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Mechanism of microRNAs Regulation and Function them in Recognition and Treatment of Cancer

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Mini Review Article

Abstract

Background: Despite of all the efforts and studies conducted on diagnosis and treatment of cancer, this disease still has many of losses annually. Cancer is a multifactorial disease that is incidence of genetic and environmental factors are involved. MicroRNA of (micro ribonucleic acid) group of non-coding RNA that have been preserved during evolution. miRNA also like that mRNA By the enzyme RNA polymerase II transcription and after the capping mechanism and Polyadenylation (Pre-miRNA) obtained that by two cutting successive reactions, mature miRNA produced and through the connection to 3'UTR, mRNA target gene affects on it.
Methods: For investigate from the articles in the database such as pubmed, Google Scholar, …. Were taken to this study we used.
Results: MicroRNA can be alter gene expression after transcription that is action in most cases performed through two way decomposition and or inhibit the translation of target gene mRNA. MIR in various cancers could have role oncogenes and tumor suppressor genes (Tumor suppressor) and also in cell cycle, cell death, apoptosis, differentiation and cell proliferation and drug resistance have an important role and can stop the progression of cancer and Hence as biomarkers for the diagnosis and treatment of cancer are available.
Conclusion: MIR expression in various cancers decreases or increases, which in most cases increase the expression of a MIR cause to reduce expression of a gene targeting and vice versa. Hence further studies about this great group of micro RNA are important and can be investigated.
Keywords: microRNA, Cancer, Oncogene, Gene expression

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Introduction

Since the discovery of the first micro-RNA molecules to date about 20 years have passed and research in this field has grown considerably. microribonucleic acids (micro RNA),are Noncoding ribonucleic acids that are evolutionarily conserved (24). miRNA (micro RNA), As regulators of gene expression was identified in 1993, Which was initially in nematode worm was discovered

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and discussed and named Lin-4. The second micro-RNA in the same worm were named let-7(1). Then By identification widespread presence of micro-RNA in among other eukaryotes organisms, increased interest studying the regulatory mechanisms. Micro RNA has a length of 25-18 nucleotides which gene expression post-transcriptional through mRNA degradation or inhibition of their translation, are controls (15). In recent years, many different types of RNA are detected. A large group of RNA, such as tRNA, rRNA, snRNA, snoRNA, siRNA and miRNA, including functional molecules that are in the group of Noncoding RNA (ncRNAs) are placed (26). Many pathways have been identified to regulate gene expression which mediated by small ncRNA are done, such as the gene silencing pathways, methylation of DNA, gene transcription and the interference RNA (RNAi) (18). miRNA due to their the small structure and especial have high stability in various environmental conditions and also against freezing and melting frequently, more resistant than other types of RNA and unlike proteins, Unlike proteins, PH acid and alkaline and different dilutions salt are well tolerated. For this reason can they presented as an ideal biomarker. Micro RNA have a key role in many biological processes, including development, cell proliferation, cell differentiation, Apoptosis, survival and migration and in addition to DNA methylation and histone acetylation as epigenetic mechanisms have been introduced and are playing an important role in regulating gene expression (24). The role of micro-RNA gene regulation now well known and function of Micro-RNA for the development of various physiological systems and maintaining cell stability and normal functioning are it necessary. Today, the issue of study micro-RNA and identify expression and performance in wide range of human diseases including various types of cancer, infections, chronic inflammatory and autoimmune diseases is considered. Micro RNA can be as oncogenes or tumor suppressor acts through inhibition of the expression of targeted genes related to cancer (14).

miRNA in control fundamental processes cellular physiological and pathological are involved (12). MiRNA expression of suppressor tumor in various cancers is reduced, resulting in increasing the growth, proliferation and metastasis, thus restoring the expression of miRNA suppressor tumor in cancer cells could be a proper treatment option for cancer treatment have been conducted many studies in this field (13). So far more than 2500 human microRNA have been known (14). Micro-RNA with targeting mRNA target genes, causing gene silencing (6). By increasing evidence of function regulation the microRNA in of multiple biological systems, the value of these molecules as diagnostic and treatment biomarkers in different diseases such as cancer , continues to rise (16). Most of application miRNA is in the field of diagnostic biomarkers and therapeutic targets (14). The aim of this paper is to review role and mechanism of action of micro-RNA in cancer diagnosis in order to detect and early treatment of cancer patients and prevent therapeutic procedures is difficult.

