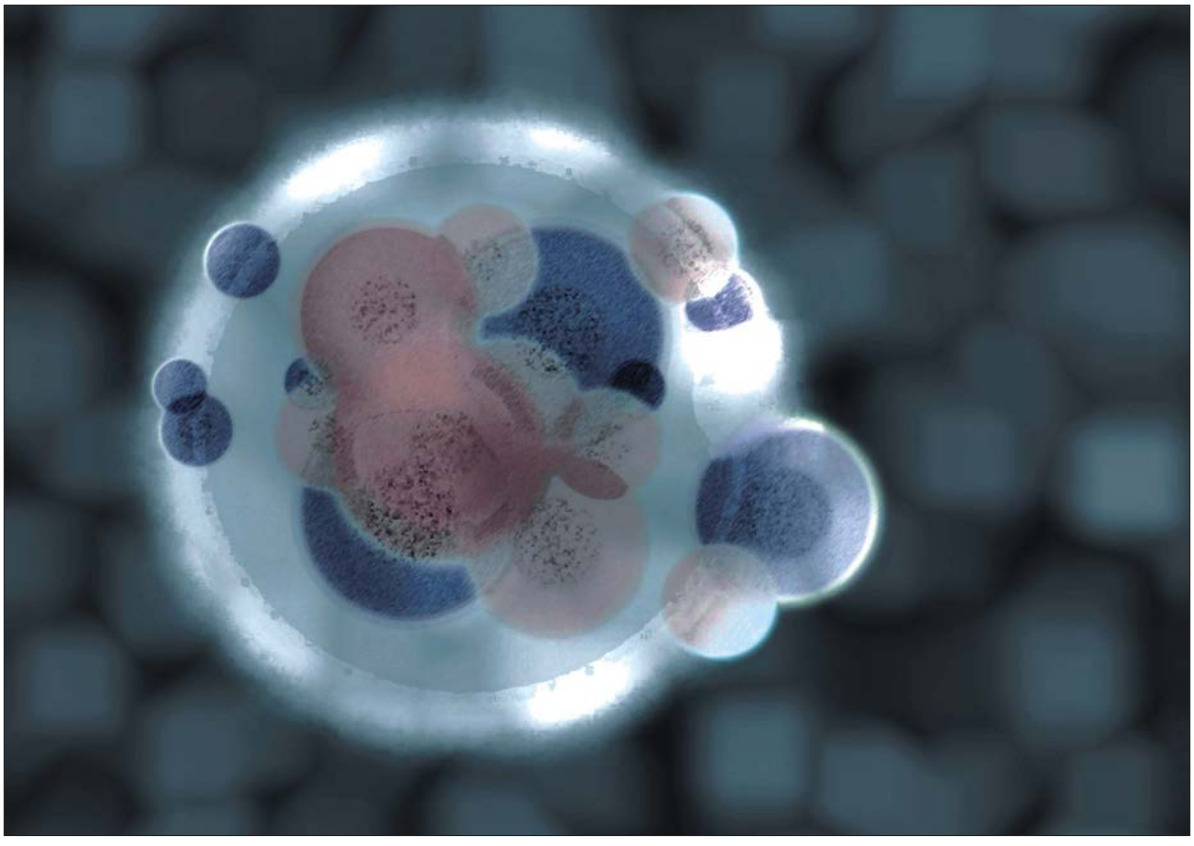

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Review Article
Microrna a New Gate in Cancer and Human Disease: A Review

[1]Ghanbar Mahmoodi Chalbatani, [1]Habibollah Mahmoodzadeh, [1]Elahe Gharagozlou, [2]Hassan Dana, [2]Elham Zeinalinia, [3]Omid Rezaeian, [1]Fereidoon Memari, [3]Milad Ardaneh, [3]Saeed Meghdadi, [2]Parisa Pilvar and [4]Nargesyousefi Rad

[1]Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran
[2]Department of Biology, Islamic Azad University, Damghan Branch, Damghan, Iran
[3]Department of Biology, Nour Danesh Institute of Higher Education, Isfahan, Iran
[4]Islamic Azad University, Pharmaceutical sciences branch, Tehran, Iran

Abstract

MicroRNAs are small noncoding RNAs with lengths of 21-22 nucleotides that participate in post-transcriptional control of gene expression. According to recent studies, 2588 microRNAs have been detected and the list is growing. Furthermore, microRNA (miRNA) plays a major role in regulating biological processes and miRNA in relation to many diseases including cancer. The deregulation connection between miRNA and cancer was discovered in 2002. Today, even more information about the main role that miRNA plays in cancer development has been uncovered, however, there is still a long way to go to understand the functions of all the microRNAs in eukaryotes. In this review, briefly explained miRNA biogenesis and discuss the roles that miRNAs play in cancer development. Finally, discussed how miRNAs can be used as biomarkers and as a new therapeutic approach in cancer.

