



# The role of microRNAs in human cancers

Mohammad-Reza Mahmoudian-Sani<sup>1,2</sup>, Ameneh Mehri-Ghahfarrokhi<sup>2</sup>, Ali Shojaeian<sup>2</sup>, Majid Asadi-Samani<sup>3\*</sup>, Tahra Luther<sup>4</sup>

<sup>1</sup>Department of Genetics and Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>2</sup>Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>3</sup>Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>4</sup>Department of General Surgery, University of Michigan, Ann Arbor, Michigan, USA

## \*Correspondence to

Majid Asadi-Samani,  
Email: [biology\\_2011@yahoo.com](mailto:biology_2011@yahoo.com)

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## Abstract

MicroRNAs consist of 18 to 25 non-coding ribonucleic acids (RNA) that can act as oncogenes or tumor suppressors and in which mutations can lead to cancer. The identification of microRNAs and their target molecules has created a new horizon for studies of causes of cancer. MicroRNAs can be used as potential biological markers in diagnosis, prediction and treatment of cancers. This review article presents findings to explain microRNAs function in human cancers.

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## Introduction

Cancer is one of most significant dilemmas of public health around the world (1). They are a group of cells, which grow uncontrollably and attack nearby tissues. Cancers, sometimes metastasis to other parts of body through blood or lymph (2). Numerous efforts have been conducted for screening, prevention and treatment of cancers to reduce death rate (3-10).

In recent years, numerous new methods have been used for early identification of cancers. In the last three decades, molecular genetic methods have been developed based on the stool protein analysis of DNA and RNA (11). The studies of microRNAs (miRNA) is one of the newest methods which has led to noble prize being granted to Andrew Fire and Craig Mello (12,13). The role of miRNAs in cancer was first recognized in chronic lymphocytic leukemia (CLL) 7 years ago, in which their profile was investigated in different cancers thereafter (14). This review is based on the key role of miRNAs in different cancers and recent studies on cancer prevention and treatment. Additionally, a discussion and interpretation on modern findings of miRNAs role in cancerous cells has been conducted.

## Materials and Methods

For this review, we used a variety of sources by searching through Web of Science,

## Key point

MicroRNAs can act as oncogenes or tumor suppressors. Mutations in microRNAs can lead to cancer. Detection of changes in microRNA expression can be used for prediction, prevention, and treatment of cancers.

PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents like; microRNA, cancer, metastasis and apoptosis.

## Definition of microRNAs

MicroRNAs are constitute of 18 to 25 small non-coding ribonucleic acids that are conserved. MicroRNAs, regulate gene expression of messenger RNA (mRNA) through inhibition of translation or cleavage of the target mRNA via the identification of 3'-UTR region after its translation (15,16). Generally, they have a basic role in modifying cellular processes such as proliferation, signal transmission, apoptosis, and tumorigenesis (17). Dysfunction in activity of these miRNAs can lead to different problems and diseases, one of the most significant being cancer. MicroRNAs can have the tumor suppressor and oncomir roles. The increase in oncomir expression leads to



severe reduction of tumor suppressor miRNAs, increased resistance, and increased activity of oncogene mRNAs that lead to tumor development and growth (18-23). The role of miRNA in cancer has gained significant attention because of these non-coding small RNAs potential for cancer diagnosis and treatment (14). MicroRNAs have different mechanisms in their contribution to cancers. One of the mechanisms is the mutation in the miRNA gene. The results of computerized analysis show more than 1000 microRNAs in the human genome, and more than fifty percent of these miRNAs are located in an area of the genome that is sensitive to mutation (19). Therefore, any alteration in miRNA expression that targets these genes leads to cancer by dysregulation in genes expression. This feature of miRNAs can be used for prevention and diagnosis of cancers (20). Table 1 demonstrates some miRNAs that have a role in cancer along with their molecular target and operational mechanism.

### Biogenesis of miRNA

MicroRNA is transcribed from genes inside the nucleus and produces pre-miRNA. Following nuclear RNase III, named Drosha, miRNA creates a precursor named pre-miRNA. The pre-miRNA is then transported to the cytoplasm by exportin-5. This molecule cleaved by another enzyme Dicer in the cytoplasm and produces double stranded sequential nucleotides (20-22). One of the strands is degraded and the other incorporated into RNA-induced silencing complex (RISC). This active complex targets the miRNA, links to the 3' UTR mRNA terminal, and operates its inhibitory effect. MicroRNA modifies gene expression through translation inhibition of protein or target mRNA degradation (Figure 1) (21).

