



IMPACT OF MICRORNAS IN CANCERS–A MINIREVIEW

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ABSTRACT

To date, hundreds of microRNAs (miRNAs) have been identified in the human genome, which play key roles in a broad range of physiologic and pathologic processes. miRNAs are endogenous small non-coding RNAs, genes of ~22 nucleotides long. They involve in gene silencing as well as regulation of gene expression. They regulate the expression of genes via targeting various signaling pathways. miRNAs also play an important role in neoplastic transformation by modulating the level of oncogenes and tumor suppressor genes and perform crucial functional roles in various basic cellular processes such as differentiation, proliferation and apoptosis. Expression pattern of miRNAs are very specific to normal tissues and tumorous tissues, therefore its deregulation are found to be associated with development of cancers and tumor progression. Additionally, they are described as key regulators in many diseases including, neurological disorders, cardiovascular diseases, viral infections and including various cancers. Further understanding of the expression and function of microRNAs in different cancers is thought to provide in the near future the development of better diagnostic and therapeutical approaches against cancer, mainly by allowing the identification of pre-neoplastic lesions and better follow-up of patients. In this review, we summarized about the impression of microRNAs in cancer.

Keywords: Cancer; MicroRNA; Tumor Suppressor; Oncogene

INTRODUCTION

MicroRNAs (miRNAs) are evolutionary conserved short non-coding RNAs of ~22 nucleotides long. These are present in all eukaryotic cells and perform crucial roles in every biological pathways.¹ Two independent studies in 1990s, recognized a small non-coding RNAs lin-4 in *Caenorhabditiselegans*. After these studies, there were no discoveries for a few years regarding functions of miRNA.^{2,3} For first time in 2002, the association between deregulation of miRNA and cancer was reported in recurrently deleted chromosomal region in chronic lymphocytic leukemia (CLL; 13q14). This study have supported the data that polycistronic miRs possess two miRNA gene- miRNA-15a and miRNA-16-1 and deletion of these miRNAs gene sequences lead to development of CLL.⁴ The reports of association between deregulation of miRNAs and cancers brought miRNAs into spotlight for more extensive research. Data from previous studies reported that altered expression of miRNAs is a rule not an exception.⁵ Many evidences have been shown that miRNAs play an important role in various cancers (Table-1) related processes like proliferation,⁶ apoptosis,⁷ invasion and migration.⁸ miRNAs not only plays a crucial roles in cancers, but also involve in various metabolic diseases.⁹

In several studies it have been noticed that a single miRNA may has not only tumor suppressor property in some types of cancer but also may function as oncogenic in other type of cancer like miRNA29 (miRNA29a/b/c), has been reported as tumor suppressor in lung cancer but also act as an oncogenic miRNA in breast cancer.

In 2012 Zaman MS tried to know the property of miRNA23b in cell line of renal cell cancer after knocking down its expression, reduced invasive property and also induced apoptosis of the cell. After that in 2013, Majid S. et al. told that loss of miRNA23, promoted bladder cancer cell migration and invasion. On the basis of gene expression pattern and cell type, same miRNA can involve in more than one signalling cascade, having diverse impact on cell growth, survival and proliferation. Additionally, nearly 60% of mRNA gene expression done under the control of miRNA. It is must to prove the utility of miRNA in human cell models.

MiRNA Biogenesis

Transcription of miRNA takes place in nucleus by RNA polymerase II to generate primary miRNA (pri-miRNA), stem loop like structure.¹⁰ Some miRNAs are transcribed by RNA polymerase III also.¹¹ miRNAs gene locus are present in the introns of either

protein-coding or non-protein-coding transcripts along with minority found in isolated regions of the genome, within the exons of noncoding mRNA genes (Fig-1).¹² miRNA biogenesis ends in the cytoplasm of the cells and transcribed as monocistronic or polycistronic pri-miRNA.¹³ This pri-miRNAs get spliced and capped with 5' m7G (7-methylguanosine cap) and 3' end get polyadenylated, same as mRNA (messenger RNA) processing during protein synthesis.¹⁴ Stem loop structure (secondary structure) get processed in nucleus by a protein complex-Drosha (RNase III enzyme) in conjunction with DGCR8 (DiGeorge Syndrome Critical region 8) resulting in ~70 nucleotides long precursor-miRNA (pre-miRNA). After this processing, pre-miRNA transported to the cytoplasm with the help of Exportin 5 (Ran-GTP dependent).¹⁵ After that, RNase III enzyme (Dicer) cleaves this pre-miRNA with the help of TRBP (trans-activator RNA-binding protein) and dsRBD protein, into ~22 nucleotides long double stranded miRNA duplex (mature miRNA). This mature miRNA gets incorporated into RISC (RNA-induced silencing complex) with Ago protein (Argonaute).¹⁶ This complex binds to its target mRNA and play its role in protein expression by mRNA degradation or mRNA repression (Fig-2).^{17,18}