Key words: Biogenesis, microrna, biological process, deregulation, gene expression

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Corresponding Authors: Fereidoon Memari and Hassan Dana. Cancer Research Center, Cancer Institute of Iran, Tehran University of Medical Science, Tehran, Iran Tel: +989123895106

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INTRODUCTION

MicroRNAs (miRNAs), small noncoding ribonucleic acids of approximately 21-22 nucleotides in length, are present in the majority of eukaryotic cells where they play an important role in a range of biological processes. MicroRNAs operate by regulating gene expression via binding to a complementary sequence in the target messenger RNA (mRNA). MicroRNAs were first discovered in 1993 in *Caenorhabditis elegans*[1] during a study of the short noncoding RNA family[2]. Twenty-three years after their discovery, miRNAs were shown to be key regulators of development[3]. In fact, the miRNA database, updated in 2014, revealed 2588 mature miRNAs in humans and at least 1915 in mice. It has been estimated that miRNAs help to regulate ~60-70% of the human genome[4]. MicroRNAs have been shown to play a role in several diseases, including some nervous and metabolic disorders and cancer[5]. A major role has also been reported in cancer stem cell differentiation[6]. Furthermore, miRNAs can function as indicators of drug resistance, as the expression of miRNAs in chemo resistant cells often differs from that in the parental chemo sensitive cells[7]. In this review, we discuss the application of microRNAs in cancer therapy and in the treatment of other diseases[8].

MicroRNA and biogenesis: The biogenesis of miRNA occurs via a well-characterized conserved mechanism. MicroRNA is intragenic RNA, with its own dedicated transcription factor[9]. MicroRNAs are transcribed, polyadenylated and capped by RNA polymerase II, producing an extended primary transcript designated pri-miRNA. A method involving the Dorsha/DGCR8 heterodimer then crops the pri-miRNA, producing a transcript of ~70 kb, an miRNA precursor known as pri-miRNA (Fig. 1).

Furthermore, the exportin-5 (XPO5) and Ran-GTP binding the pre-mRNA and also the export of this molecule from the nucleus into the cytoplasm[10]. The pre-miRNA is known by the RNase III dicer protein and manufacturing a mature miRNA duplex of twenty-two nucleotides. miRNA the double strand binding to the RNA-inducing silencing complex (RICS). RISC is combined of the transcription-responsive RNA-binding (TRBP) and Argounaute2(Ago2)[11]. It retains the mature strand fragment whereas the complementary strand is removed and degraded[12]. In as result, the most 3 basic steps of miRNA biogenesis mature are dicing, export and cropping of pri-miRNA.

MicroRNA and cancer: The first study reported in 2002 that the miR15a/16-1 cluster is usually deleted in chronic

