38] Chen *et al.* stated that lncRNA LINC00461 is capable of acting as a miR-942 ceRNA and affecting the survival of cases of RCC by controlling the expression of SALL1, METAP1, and DCAF11.^[39] In another study, Luo *et al.*, in acute kidney injury expressed that miR-942-5p expression was decreased in the LPS-treated HK-2 cells, and miR-942-5p overexpression is capable of inhibiting LPS-induced inflammation and apoptosis of HK-2 cells by targeting FOXO3.^[40]

Prostate Cancer

As the most prevalent cancer in men, prostate cancer is observed in one out of every nine men at the age of 65.^[100] Despite the efficiency of surgical operation and radiotherapy for most cases, prediction in the individuals experiencing higher degrees of the disease is limited.^[101] The affected cells have a high susceptibility to metabolic variations.^[102,103] McDonald *et al.*, stated that the expression of miR-942 decreases in high-grade compared to low-grade prostate cancer cases at biopsy.^[41] Li *et al.*, demonstrated that miR-942-5p were repressed in PC3 cells but upregulated in DU145 cells.^[42]

MiR-942 Regulatory Mechanisms

Figure 2 shows the influence of miR-942 on molecular pathways and the related interaction with other genes. MiR-942 is mainly related to carcinogenesis and cancer progression by well-known pathways, such as TGF- β signaling pathways, Wnt pathway, JAK/STAT pathway, PI3K/AKT pathway, Apoptosis pathway, Hippo signaling pathway, Lectin Pathway, Interferon-gamma signaling, Signaling by G-protein coupled receptor, Developmental genes, nuclear factor-kappa B pathway, Mesodermal commitment pathway, and T-cell receptor signaling in cancer. All the mentioned pathways have a relationship

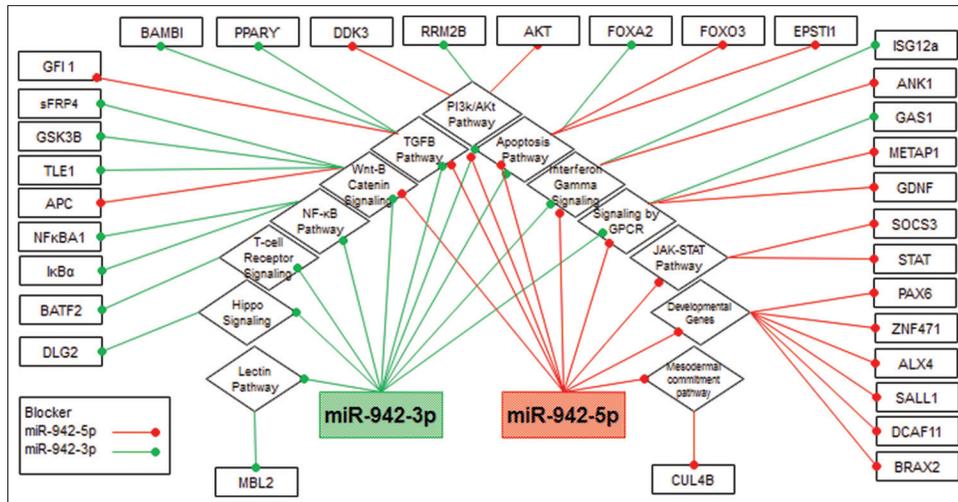


Figure 2: The overview of miR-942 contribution in different cellular pathways, which mediated mechanisms involved in cancer progression. Totally, miR-942 working as oncogene to regulate genes such as Apoptosis, which by own have interactions with cell cycle control. In the other side, miR-942 have a hand in controlling the pathways of transforming growth factor-beta signaling pathways, Wnt pathway, JAK/STAT pathway, PI3K/AKT pathway, hippo signaling pathway, lectin pathway, interferon gamma signaling, signaling by GPCR, developmental genes, nuclear factor kappa B pathway, Mesodermal commitment pathway, and T-cell receptor signaling, which targeted by miR-942 and also involved in carcinogenesis, and other pathways which all of them function in cell proliferation and oncogenesis. peroxisome proliferator-activated receptor gamma $\text{I}\kappa\text{B}\alpha$

with each other. Furthermore, they have a significant influence on the progression, proliferation, or rapid growth, migrating and, invading the cancer cells, as well as cell differentiation in a variety of tumors.