Micro-RNA biogenesis: MicroRNA biogenesis takes place in the nucleus and cytoplasm. First, RNA polymerase II in core from on the protein coding genes transcribed the pri-miRNA. Pri-miRNAs hairpin structure (stem-loop) that to have the tail at end of pOly A 3' and 5'cap at the end of their CAP, pri-miRNA by a complex containing the enzyme RNAse III for cutting double-stranded RNA called Drosha and binding protein to double stranded RNA DGCR8, converted into pre-miRNA and pre-miRNA by using Exportin5 transported to the cytoplasm. Final processing in the cytoplasm by complex Dicer / TRBP on pre-miRNA is done. Dicer action led to the creation of double stranded RNA with a length 18-24 nucleotides that which is includes a strand leader (guide strand) and a strand follower (passenger strand). The strand follower is

destruct, the strand leader whit binding to argonaute protein provides silencing inducing complex miRNA (miRISC), This complex is complementary of head 3 'UTR from target mRNA, if the sequence miRNA with target mRNA is fully complementary, And connection is complete, causing destruction of the target mRNA, and if connection between miRNA and mRNA is incomplete causing translation is inhibited, so that each miRNA can targeting multiple mRNA (22,27). Figure 1 shows the miRNA biogenesis stages.

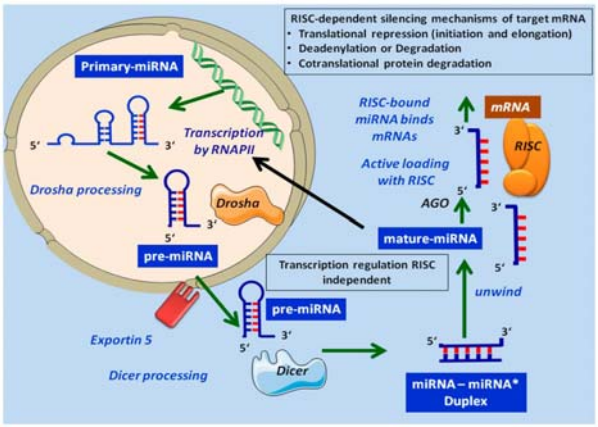

Figure 1. miRNA biogenesis stages in the core and cytoplasm

Identification of micro-RNA target molecules: One of the most important issues related to micro RNA is identify target molecules. Creating a few complementary base pairs for performance interaction between micro RNA and sequence of target molecule is essential. In most cases, Creating a complementary base pairs in 6-7 nucleotides takes place which that usually consists nucleotides 2 to 9 from end of '5 micro RNA and to this region say "seed". The rest of the micro-RNA base, are shown limited pairing capacity to the 3 'UTR sequences adjacent sites seed and the same transient connections to micro-RNA gives allow connection to multiple inner sites at a 3 'UTR. mRNA that preferentially are paired by 7-8 nucleotide from seed sequences, Based on criteria such as developmental protected target sequence and thermodynamic stability interactions taken between the rest of the Bases micro RNA and sequences on both sides in the 3 'UTR are divided. In another type of pairing target Micro mRNA: RNA take place incompelete pairing in the region of '5-seed, but by pairing an additional base in the end of '3 Micro-RNA will be compensated (29). From the different calculation methods to predict the target sites Micro-RNA is used, including computer algorithms, but since pairing with the target sequence is incomplete and limited, it is still difficult to accurately predict the sites the target micro RNA. Numerous studies and bioinformatics software to detect micro-RNA targets from the sequence seed are used. For example, 1000 micro-RNA genes for 1 percent human genome is estimated and It is likely that more than one-third of the human genome by micro-RNA to be set (2,9,10,16,17,19,15). One of the algorithms predicting target molecule, based on the pairing and protected micro-seed -RNA sequence in the 3 'UTR of different species will be designed (31).

