

Review Article

Comprehensive analysis of microRNA (miRNA) in cancer cells



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ABSTRACT

MicroRNAs (miRNA) are a group of small non-coding RNAs that regulate gene expression at the RNA level. MicroRNAs have positive regulatory effects on protein translation processes and often induce their performance by binding to the 3'-UTR mRNA region. Also, microRNAs are involved in various cellular processes, including development, cell division, cell signaling, and cell growth, and generally play an effective role in the cell cycle and control of physiological processes and cell pathology. Several studies confirm that microRNAs play an important role in the initiation and progression of cancer, and many of them act as oncogenes and tumor suppressors. On the other hand, microRNAs are important stimulating factors that can act as biomarkers in the diagnosis and prognosis of various types of cancer, and in many cases, the occurrence of mutations in microRNAs and open-reading templates can lead to cancer. MicroRNAs also play an effective role in regulating gene expression. Biological studies have shown that about 30% of all genes and the majority of genetic pathways are regulated by microRNAs. In general, microRNAs and their target molecules are potential biological goals for primary screening, targeted treatment, and pharmaceutical resistance, and identifying them provides a clear prospect for a better understanding of the pathways leading to cancer.

1. Introduction

MicroRNAs are a group of non-coding, intragenic, and single-stranded RNAs with a length of 18-25 nucleotides, which are complementary to mRNAs of protein-coding genes and can prevent the expression of related genes and proteins. MicroRNA biogenesis takes place in the nucleus and cytoplasm. Considering the role of MicroRNAs in the process of proliferation and differentiation, it is expected that the disruption of the expression of MicroRNAs is

related to cancer. Oncomirs are a group of MicroRNAs that can act as oncogenes or tumor suppressors by reducing the expression of cancer-related target genes [1-3].

More than 50% of microRNA genes are present in genomic regions related to cancer or fragile areas, which undergo the process of deletion or duplication, which indicates their role in malignant transformations [4-6]. MicroRNAs control gene expression after

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transcription by binding to the region of 3'-UTR mRNA by inhibiting the translation of mRNAs or inducing their degradation. The primary transcripts of microRNAs are converted into mature microRNAs during 2 processing steps [4, 5]. MicroRNAs were first discovered in nematodes in 1993 by Li et al. and subsequently identified in chronic lymphocytic leukemia [7].

Subsequent studies showed that the region contains 2 genes encoding miRNA-16-1 and miRNA-15a, which are transcribed polycistronically [8].

In 2004, microchip analysis was used to characterize miRNAs in humans and mice. The microchips contained 245 different miRNAs that were identified by Northern blot and RT-PCR methods. MicroRNAs participate in many reactions and play an active role in various cellular processes, including cell signaling and cell growth and division. MicroRNAs also participate in physiological processes such as apoptosis, insulin secretion, blood supply, and tissue differentiation. Clinical studies have

shown that MicroRNAs play an effective role in defending the body's immune system, especially against viral diseases [9]. MicroRNAs are transcribed by RNA polymerase II in the nucleus. Then this 2-stranded precursor is converted by Drosha, which is a type of endonuclease III, into a stem-loop structure with a length of 60-75 nucleotides. Preformed miRNA is transferred to the cytoplasm by Exportin 5 protein and processed by cutting enzymes. Then, by binding to the AGO protein, it turns into the RISC silencing complex. The binding site of mature miRNA is the 3'-UTR mRNA region of the target gene. In general, miRNAs inhibit protein synthesis. Target gene regulation by miRNAs depends on the degree of complementarity of miRNAs with the 3'-UTR mRNA region. MiRNAs with high degrees of similarity break the target gene, while lower degrees of similarity can cause gene silencing or decrease the expression of the target gene (figure 1)[10-12].