As can be seen in Table 2, MiR-942 participates in several pathways. The results of our bioinformatics work using DIANA-miRPath based on Tarbase, microT-CDS, TargetScan and KEGG pathway show that miR-942 is associated with various other pathways including ECM-receptor interaction, thyroid hormone synthesis, thyroid hormone signaling pathway, arrhythmogenic right ventricular cardiomyopathy, TGF-beta signaling pathway, hippo signaling pathway, vascular smooth muscle contraction, and Lysine degradation which targeted by miR-942-3p and-5p and also included in carcinogenesis.

Conclusion

MicroRNAs make significant contributions toward the regulation of genes, and microRNA dysregulation could be regarded as a distinctive feature in cancer. According to several investigations, miR-942 is categorized in the ncRNAs contributing chiefly to the invasion and migration steps, and in the proliferation or rapid development of cancer cells. According to the majority of the studies, unlike miR-942-3p is an oncogene, miR-942-5p acts as one of the tumor suppressors. The mechanism through which miR-942 up-regulation or downregulation involves in the tumor expansion as well as carcinogenesis is complicated. Furthermore, it includes various levels that mostly having a significant effect on cell proliferation and hence tumor growth despite its unknown features. According to the results of prior investigations, variations in expressing miR-942 are firmly associated with the severity of

cancer tumor development. Hence, they may be potential candidates for measuring the degree of cancer, prognosis, response to therapy, and even as a possible therapeutic option for solid tumors. Serum miR-942 levels have a direct connection with the progression of the disease and reduced survival rate. Considering the functional mechanisms of miR-942 in cellular pathways, it is promising for the diagnosis of the disease progression, stage, as well as the prognosis and measuring the effectiveness of therapy. Moreover, it shows considerable potential for increasing miR-942 expression as a therapeutic option as effective as anti-tumor medications. According to the obtained results, miR-942 is proposed as a potential candidate for a prognostic marker for early discovery of tumor growth, metastasis, and progression.

Materials and Methods

As previously discussed, two strategies were adopted by the authors. In the first strategy, all the published articles after the year 2000 were surveys in PubMed, Scopus, Embase, Cochrane, and Google Scholar databases using keywords of MIRN942, MiRNA942, Hsa-Mir-942, MicroRNA 942, and Hsa-miR-942. The relation to the biological mechanism (s) and expression of miR-942 in growing tumors in any type of cancer was selected as inclusion criteria.

In addition, the second strategy tried to find the targeted genes by miR-942 and relative pathways involved in carcinogenesis in the base of prediction in relative of databases specific for microRNAs such as Software available in DIANA Tools (<http://diana.imis.athenainnovation.gr/>) including MicroT-CDS as well as Tarbase and also Target Scan (<http://www.targetscan.org/>), miRDB (<http://www.mirdb.org/>), miRwalk (<http://mirwalk.umm.uniheidelberg>.

Table 2: Interactions derived from databases in different pathways for hsa-miR-942-5p and-3p

KEGG pathway	Related genes	
	miR-942-5p	miR-942-3p
ECM-receptor interaction	COL4A5, COL24A1, ITGB6, COL6A6, DAG1, ITGA10, COL11A2, LAMC1, ITGA7, FN1, CD47	-
Thyroid hormone synthesis	ADCY7, TPO, PAX8, PLCB1, HSP90B1, TG, ITPR2, ADCY4	ATP1B1, PLCB1,
Thyroid hormone signaling pathway	NRAS, RAF1, THRA, PLCZ1, MED1, PLCB1, PLCG1, NCOA2, THRB, PLCE1 , PFKFB2, ATP2A2, FOXO1, CREBBP, SIN3A	ACTB, ATP1B1, PLCB1, TSC2, DIO2
ARVC	CACNG8, TCF7L2, ITGB6, PKP2, CTNNA1, SLC8A1, DAG1, ITGA10, ITGA7, CTNNA3, LMNA, ATP2A2	ACTB, SLC8A1
TGF-β signaling pathway	SMAD2, INHBA, ZFYVE16, SMAD4, ACVR1C, BMPR1A, BAMBI, CREBBP, BMPR2	CDKN2B, ZFYVE16, SKP1
Hippo signaling pathway	YWHAH, SMAD2, BTRC, PPP2R2C, TCF7L2, CCND2, GLI2, WNT2B, WNT3, AMOT, TP53BP2, SMAD4, CTNNA1, NKD1, RASSF6, BMPR1A, CTNNA3, WNT9B, FBXW11, SERPINE1, BMPR2	ACTB, YWHAZ, PPP1CB
Vascular smooth muscle contraction	ADCY7, GUCY1A3, ROCK2, PLA2G4F, RAF1, KCNMA1, SPECC1L-ADORA2A, PLCB1, PPP1R12A, GUCY1A2, PRKG1, ITPR2, ADCY4, MYLK	GUCY1B3, ACTG2, PLCB1, MYLK3, PPP1CB
Lysine degradation	WHSC1L1, SETD7, PLOD2, ASH1L, KMT2E, KMT2C, EHMT1	-