Role of miRNAs in Cancer

In 2002, Calin et al. have reported the first evidence regarding association between deregulation of miRNA and cancer. They were the first one to explain association between the frequent deletions of miRNA-15a/miRNA-16-1 in CLL and concluded in their study that these miRNAs perform tumor suppressor activity.⁴ This study was a major breakthrough in miRNAs research in cancer, fascinated the mind of many researchers to focus on the cause of the altered expression of many miRNAs in tumors and many other diseases. In comparison to normal tissues, cancerous tissues, showed aberrant expression, associated with abnormal epigenetic changes like methylation of their miRNAs promoter region.¹⁹

Other studies anticipated that the reason of miRNAs deregulation was the aberrant expression of enzymes, involved in the biogenesis of miRNAs. Afterward this fact was proven by a study in which expression of two proteins of biogenesis pathway, Dicer and Drosha decreased in 39% in patients of ovarian cancer.²⁰ Another regulatory process of expression of miRNAs are under the control of activity of transcription factor.²¹ Example of transcription factor regulated cancer process is oncogene Myc aggravates miRNA-17/miRNA-92.²² miRNAs interferes

with modulation of cellular methylation via the regulation of enzymes involved at epigenetic level. In the lung cancer study, researchers group reported that miR-29 family act as an important regulator for ex-novo expression of DNA methyltransferases, DNMT3a and DNMT3b.²³ Recent studies have revealed the hepatocyte growth factor receptor, c-MET affects miRs. Additionally, c-MET with other transcriptional factors such as ELK-1 and AP1 promotes expression of onco-miRNA cluster miRNA-221/222, while induce a negative impact on miRNA-27a. Data from several studies have also explained about the association of deregulated expression of c-MET with the altered expression in pathways in cancers.^{24,25} Moreover, expression of miRNAs can also be controlled by nuclear receptors.²¹ As an example in cancer, an altered expression of nuclear receptors like androgen and estrogen receptor α is linked with the aberrant expression of various miRNAs.²⁶ Many miRNAs show drug resistance like miR-19, miRNA-21 and miRNA-221/miRNA-222 and they get up-regulated in response to this process,^{24,27,28} whereas other found to be down-regulated such as miR-130a and miRNA-298, these miRNAs explained the biological role of miRs in drug resistant phenomenon, which is considered to be tissue

specific.^{29,30} Instantaneously, miRNA-27a involve directly in a drug resistance processes in leukemia while it shows indirect response toward susceptibility of drug in ovarian cancer.³¹

Oncogenic and Tumor Suppressor miRNAs

After dysregulation of miRNAs, it can promote abnormal post transcriptional regulation of oncogene or tumor suppressor gene expression. On the basis of this mechanism, MiRNAs are classified in two categories, oncogenic miRNAs and tumor suppressor miRNAs.³² miRNAs show distinctive expression patterns in tumorous tissues in comparison to normal tissues.³³ Oncogenic miRNAs found to be up-regulated in cancers, so they are named as oncomirs, and involves in the negative regulation of tumor suppressor genes. This process promotes differentiation of cells, cell cycle arrest or apoptosis. Wong et al. (2008) reported about the oncogenic miRNA-184 plays a key role in anti-apoptosis and propagation of squamous cell carcinoma of tongue.³⁴ Bullrich et al. in 2001 have documented the tumor suppressor miRNA-16-1 and miRNA-15a,³⁵ these miRNAs show inverse relation with the Bcl2.³⁶ Several reports are indicating that more than half of the genes of miRNAs are present in cancer associated genomic region or on fragile

location. The participation of miRNAs have been seen in different types of cancers including lung, breast, colon, thyroid, prostate and gastric [20-24]. Majority of the researchers are trying to know about the target of miRNAs in cancers because its effect is produced by the targeting on multiple mRNAs, some miRNAs have the property to show its effect by using same pathway. Song T et al, in 2017 have found that the expression of miRNAs have difference in expression of one cancer to the others cancer type. Such type of property may help to distinguish one cancer to the other cancer.^[26]

MiRNAs Role in Cancer Diagnosis and Prognosis

miRNAs possess the property of regulating cell growth and apoptosis, which help in the pathogenesis of cancer, a process due to deregulation of cells apoptosis. Altered expression of specific miRNAs have been recognized the role of miRNAs in pathogenesis of cancer. Misexpression of miRNAs also help in determining the initiation and advance stage of different forms of malignancies. miRNAs also act as diagnostic³⁷ and prognostic markers in

cancers.³⁸ Recently, Scientists have attracted towards circulating miRs which emerge as an diagnostic and prognostic biomarker in cancer. These biomarkers show abnormal expression in solid and hematologic neoplasm.