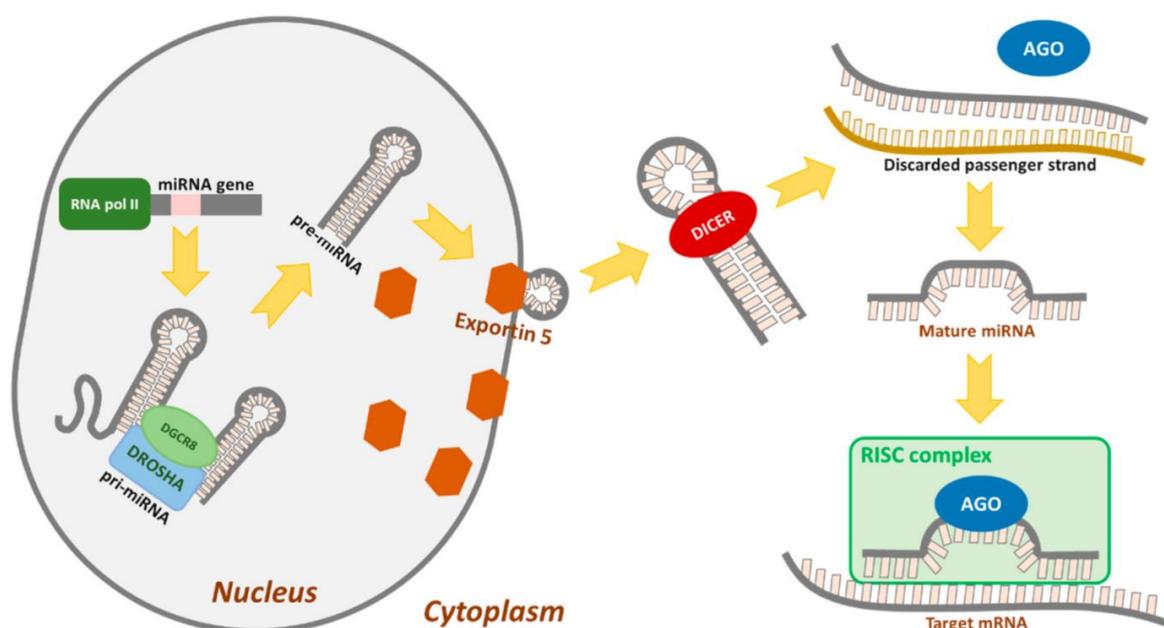


Fig. 1. Schematic illustration of miRNA synthesis process [13]. This figure is under CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

2. Investigating the expression of MicroRNAs in cancer cells

MicroRNAs show different behavior in cancer cells. A group of MicroRNAs known as oncomirs is overexpressed in cancer cells.

This action causes tumor inhibitors to decrease in cancer cells. MiRNA-21 is overexpressed in most cancers, which decreases tumor suppressors such as PDCD4, PTEN, and TPM1 [14-16]. Another group of

microRNAs in cancer cells has a decrease in expression. Since the targets of these microRNAs are proto-oncogenes, the reduction in the expression of these microRNAs leads to the increase of proto-oncogenes in the cell. Let7 is reduced in most cancer cells, and RAS proto-oncogene is one of the targets of this microRNA [17, 18]. Another

group of MicroRNAs targets DNA methyltransferase. Decreased expression of these MicroRNAs leads to reduced expression and lowers tumor suppressors in cancer cells. In general, MicroRNAs that have decreased expression are called tsmiRNAs. Table 1 shows the types of MicroRNAs that are disrupted in cancer cells [19, 20].

Table 1. Types of MicroRNAs that are disrupted in cancer cells

MicroRNAs	target gene	consequences	Expression
MiRNA-21	Tumor inhibitor	Reduction of PTEN, PDCD4, reduction of apoptosis, and increase of cell growth	Increased expression
MiRNA-10b	Tumor inhibitor	Reduction of HOXD10, increase in invasion, and cell migration.	Increased expression
MiRNA-373	Tumor inhibitor	Reduction of CD44, reduction of cell attachment to the substrate	Increased expression
Let-7	DNA methyltransferase Oncogene	Increasing RAS, increasing cell proliferation	Reduced expression
MiRNA-206	DNA methyltransferase Oncogene	Increasing ER-alpha, increasing cell proliferation	Reduced expression
MiRNA-450a	DNA methyltransferase Oncogene	Increasing DNMT, Epigenetic silencing of tumor suppressor genes	Reduced expression