MicroRNA biogenesis is a multistep process. First, miRNA genes are transcribed by RNA polymerase II in the nucleus. The resulting primary transcript is cleaved by Drosha and

DGCR8 to produce pre-miRNA. After exportin-5- and RanGTP-mediated transport to the cytoplasm, the pre-miRNA undergoes its final processing step, which consists of Dicer-dependent cleavage just below the stem loop to produce a duplex molecule. The duplex is then separated and usually one strand is selected as the mature miRNA and directed to target-specific mRNAs (13,24).

### MicroRNA expression modification in human cancers

The reduction of miRNA expression can have an important role in cancer progression. However, it is not clear how these miRNAs change cancer expression, while most disorders of miRNA are related to disorders in P53 expression (22). Specific areas of P53 have site binding to miRNA pro-motor. There is a significant difference in translated mRNA activity level in HCT-116 cell lines with P53 knock out gene in comparison with normal cells. Findings demonstrated that lack of normal P53 might be an important mechanism in miRNA modification disorder (23,25). Based on these studies, the improper miRNA expression in lung cancer can cause somatic genetic changes, such as DNA mutation and chromatin structure changes, that regularly have important roles in translation inhibition in most genes such as tumor suppressor genes and genetic deficiency in human carcinogens (26). Findings demonstrated that miRNA expression in normal tissues is higher in comparison with tumor tissues. This finding led to the theory that miRNAs have a role in cellular distinction. In some cases, the expression reduction has an important role in tumor formation and progression. There is a close relationship between miRNA expression pattern and cell distinction. Their classifications in different types of cells can help disease prognosis. Lower signaling pathways play an important role in cancer progression (27). In contrast to mRNAs, miRNAs are stable and can prevent cellular proliferation. MicroRNA depends on

**Table 1.** microRNAs and their objectives in cancer

MicroRNA	Effects on cancer	MicroRNA target molecules	Involved molecular mechanisms
miR-9-3	Reduction in breast cancer	P53	Role in programmable death depends on p53
miR-15a and miR-16-1	Non-small cell lung cancer reduction	Cyclin D1 Cyclin D2 Cyclin E2	Halt in G1-G0 cellular cycle step
miR-17-92	Increase in B cell Lymph and medulloblastoma	P21, N-Myc	The progression of cellular cycle through G1-S, working with sonic hedgehog for increased proliferation
miR-25	Increase in gastric cancer	P57	The Cip/Kip (Cdk interacting/Kinase inhibiting protein) suppression kinase suppressors related to the cyclin through 3'-UTR
miR-101	Reduction in liver cell carcinoma	Mcl-1	Progress in programmable death and tumorigenesis suppression
miR-122	Reduction in liver cell carcinoma	Cyclin G1-P53	Protein P53 induced resistance and transcription activity of attack capability reduction through cyclin G1
miR-128	Reduction in glioma	E2F3a	Cellular growth inhibition
miR-143	Reduction in colorectal cancer	KRAS	The inhibition of justified kinase fixed phosphorylation by external signal in cancer
miR-145	Reduction in lung adenocarcinoma and colon cancer	EGFR 1GF-IR	The inhibition of cancerous cell growth that epidermal growth factor (EGFR) mutated
miR-512-5P	Reduction in gastric cancer	Mcl-I	Induction of apoptosis in cancerous cells