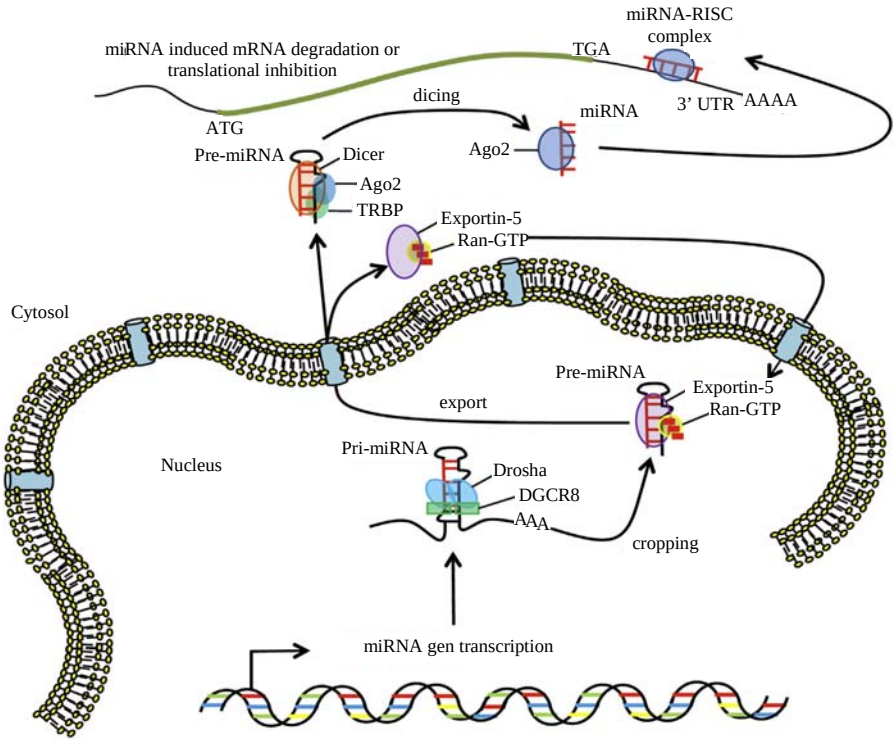

Fig. 1: Schematic review of miRNA biogenesis and miRNA-RISC activity

lymphocytic leukemia (CLL), significantly that these two microRNAs is TSGs[13], after this 1st study a large variety of microRNA are found deregulated in cancer[14]. Expression analysis of normal tissue, however, there are also microRNAs which are overexpression in cancer. For instance, the transgenic expression of miR-21 and miR-155 is enough to induce lymphomagenesis in mice[15]. Furthermore, characterizations of Dicer knockout races have analysis the significance of the miRNA control system as such as in both typical and cancerous cells[16]. Tumors regularly display reduced levels of developing miRNAs[17]. Diminished Dicer expression level has been found in the human tumor[18]. This framework is not without limitation: one miRNA can target multiple cellular pathways and is communicated everywhere throughout the body. There is a possibility of off-target or undesired impact[19].

MicroRNA and human cancer database: In reality, it has been utilizing computational expectations and trials, for instance miRNAMap2.0, miRBase, miRGen, miRGator v2.0 and miRecords. Other databases, such as Targetscan, Pictar and TargetMiner, are based on an algorithm intended to foresee microRNA focuses as indicated by a complementary pairing sequence[20].

Another database, TarBase, uses confirmed microRNA objectives, even when RNA hybrids are based on hybridization among miRNA and mRNA[21]. There are additional databases that give data on numerous illnesses, such as PhenomiR 2.0, mir2Disease and MicroCosm[22]. This review presents many recently revealed internet based tools that are mainly for determining the relationship amongst miRNA and cancer (Table 1).

SomamiR DB 2.0: Circular RNA (CircRNA) and long noncoding RNA (lncRNA) can periodically impart target mRNA to miRNAs. These can frame a contending endogenous RNA network as a community between the cRNA network and cancer[23]. SomamiRDB 2.0 was produced to perform a search of somatic mutations in miRNAs and ceRNAs (mRNA, CircRNAs and LncRNAs) to help to researchers find a function to search these mutations in human malignancy[24].

miRCancer: miRCancer is web based and holds reserve records of miRNA and cancer associations gathered through data processing[25]. miRCancer has records of >3,764 miRNA tumor relationships from 2,611 distributions, which adds up to 236 miRNA expression profiles from 176 human malignancies. miRCancer is simple and available on the web and the database can be searched via miRNA name, cancer type or a blend of both[26].

Relation between specific cancer and miRNA database

HNOCDB: A great aspiration of humans is improving treatment and medical care. For example, oral carcinomas, such as tongue, salivary gland, thyroid, pharyngeal, nasopharyngeal, oropharyngeal and laryngeal cancer are the most typical cancers in the world and curious to treat due to their area[27]. HNOCDB (http://gyanxet.com/hno.html): The genes were characterized according to the types of cancer and have three main important options for the user," genes", "miRNA " and chromosome association with interesting cancers[28].