3. DNA methylation

DNA methylation occurs normally in all vertebrate cells. CpG Island in the gene promoter plays an important role in the methylation and transcription of miRNAs. In this process, carbon number 5 of the cytosine ring in CpG dinucleotides plays an essential role. Methylation is done by DNMT (DNA methyltransferase) and using (S-adenosyl-methionine) SAM as a methylating group. In normal cells, miRNAs associated with CpG islands are usually unmethylated. These miRNAs lead to histone configuration in euchromatin and provide access to TFs, H3K4, Co-Act, HATs, and HMT factors and form the transcription complex that includes RNA polymerase II, TAF (TBP-associated factor), TBP(TATA-binding protein) and finally transcription of primary and mature miRNAs is done. In tumor-bearing cells, promoter CpG Island associated with intergenic and intragenic miRNAs is abnormally hypermethylated. In this process, DNMT using HMTs, HDAC, and MBD leads to compact chromatin structure and finally, access to transcription factors is blocked and miRNAs are turned off [21-25].

4. Identification of target molecules in microRNAs

One of the most important topics related to microRNAs is the identification of their target molecules. MicroRNAs usually attach to the 3'-UTR end of mRNA. For this reason, the isolation of full-length genomics has been expanded in the last few decades [26]. In the complete isolation of the gene, the Rapid Amplification of cDNA Ends (RACE) technique is used, in this technique, in addition to the central CDS region, the 3'-UTR and 5'-UTR regions are also isolated [27]. The presence of complementary base pairs is necessary for the interaction between microRNAs and the sequence of the target molecule. In these interactions, usually 2-9 nucleotides at the 5' end of microRNAs, called the seed region, are paired with 6-7 nucleotides at the 3'-UTR end [26].

Other base pairs of microRNAs show a limited connection with the 3'-UTR sequence, which makes microRNAs able to bind to several positions in the 3'-UTR. Many software and computer algorithms have been used to detect the target location of microRNAs from the seed sequence. Bioinformatics studies have shown that more than a third of the human genome is regulated

by microRNAs, and about 1000 microRNAs have been estimated for one percent of the human genome [28-33].

5. MicroRNAs and cancer

Cancer is the result of the departure of cells from the normal path. Avoiding cell death, unlimited proliferative potential, tissue invasion, and metastasis lead to the development of malignant cancers. The effect of microRNAs in the development of programmed cell death, differentiation, and proliferation has been proven. The structure and function of microRNAs show that some microRNAs are abnormally expressed in cancer. There is also a significant relationship between the performance of tumors in different stages of cancer and the expression of microRNAs. However, in different cancers, the expression level of microRNAs is different, which can be caused by the difference

between the origin of cancer cells and the surrounding stromal tissue (Table 2) [34].

In general, microRNAs can act as regulators of epigenetic factors. This is even though epigenetic factors also cause the inactivation of microRNAs through excessive methylation or histone changes. Gene deletions, exogenous silencers, and non-expression of transcription factors also decrease the expression of tumor-inhibiting microRNAs [35]. In general, microRNAs lead to the reduction of tumor genesis and cancer by targeting proteogenic mRNAs and silencing them, reducing the expression of tumor suppressor genes, regulating cell differentiation, and programming cell death [34].