In 2008, serum miRNA-21 level were detected in diagnosis and prognosis of diffuse large B cell lymphoma (21). Chen *et al.* have validated these results in healthy controls as well as the sera of DLBCL patients of Chinese population (47). Fayyad –Kazan *et al.* have seen the up-regulated expression of two plasma miR-150 and miR-342 in AML in comparison to healthy controls, this finding suggest that these miRs acts as novel, specific and potential biomarkers for early stage diagnosis of AML (22). Apart from these circulating miRs are reported not only in AML, DLBCL as well as CLL. Recent study confirmed that differential expression of circulating miR-222, Mir-29a and miR-195 are better biomarker to identify the B- cell CLL patients from healthy subjects (48). Additionally, up-regulation of plasma miR-155 acts as an early diagnostic biomarker of the disease (23).

Table 1: Different types of miRs used as a biomarker in various cancers (Modified table, taken from the review of Lan H, 2015).³⁹⁻⁷¹

miRs as Biomarkers	Cancer Type
miR [*] -21,22,26, 29, 31, 122, 124, 135, 139, 200b, 222, 223, 181a, 181b, 200c, 203	Liver ^{39-41,42}
miR-20a, 21, 141, 145, 221, 30c, 622, 10b, 1285, 373, Let-7c, 7e, 26a, 195, 375	Prostate ⁴³⁻⁴⁶
miR-10b, 21n, 30a, 92a, 125b,141, 145, 200, 801, 155,191, 203, 210	Breast ⁴⁷⁻⁵¹
MiR-200, Let-7, 21, 29a, 92, 93, 126, 127, 132, 155, 214, 182, 205, 144, 222, 302, 30c, 213,429	Ovarian ⁵²⁻⁵⁶
miR-21, 15b, 16, 155, 17, 19b, 25, 29c, 30c, 106a, 148a, 197, 126, 451, 372, 660, 28-3p	Lung ⁵⁷⁻⁶¹
miR-21, 130, 145, 150, 205, 105, 203, 210, 642b, 22, 122, 505, 636	Pancreatic ⁶²⁻⁶⁶
miR-15b, 18a,29a, 141, 92a, 335, Let-7g, 20a, 21, 92, 181b, 760	Colon ⁶⁷⁻⁷¹

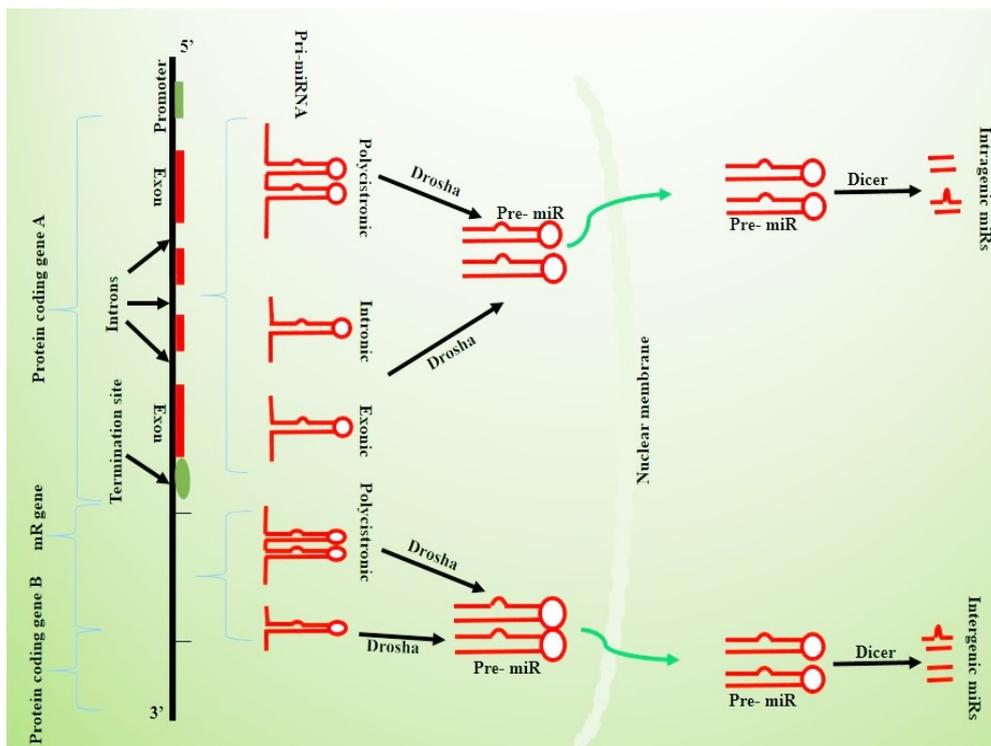


Figure 1: Showing origination of intragenic miRNA and protein coding gene as well as origin of intergenic miRNA from miRNA genes found between protein coding genes.