From the result, HNOCDB is the best database that has good classification of the miRNA, genes and chromosomes involved in head, neck and oral cancer[29]. Databases focus on a specific kind of malignancy, such as HNOCDB, miREC, the renal cancer gene database, the pancreatic cancer database and the other cancer databases, are valuable to those specialists who need to concentrate the that part of the miRNAs in the growth of biogenesis and evolution. Different databases (CanEvolve, CancerNet, miRCancer, OncomiRdbd, AutomiRDb and ProgmiR) that review the part of miRNAs in various tumors can be used to see the master plan of a specific miRNA in various pathologies[30].

MicroRNA as a biomarker: In recent years, the literature reported a large number of evidence on microRNAs being concerned with all types of cancer and maladies[31]. New invention in molecular biology, such as microarray and next-generation sequencing (NGS), allow us to extensively research the connection between microRNA and cancer by analyzing the whole expression profile of this class-noncoding RNA in tumor tissue or blood[32]. In 2005, researchers used microarray to define six humans solid cancer[33]. The resulting profile gain from normal and tumor tissue displays that then prevalent idea that micoRNAs were only downregulation in cancer was wrong. Also, miR-21, miR-17-5p and miR-191 were shown to be overexpressed in some cancer[34]. A study conducted on 22 completely different growth varieties showed that a microRNA expression profile is ready to classify tumors per tissue of origin with accuracy more than ninetieth microRNAs are shown to even have a job in cancer progression and may well be helpful for the prediction of pathological process outcome in patients[35].

Recently, miRNA profile expressions of 82 colorectal carcinoma patients[35], discovery that a microRNA profile is ready to discriminate between large intense recurrences to lymph nodes, liver, between colorectal liver and first internal organ neoplasm[36]. Now used to as a clinical factor, microRNA have analysis in different studies as a biomarker for treatment therapy[37-38].

Table 1: Web-based tools for miRNAs in human cancer

Web-based tool	Website	Last update	Usefulness
SomamiR DB 2.0	http://compbio.uthsc.edu/SomamiR/	2016[a]	Browse somatic mutations in: • miRNA • Experimentally identified miRNA target sites by CLASH, PAR-CLIP and HITS-CLIP experiments • Predicted miRNA target sites • Biological pathways • Genes associates with cancer risk that contain miRNA
miRandola	http://mirandola.iit.cnr.it	June, 2015	Retrieve information on extracellular/circulating microRNAs, including: • Mature miRNA • Long non-coding RNA • miRNA family • miRNA type • Malignant cell lines • Potential biomarkers
PROGmiR	www.compbio.iupui.edu/progmir	December, 2012	Study the prognosis biomarker potential of different miRNAS in several types of cancer and overall ssurvival query
AutomiRDB	http://www.chen-lab.com/index/php	2014[a]	Groups all the miRNAs that are experimentally confirmed to have an association With autophagy in cancer
OncomiRdbB	http://tdb.ccmb.res.in/OncomiRdbB/index.htm	2014[a]	Retrieve microRNAs with knows breast cancer associations from miRNA databases, including miRBase, miR2Disease and PhenomiR
miRCancer	http://mircancer.ecu.edu	December, 2015	Stores reccords of miRNA and cancer associations collected through data mining
CancerNet	http://bis.zju.edu.cn/CancerNet	2015[a]	Focuses on protein-protein interactions associated with cancer
canEvolve	http://www.canevolve.org	2013[a]	Tool for oncogenomic analysis
HNOCDB	http://gyanxet.com/hno.html	2012[a]	Presents a classification of miRNAs, genes and chromosomes involved in HNOC
miREC	http://www.mirecdb.org	May, 2014	Search known miRNAs involved in endometrial cancer
Renal Cancer Gene DB	http://www.juit.ac.in/attachments/jsr/redb/homenew.html	2012[a]	Contains miRNAs contributing to the etiology and pathogenesis of different Types of renal concer
Pancreatic Cancer DB	http://www.pancreaticcancerdatabase.org	July, 2015	Retrieve experimentally demonstrated molecular alterations of mRNA, protein and miRNA levels associated with pancreatic cancer
Sarcoma microRNA Expression DB	http://www.oncomir.umn.edu/	2010[a]	Presents differentially-expressed miRNAs in sarcoma
miRBase Tracker	http://www.mirbasetracker.org	2014[a]	Presents all the known miRNA sequences and variants and keeps track of annotation changes for eah miRNA entry