miRNA and cancer: All cancers origin from the uncontrolled growth of cells and cell output from set correctly pathways, proliferation and differentiation. Escape from cell death, or apoptosis, mutations in beam oncogenes and creating oncogenes and mutations in tumor suppressor genes, all from the causes of cancer.

Micro-RNA interactions with target genes, determined their role in development, apoptosis, differentiation and cell proliferation and confirms the direct performance of Micro-RNA in cancer (28). After the emergence of micro-RNA in mammals and studies about the role of these molecules in cancer were conducted, proved two important issues, first, miRNA in cancer, have different expression and the second miRNA expression changes in tumor type, create a specific symptoms in each person. As mentioned above, according to the type of miRNA expression changes in cancer cells, into two groups oncogenic and tumor inhibitor or tumor suppressor was divided. MiRNA expression of oncogenes increase in tumor cells and in contrast, tumor suppressor miRNA expression is reduced in cancer cells (12). Because incorrect adjustment of miRNA

in tumor tissues can result in mutations, epigenetic changes, eliminated genomic, or changes in processing miRNA. Finally incorrect expression and or suppression of a miRNA miRNA can cause tumorigenesis or tumor progression. The use of micro-RNA to classify tumor more appropriate than mRNA, This issue due to incomplete coupling between target miRNA and mRNA. For this reason micrometer micro-RNA can be identify expression of several hundred genes and result in multiple pathways in one instance, if only require small amounts of total RNA (7).

Some types of micro-RNA act as oncogenes or tumor suppressor that called oncomir. The oncomir are present in various cancers and often in regions of the genome that have deletion, duplication, or mutations were found (32). Table 1 shows of altered expression levels of some miRNAs involved in different human cancers.

Table 1. Some micro-RNA involved in different human cancers with altered expression levels

Type of cancer	Reduced expression	Increased expression
Bladder	miR-29c, miR-26a, miR-30c, miR-30e-5p, miR-145, miR-30a-3p, miR-133a/b, miR-195,miR125b, miR-199a	miR-17, miR-23a,b, miR-26b, miR-103-1, miR-185, miR-203, miR-205, miR-221, miR-223
Lung	let-7, miR-34 family, miR-143, miR-145, miR-124a	miR-17-92 cluster, miR-21, miR-155, miR-191, miR-205, miR-210
Thyroid	miR-30d, miR-125b, miR-26a, miR-30a-5p	miR-146b, miR-221, miR-222, miR-181b, miR-155, miR- 197, miR-224, miR-346
Ovary	miR-199a, miR-140, miR-145, miR-125a,b, let7	miR-200a/b/c, miR-141, miR-18a, miR-93, miR-429
Breast	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	miR-21, miR-22, miR-23, miR-29b-2, miR-96, miR-155, miR-191, miR-181, miR-182, miR-27a, miR-210
Esophagus	miR-203, miR-205	miR-194, miR-192, miR-200c, miR-21
prostate	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	let-7d, miR-195, miR-203, miR-21, miR-181, miR-106, miR-363, miR-221
Colorectal	miR-143, miR-145, let-7, miR30 -3p, miR-124a, miR-129, miR133 b, miR328	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
Chronic lymphocytic leukemia	miR-15a, miR16-1, miR-29, miR143, miR-45,miR-30d, let-7a, miR-181a/b, miR-223, miR-92, miR-150	miR-21, miR-23b, miR-24-1, miR-146, miR-155, miR-106b, miR-195, miR-221, miR-222

The use of microRNA in cancer treatment:

Expression of microRNA disorder with specific pathological state and response to therapy in a variety of tumors associated have been shown. Recently in cancer treatment from itsself microRNA or AMO (anti-microRNAantisense oligodeoxyribonocleotide) alone or in combination with medications, chemotherapy and radiation are used (8).