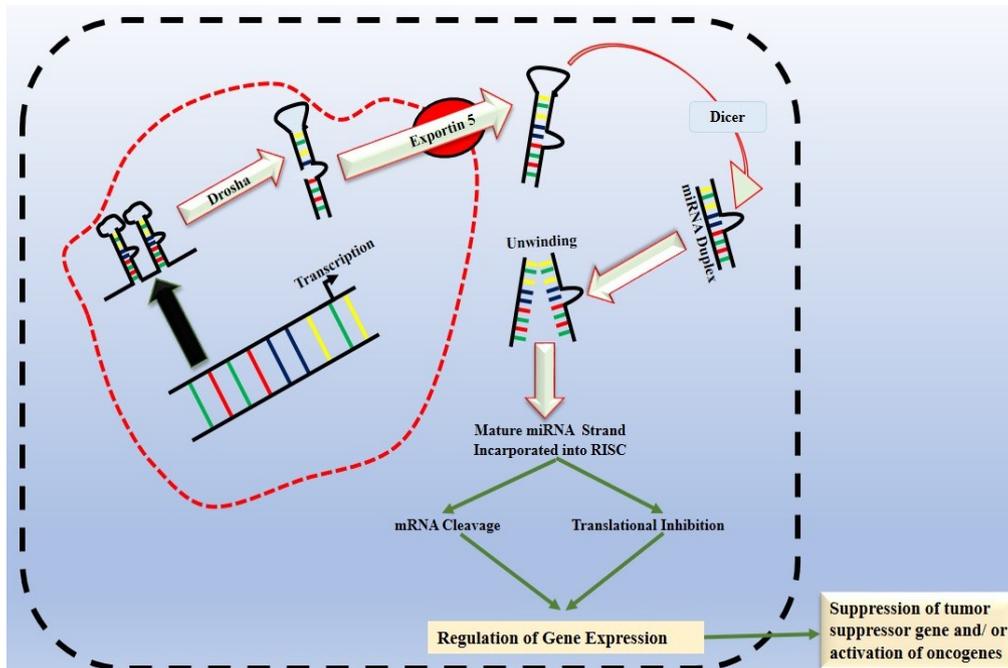


Figure 2: Showing miRNA biogenesis, miRNA gene transcribed in the form of pri-miRNA (secondary structure) with the help of RNA polymerase II/III and get converted in pre-miRNA (~70 nt long) with the help of Drosha and DGCR8 protein complex, in next step it goes to cytoplasm via Exportin 5 transporter protein (Ran-GTP dependent). In the cytoplasm Dicer cut this secondary structure and form mature miRNA duplex. miRNA duplex get separated and incorporated into RISC complex and then binds to its target mRNA after binding, it participate in protein expression, which may help in tumor suppression or may act as oncogenes. (Modified from the review of Singh P. et al; 2016)

CONCLUSION

Several studies have been addressing on the impact of miRNAs in tumor development, resist cell apoptosis, dodge growth suppressor, promote angiogenesis, metastasis and invasion. The function of same miRNA or different miRNA may act as tumor suppressor as well as tumor progressor under certain circumstances because of this miRNAs have the ability to act on multiple targets. Their function in cancer progression could be due to few specific targets. Because of all the different types of property of miRNAs, represent a big challenge for researchers to

identify the targets of this small miRNAs, which involve in cancer and promote malignancy and apoptosis inhibition. miRNAs could be a used as powerful biomarkers in diagnosis, prognosis and therapeutic targets. However hard work are needed to know about miRNAs on huge amount of the patients population, using advanced techniques like sequencing to validate as diagnostic biomarkers and prognostic biomarkers as well as therapeutic targets. But there are several problem during the development of miRNAs therapeutic strategies like validation of the targets and specific miRNA delivery system.

Nowadays researchers are directing towards secreted exosomal packed miRNAs of the clinical samples. Because packed miRNAs are more stable due to this behavior, it may be used as a potential biomarker for clinical applications. Exosomal miRNA biomarkers are still in early developing stage and their potential value in clinical diagnosis are in weighting to be fully explored in clinical applications. The future researches are needed to boost the knowledge about miRNAs in the field of its role in biological scenario, tumorigenesis, and also about cancer prognosis, treatment and diagnosis.

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