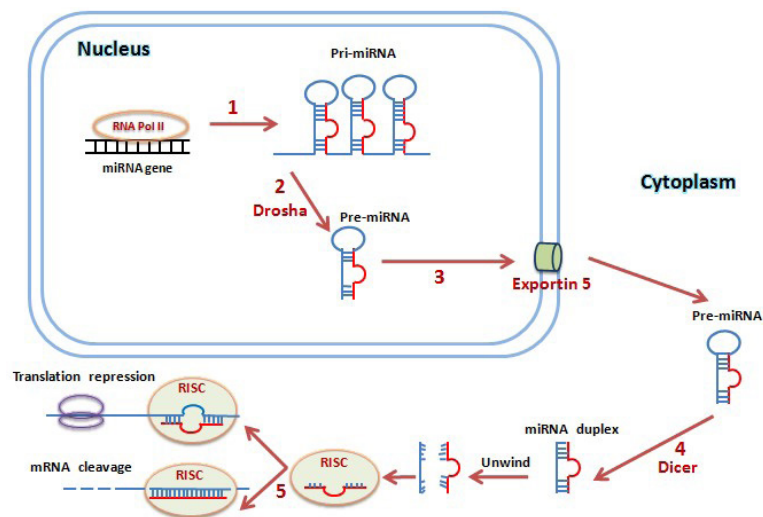


Figure 1. Biogenesis of miRNA.

complimentary 3'UTR of the target mRNA. The mutation in the oncogenic 3'UTR mRNA area can prevent miRNA inhibition that is an important mechanism in cancerous cell inhibition (28).

### Different mechanisms may lead to miRNA gene change

#### Chromosome disorder

Omission, increase and mutation are examples of these anomalies (29,30).

#### Epigenetic

DNA methylation and histone changes are among the changes that can affect miRNA expression production. On the one hand, they control the epigenetic mechanisms, and on the other hand, miRNA can target the main epigenetic players (31).

#### Single-nucleotide polymorphism

Genetic changes are important factors in breast cancer susceptibility prediction. One polymorphism in miR-24 is reported to be located between the miRNA links to mRNA related to dihydrofolate reductase. This polymorphism lead to the loss of miR-24 function, an increase in dihydrofolate reductase (DHFR) expression, and resistance to methotrexate (31).

#### Deficiency in the miRNA biogenic machine

The miRNA enzyme levels, such as Dicer and Drosha, can reflect the cell oncogenesis of a cellule. Studies that looked at, the expression level of these enzymes in breast cancer showed the significance between their levels and disease condition. It is recognized that some proteins, such as SMAD with Drosha, accelerate their maturity. P53 interacts with Drosha and increases the maturity of miRNAs that affect inhibitors of cell growth (32-34).

#### MicroRNAs and apoptosis in cancer

The genes involved in apoptosis are divided into two

groups; genes that have a role in the start of apoptosis (pro-apoptotic) and those that prevent apoptosis (anti-apoptotic). Both genes in apoptosis have modification potential through miRNAs. Each miRNA alone can have both pro-apoptotic and anti-apoptotic roles. This role is determined by type of gene and cell. In cancerous cells, the major reduction of miRNAs in pre-apoptotic genes has been observed. P53 protein controls apoptosis by the modification of the rate of miRNA expression (35). Since P53 is a transcription factor, it causes the transcription of miR-334, miR-215, miR-192 family genes (36) and also increases the expression of many tumor suppressor miRNA (including miR-34 a, miR-34b, miR-15- a/ 16, let-7a). An inhibitor miRNA and pro-apoptotic miR-34a is activated by P53 directly (37,38). The high expression of miR-34a in malignant neuron tumor cells causes apoptosis (38). MicroRNAs have a main role in the apoptosis pathway and cell proliferation by targeting miR-34a. They included CDK4 MYCN and E2F5 too. Generally, miR-34a expression causes the severe changes of gene expression and apoptosis development (37). Specifically, let-7 induces apoptosis modification through targeted caspase-3 (39). miRNA-15a/16 stimulate apoptosis by targeting Bcl-2. Overexpression of BCL2 as an anti-apoptotic occur, by the increased in human cancers such as breast and B lymphocyte cancers. The level of miRNA expression has a reverse relationship with BCL2 expression in CLL cells. Additionally a significant reduction of miRNA levels in 68 percent of patients affected with CLL was detected (40,41).

#### MicroRNA polymorphism and cancer susceptibility

One of the factors that can affect miRNA function is single nucleotide polymorphism (SNP). Numerous investigations have been done to understand the SNP role in miRNA precursor and its effect on expression and function (including its effect on cancer susceptibility and other diseases). SNP and its correlation to diseases such as cancer might present a better understanding of individual's risk in a population. Lots of sequential target

miRNA are polymorphic and these polymorphisms have a high frequency in different populations, while they affect gene expression too (42). The ability to link miRNA to the target position that is created as a consequence of special polymorphism alludes to the difference in several genetic disease. Finding the risk factors for individuals that develop cancer has been a great challenge in medical science, since the use of investigating polymorphism in an individual's genetic construct can help to early detection.