Table 2: MicroRNA and Human disease

Disease types	miRNA	Up/Down Regulation
Cardiac hypertrophy	miR-23a, miR-23b, miR-24, miR-195, miR-199a and miR-214	Up
Down syndrome	miR-99a, let-7c, miR-125b-2, miR-155 and miR-802	Up
Alzheimer	miR-9, miR-128a and miR-125b	UP
Rheumatic arthritis	miR-155 and miR-146	Up
Systemic lupus erythematosus	miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR-342, miR-299-3p, miR-198 and miR-298	Up
	miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112 and miR-184	Down
Psoriasis	miR-203	Up

MicroRNA and Cancer treatment: In recent years, cancer drug therapy has increased the cure rate from malignant tumors and decreased the rate of cancer-related mortality worldwide[39]. However, novel drugs with improved target specificity are needed. The use of microRNA is a novel and exciting approach to the development of cancer therapeutics, allowing for the targeting of specific molecular mechanisms or cellular processes related to malignancies[40]. Advances in *in silico* tools have aided the design and manipulation of microRNAs and their target genes. Furthermore, the use of siRNA allows for the inhibition of multiple targets[41]. Recent progress in the development of efficient carriers for transferring small RNAs intracellularly, such as nanoparticles and viral systems, has aided the application of microRNA technology[42]. In addition, mRNA antagonists can be used as therapeutic tools to inhibit oncogenic miRNA[43]. Anti-miRs are single-stranded RNA molecules of 21-23 nucleotides in length that bind to target microRNAs and inhibit their function[44]. The adaptation of tumor cells to respond to therapeutically-evoked pathway changes[45] is one of the challenges faced when delivering microRNAs *in vivo*. One of the most effective approaches to overcome such problems is the use of nanoparticles that are able to deliver small interfering RNAs (siRNAs) and microRNAs in a neoplasm-specific manner[46].

SNPs in miRNA and role in human disease: Single nucleotide polymorphisms (SNPs) happen within 1% or more of the population[47]. There are around 8-10 million SNPs in the human genome and happen once in 300bp in both the coding and non-coding regions of the gene[48]. Nowadays, more attention has been paid by researchers to the SNPs in the non-coding region. In general, we call the mregulatory SNPs (rSNPs) because they impact on transcriptional regulation or post-transcriptional gene expression. rSNPs control and change function in cells at the different level of gene regulation. For instance, they can affect the transcription factor[49] of gene splicing[50]. They can likewise influence the half-existence of messenger RNA (mRNA), which can result in diminished protein levels through mRNA–microRNA (miRNA) cooperation. SNPs in miRNA target sites within the 30-UTR of mRNAs are observed as poly-miRTSs[51].Given that there are roughly 19000-20000 genes within the human genome, this implies that the bulk of the genes might be controlled by miRNAs[52]. Most of miRNA SNPs are link to with maladies[53]. Their biological function is hard to elicit given that adjustment in any miRNA can have vast genome-wide impacts, as can interaction with hundreds of different mRNAs[54]. Furthermore, new research has demonstrated how miRNA work in targeted genome editing with the in vitro method to prepare novel instruments for complicated confirmation of miRNA SNP consequence[55].

It was discussed that how microRNA play a critical role in a large range of development processes including metabolism cells, apoptosis and progress timing[56]. Other roles of microRNA in the body include neuronal gene expression, stem cell division and muscle differentiation[57]. MicroRNA as a major source in the development of cancer cells is still very much unknown[58]. According to the latest research, microRNA can lead to a malignant tumor within the cell[59]. In addition, there is some microRNA relevant to the human disease in Table 2.

CONCLUSION

In recent years, microRNAs have been studied as promising potential screening and prognostic biomarkers for cancer. MicroRNA profiling in a wide range of cancer types could provide insight that may be valuable in the development of effective, rapid and economical diagnostic assays for cancer and drug resistance, which may reduce the duration of hospital stays and treatment costs. Such advances represent new frontiers in microRNA-based cancer therapeutic strategies but the challenge of tumor-specific treatment remains an obstacle to be overcome.

SIGNIFICANCE STATEMENT

This study will help the researcher to uncover the critical areas of miRNA biology of cancer that previous generations of researchers could not explore. Thus a new theory on the

answer to the obstacle relates to the microRNA and cancer such as nanocarrier for transfer microRNA, there are some of the genetic disorders that researchers can gain to it.

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