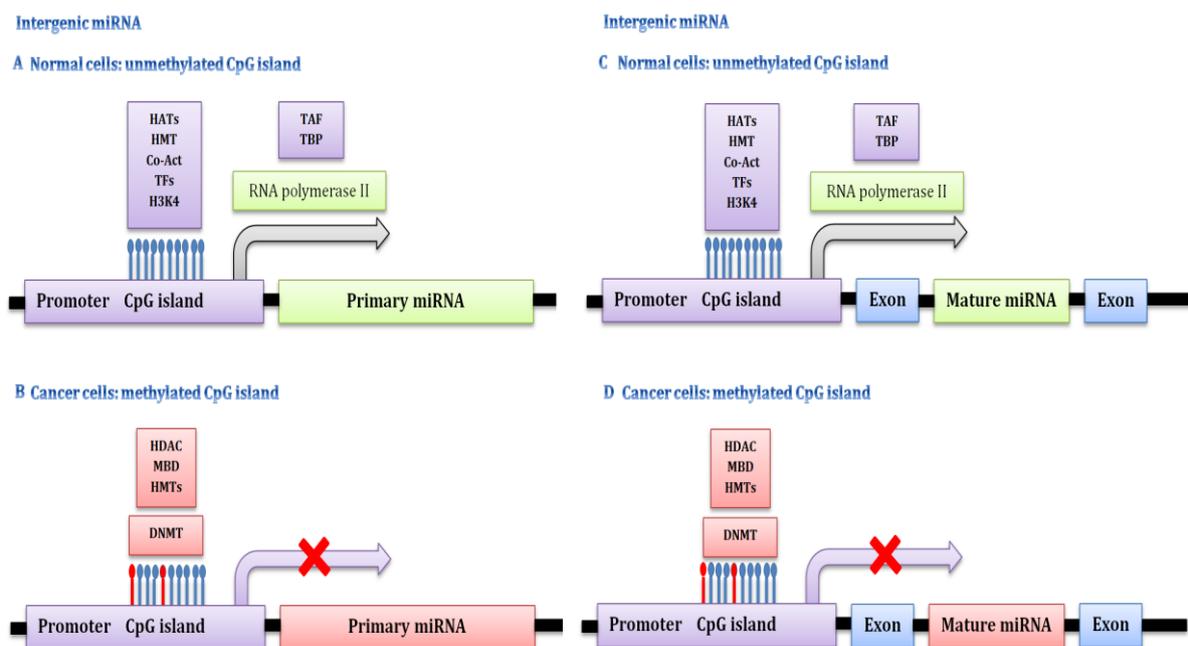


Fig. 2. A schematic model of DNA methylation-dependent miRNAs in normal & cancer cells [21, 22]. A. Normal cells: unmethylated CpG island (Intergenic miRNA) B. Cancer cells: methylated CpG island (Intergenic miRNA) C. Normal cells: unmethylated CpG island (Intragenic miRNA) D. Cancer cells: methylated CpG island (Intragenic miRNA). TF: Transcription factor; Pol II: RNA polymerase II; HDAC: Histone deacetylase; MBD: Methyl-CpG-binding domain protein; TAF: TBP-associated factor; TBP: TATA-binding protein; Co-Act: Co-activator; HMT: Histone methyltransferase; DNMT: DNA methyltransferase; HAT: Histone acetyltransferase.

Table 2. Changes in microRNA expression in different human cancers [34]