### Metastamir and its relationship with cancer

Metastasis is a multiple phase process that requires different modifications in each phase. MicroRNAs identified as primary modifiers of genes create new possibilities for more effective metastasis inhibition (43). Metastamir belongs to the miRNA family that have a role in different migration phases and cellular attack but does not have any role in tumor formation (44,45). It is recognized that metastamir R has pre- and anti-metastasis effects, while this impact is very important in metastasis control and modification of cancers. In fact, members of this family are divided into activators and inhibitors of metastasis, and mutations in metastamir have important pathogenic consequences. One of the important findings of metastamirRs, is that, its expression in metastatic breast cancer severely reduces miR-31. Indeed, miR-31 is a type of miRNA with pleiotropic function that inhibits breast cancer metastasis through inhibition of some pre-metastasis genes such as *ITGA5*, *fzd3*, *RDX*. This miRNA(miR-31) inhibits several phases of metastasis including invasion, anokis and colonization (46).

### Discussion

Cancer is one of the leading causes of death in many people. Therefore, new treatments, especially molecular treatment, can be a beneficial strategy to treat and reduce cancer. Common treatments for cancer, such as chemical therapy and radio-therapy, despite their relative improvement, are not considered as complete and certain treatments. Numerous researches has been conducted to discover useful cancer treatment with the most response and least complications (47,48). The use of molecules in disease treatment was applied after miRNA function in gene expression modification was discovered (20,49). There are several treatment methods in this entity that include inhibition by oligonucleotide inhibitors, miRNA replacement or coding miRNAs by virus vectors. Some researchers believe that miRNAs can affect malignant cell's features such as invasion, angiogenesis, metastasis and apoptosis (28). Apoptosis is a complicated process in which several miRNA roles have confirmed. Some miRNAs promote apoptosis while others inhibit it. MicroRNA demonstrate a vital role as inhibitors of tumorigenesis (50). Tumor inhibitory miRNAs such as miR-145, let-7, miR-16-1, and miR-15a are usually shown to be reduced in most cancers. Other miRNAs are oncogenic, such as miR-155, miR-21 or genic cluster miR-17-92 (51,52). There is great anticipation to apply miRNAs in treatments. The

different roles of miRNA in several genes and pathways make them significant candidates for treatment of cancers (41). There have been studies that use of miRNAs for cancer inhibition. Leo et al demonstrated that miR-34a can inhibit proliferation of prostate cancer cells and prevent the progression and metastasis in a mouse model (53). Additionally, miR-34a is the first miRNA used in clinical experiments to treat liver cancer (54). Several miRNAs are in progress for use in the clinic (55). A method to determine the use of miRNA as successful inhibitors is the identification of miRNAs that can target gene collection or metabolic pathways is the using of algorithms and bioinformatics (56). The use of miRNA has advantages over other methods for treatment. For example the use of a small molecule for targeting a protein or enzyme can create reparative mechanisms in the same pathway. However, the possibility of such a mechanism is low because miRNAs simultaneously can affect multiple pathways or target different parts of a pathway, but miRNA are small molecules that have fewer antigenic sites in comparison with peptides and proteins (57,58). Several miRNAs with different and complicated contributions to tumorigenesis, metastasis and angiogenesis have a role in cancer treatment. MicroRNAs can have significant functions on the prevention and recognition of cancers. However, more questions exist on this subject of work that should be investigated with further researches.

### Conclusion

Understanding the exact genetic and epigenetic mechanisms that causes gene expression modification leads to increased awareness in diagnosis, treatment, and management of different diseases such as cancer. The identification of tumor miRNA that spreads in blood flow during gradual progression of disease is a key method in timely cancer diagnosis. According to the potential abilities of miRNAs, a possibility for application of these molecules in effective and certain cancer treatment is exists. However, further studies are needed to identify specific miRNAs and their target genes, thus their use can be applied to treatment of diseases.

### Authors' contribution

Performing the data search and preparing the primary draft conducted by MRMS, AMG, AS and MAS. MAS and TL edited the manuscript. All authors read and signed the final paper.

### Conflicts of interest

The authors declare no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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