In general, through inhibition of oncogenic microRNA and artificial microRNA or cut it by pairing with mRNA, microRNA artificial induction of pairing with mRNA, Induction of Tumor suppressor microRNA and reduction of microRNA expression by epigenetic factors such as promoter methylation, Can be prevent cancer progression. Of Antisense oligonucleotides which paired with microRNA, can be used to reduce microRNA expression, such as Antagomir that of this same type (4). The advantages use of miRNA as therapeutic targets in cancer is that a miRNA can targeting multiple mRNA and on the other hand, an mRNA, can target of several miRNA.

There are two methods for regulating the expression of miRNA in cancer, the first method, the inhibition of oncogenic miRNA expression by using syntetic anti-miRNAs or miRNA antagonists or Locked nucleicacids (LANs), For example the use of antisense oligonucleotides (Antisense) which their sequences supplements the mature miRNA oncogenes within the body (20). The second method about tumor suppressor miRNA are done that in various cancers decreased their expression, in this case treatment by restoring the expression of miRNA in normal mode can be performed, for the purpose of miRNA replacement therapy is used (13).

Treatment methods with micro-RNA: Here are two methods mentioned:

1. Use of microRNA mimic: In this method of microRNA that has the role tsmicroRNA, usually as double-stranded that is Dicer product, transferred into cells. Like the other methods have been used in in vitro and in vivo. In 2010, LPH nanoparticle that with a single-stranded anti-tumor antibodies were combined, could be purposefully Mir-34a transmit to melanoma cells (13).

2. Using of precursor protein the microRNA: In this method, gene related to microRNA in a expression vector imported that can be a viral or plasmid, in designing of vector, issues such as the promoter, gene fragment are considered (30). Of lentiviral and Adenoviral are used for both differentiated cells that are not dividing and also dividing cells. But since Adenoviral, do not enter within the genome, in the dividing cells gradually disappearing (25). The main problem use of expression vectors in vivo that is often the host immune system eliminates them (30). In one experiment, by raising the the expression of K-ras in mice, As conditional created lung cancer, it was found that intranasal administration of adenoviral expressing let-7a reduces tumorigenesis (23).

Methods

In order to investigate about micro RNA and their function In the cancer, focused on studies have been done on the field, and to conclude, and from articles in databases such as springer, pubmed, science direct, Google Scholar were brought , used for present study.

Results

Considering the fact that most common techniques for early cancer screening can not diagnose disease, Identification of tumor micro RNA are released in the bloodstream during the gradual progress of the disease, is a key way in early detection of cancer. Micro-RNA by binding to target mRNA, causing inhibits their translation or decomposition, and increase or decrease the expression of micro-RNA are involved in apoptosis or cancer, Due to the importance of micro RNA to detect and treat cancer, led to studying and tracing techniques have a growing trend in recent years. Specifying the target miRNA molecules and study their molecular interference effects In the signaling pathways, will help to easier and more effective understand of cancer. miRNA in cancer treatment are also considered, and to make effective changes In these molecules can be affected them the target molecules. Although obstacles and difficulties as well, including a miRNA can be Control a large number of expressed targets genes, therefore, any change in the it can cause targeting genes other than the original target genes. There is

very few information on the factors that affect the expression of microRNA, however, many studies confirming the fact microRNAs have an important role in the onset and progression of Cancer. Thus, miRNAs are useful and powerful tool in the diagnosis and prognosis of diseases, including cancer and are also effective in the treatment and control of cancer.

Discussion

In the total miRNA are a category of Noncoding small RNA which that regulated the expression of genes at the level of RNA or transcription, and given the role of miRNA in proliferation and differentiation processes, is expected to disrupt their expression related to cancer.

Conflict of Interests

Authors have no conflict of interests.

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