Types of cancer	Increased expression	Reduced expression
Breast	miR-21, miR-22, miR-23, miR-29b-2, miR-96, miR-155, miR191, miR-181, miR-182, miR-27a, miR-210	miR-205, miR-143, miR-145, miR10b, miR-125a/b, miR-155, miR17-5p, miR-27b, miR-9-3, miR-31, miR-34 family, let-7
Ovarian	miR-200 a/b/c, miR-141, miR-18a, miR-93, miR-429	miR-199a, miR-140, miR-145, miR-125a,b, let7
Colorectal	miR-18, miR-224, miR-10a, miR-17-92 cluster, miR-21, miR-24-1, miR29b-2, miR-31, miR-96, miR-135b, miR-183	miR-143, miR-145, let-7, miR30 -3p, miR-124a, miR-129, miR133 b, miR328
Lung	miR-21, miR-155, miR-191, miR 205, miR-210 miR-17-92 cluster	let-7, miR-34 family, miR-143, miR-145, miR-124a
Glioblastoma	miR-221, miR-222, miR-21	miR-181a, miR-181b, miR-181c, miR-125a, miR-125b
Esophageal cancer	miR-194, miR-192, miR-200c, miR-21	miR-203, miR-205
Stomach-intestinal	miR-106b-25	miR-15b, miR-16
Pancreas	miR-221, miR-376a, miR301, miR-21, miR-24-2, miR-100, miR-103, miR107,miR125b-1, miR-155, miR-181, miR-106, miR-363, miR-301, miR-212, miR-34a376	miR-375, let-7, miR-200, miR200b
thyroid	miR-146b, miR-221, miR-222, miR-181b, miR-155, miR-197, miR-224, miR-346	miR-30d, miR-125b, miR-26a,miR-30a-5p
prostate	let-7d, miR-195, miR-203, miR-21,miR-181, miR-106, miR-363, miR-221	miR-128a, miR-101, miR-125a/b, miR-15a, miR-16-1, miR-143, miR-145, miR-23a/b, miR-200, miR-330, miR-331
Bladder	miR-17, miR-23a,b, miR-26b, miR-103-1, miR-185, miR-203, miR-205, miR-221, miR-223	miR-29c, miR-26a, miR-30c, miR-30e-5p, miR-145, miR-30a-3p, miR-133a/b, miR-195, miR125b, miR-199a

6. Conclusion

Approximately, 2694 mature human microRNAs have been identified, which have a significant impact on many human diseases, including neurological disorders, cardiovascular problems, diabetes, and cancer [36-41]. Today, microRNAs are widely used in cancer treatment and radiation therapy (RT). The results have shown that the high expression of miR-20b-5p in tumor cells makes these cells more sensitive to radiation therapy, which has led to an increase in the efficiency of this treatment method [42]. Xiang et al. showed that miR-139-5p in bone marrow mesenchymal stem cells (BMSCs) delays tumorigenesis and metastasis of bladder cancer cells in vivo by inactivating the p21 factor [43]. Also, microRNAs have an important regulatory role in diseases and are used as promising biomarkers for cancer diagnosis and prognosis. For example, miRNA-21 and miRNA-155 in serum samples can identify people with breast cancer from normal people with 100% accuracy [44]. Some microRNAs are disrupted in SARS infection. In general, microRNAs can interact with other molecules such as viruses and bacteria, and act as mediators for viral infections. Analysis of microRNA expression profiles and RNA-seq in COVID-19 patients showed that MIR302C-5p microRNA 302c-5p [Homo sapiens (human)] (hsa-miR-302c-5p)

and MIR16-5p microRNA 16-5p [Homo sapiens (human)] (hsa-miR-16-5p) are related to the regulation of pro-inflammatory cytokines, maturation, and differentiation of immune cells [45]. MicroRNAs can specifically bind to the target gene and repress it. The therapeutic performance of microRNAs in human trials largely depends on their incorporation into the target site and appropriate concentrations. Nanocarrier systems have a high potential to overcome existing challenges. Nanocarrier systems provide high stability during systemic circulation, efficient loading, and protection of microRNAs against nucleases, endosomal escape, and specific cell targeting. It is expected that microRNA-based nanotherapies will be used in cancer treatment in the next 5 years [46].

In general, microRNAs are important functional molecules that are included in the group of non-coding RNAs. The applications of microRNAs in the cell are so many that it sometimes makes it difficult to recognize their function. It is possible that the expression of microRNAs can be regulated through the synthesis of pre-microRNAs or antisense oligonucleotides. Also, microRNAs participate in many pathological and biological cellular processes, and the occurrence of mutations in them can lead to cancer. Several studies

confirm that microRNAs play an important role in the initiation and progression of cancer, and depending on the type of microRNAs they control, they can inhibit tumors or oncogenes, which show a promising perspective for cancer treatment [47]. In general, these factors have caused scientists to use microRNAs as an important medicinal agent in the treatment of many diseases.

Conflict of Interest

All authors state that they are free of any conflicts of interest related to this paper.

Author's contributions

All authors confirm that they have read and approved this manuscript.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

Ethics approval and consent to participate

The authors did not use human or animals in the research.

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