ARVC: Arrhythmogenic right ventricular cardiomyopathy, TGF-β: Transforming growth factor-beta

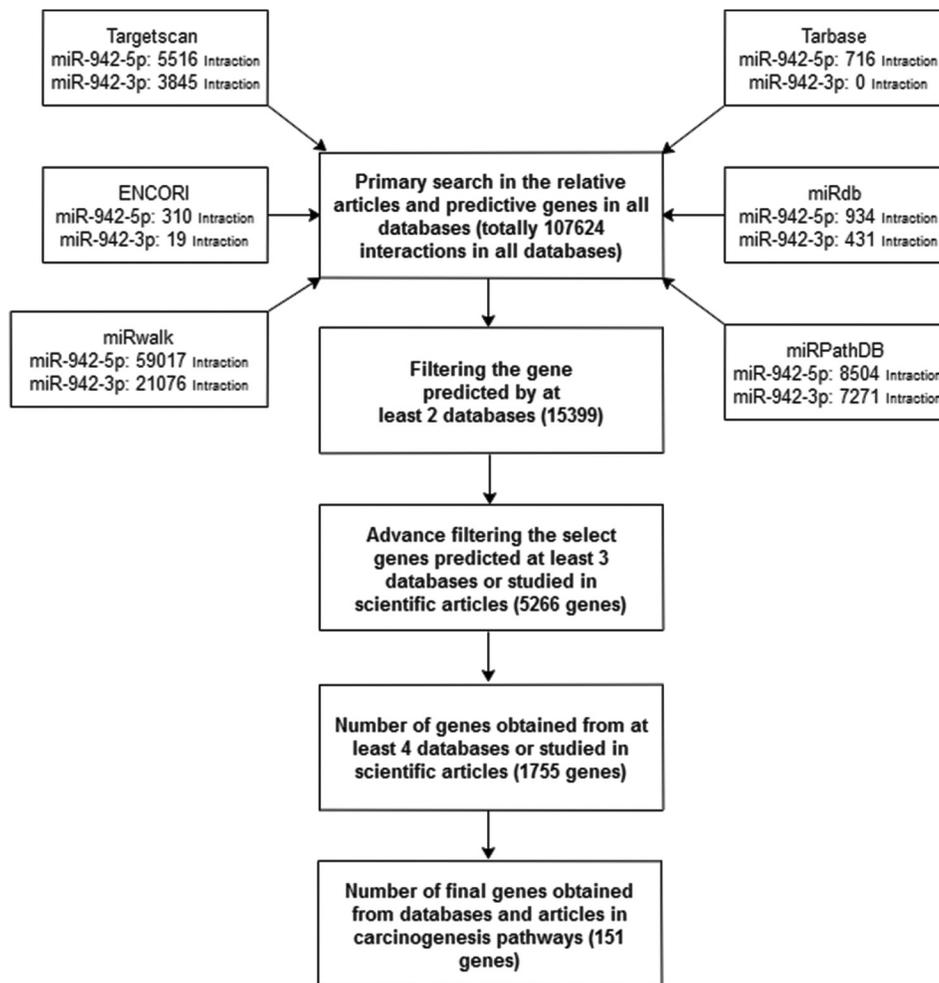


Figure 3: The strategy of search the genes targeted miR-942 in cancers

de/), ENCORI (<http://starbase.sysu.edu.cn/>) and finally miRPathDP (<https://mpd.bioinf.uni-sb.de/>). In the first phase of the search, we found 107624 genes, which were predicted to interact with miR-942. The filtering was performed on the basis of calculated scores in each database and inclusion in carcinogenesis. Ultimately, we reached 15399 predicted genes that were repeated at least in two databases and had a correlation with carcinogenicity. Then filtered genes were selected in the base of their repeats in three and four databases or studied in scientific articles [Figure 3]. The pathways chose according to the KEGG database (available at www.genome.jp/kegg/pathway.html).

Ethical approval

This study was completed without any testing on human or animal models by any of the authors.

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Conflicts of interest

There are no conflicts of interest.

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