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Review Article

MicroRNAbased Novel Strategies for Cancer Treatment

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Abstract

MicroRNAs (*mir*NAs) have garnered tremendous interest in cancer biology research in the recent decade. *mir*NAs are a group of short non-coding RNAs,20–24 nucleotides in length, thatare found in animals and plants.Theycan reduce the expression of genes involved in numerous vital cell processes. Recent evidences indicate a key role played by *mir*NAs in the initiation and development of human carcinogenesis. These function including: the regulation of oncogenes, tumor suppressor genes, and several tumor-associated genes to that of processes such as cell proliferation, apoptosis, and angiogenesis. Clinical trials aimed at improving *mir*NA profiling for clinical diagnosis and prognosis of different disorders are now underway. In this review, we have summarized the physiological role of *mir*NAs and theirdiagnostic and therapeutic potential inclinical assessment.

Keywords: biogenesis, cancer, microRNAs, regulation, therapeutic

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1. Introduction

MicroRNAs (*mir*NAs) are a subset of small (18 to 24 nucleotides) non-coding RNA molecules, which were discovered in 1993 in the nematode *C.elegans*in relation with the gene lin-14 (1-3). MicroRNAs play vital roles in several biological pathways in multicellular organisms, including mammals(4).They are involved in differentcellular processes like proliferation, differentiation,metabolism, cell cycle, and apoptosis of normal cells, as well as in the pathogenesis, invasion, and tumorigenesis of various malignancies(5-7). About 3,000 potential human microRNAs have been identified(8). They directly bind with the 3'UTR region of target messenger RNAs (mRNAs) and downregulategene translation.Bioinformatic analyses have revealed that *mir*NAs can regulate approximately 60% protein-encoding genes in the human genome(9). Recent evidences highlight the importance of noncoding RNA as global regulators in the development and progression of cancer through their specific mRNA interactions. In addition, *mir*NAs can target multiple effectors of cell proliferation, differentiation, and survival pathways (10). Hence, it is important to find the precise function of *mir*NAs in carcinogenesis and investigate

the basis of their actions.Therapeutic targeting of *mir*NAs in cancer could open a new avenue for the use of *mir*NAs in cancer therapy(11).In current review, we summarize the identification and characterization of *mir*NAs and also discusstheir roles in human cancers and tumorigenesis.The various types of RNA molecules are shown in Figure 1.

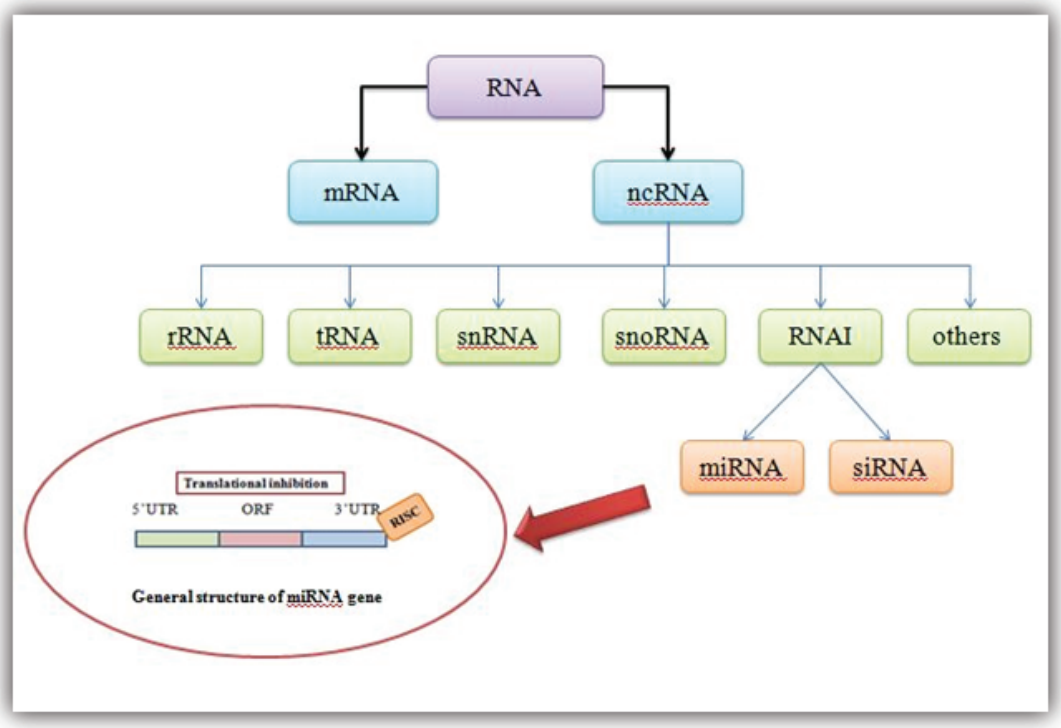

Figure 1: Type of RNA molecules. RNA have two subclass including; mRNA and ncRNA.

2. MicroRNA Biogenesis and Its Regulation

The biogenesis of *mir*NAs involves an initial transcription of a large primary transcript (pri-*mir*NA) by RNA pol II which in the 5' to 3' direction' (12, 13). In the nucleus, the pri-*mir*NA is capped, polyadenylated, and then cleaved by the RNA-binding protein DGCR8/Pasha and RNase type III (Drosha) into an ~60–75 nucleotideslong structure identified asa precursor *mir*NA (pre-*mir*NA) (14, 15). The Ran/GTP/Exportin-5 complex is known to act as atransporter of pre-*mir*NAs. Subsequently, Dicer (RNase III enzyme) cleaves the double stranded mature RNA duplex into an ~ 19– 24 nucleotideslong structure (16),which is incorporated into the RNA-induced silencing complexs (RISCs) and guides the translation of mature *mir*NA(according to Figure 2) (17). The 'seed' sequence in the mature *mir*NA recognizes and binds to itscomplementary 3′ untranslated region (UTR) on the target mRNA, forming RISC which subsequently cleaves the target mRNA. Some evidences also suggest that the 5' end of the mature *mir*NA or open reading

frame of the aim mRNA are involved in the recognition process across the genome (Figure 1) (18-20). Reports estimate that about 30%of the human genomeis controlled by *mir*NAs and this makes *mir*NAs one of the biggest groups of target specific regulatory molecules in the body(21).

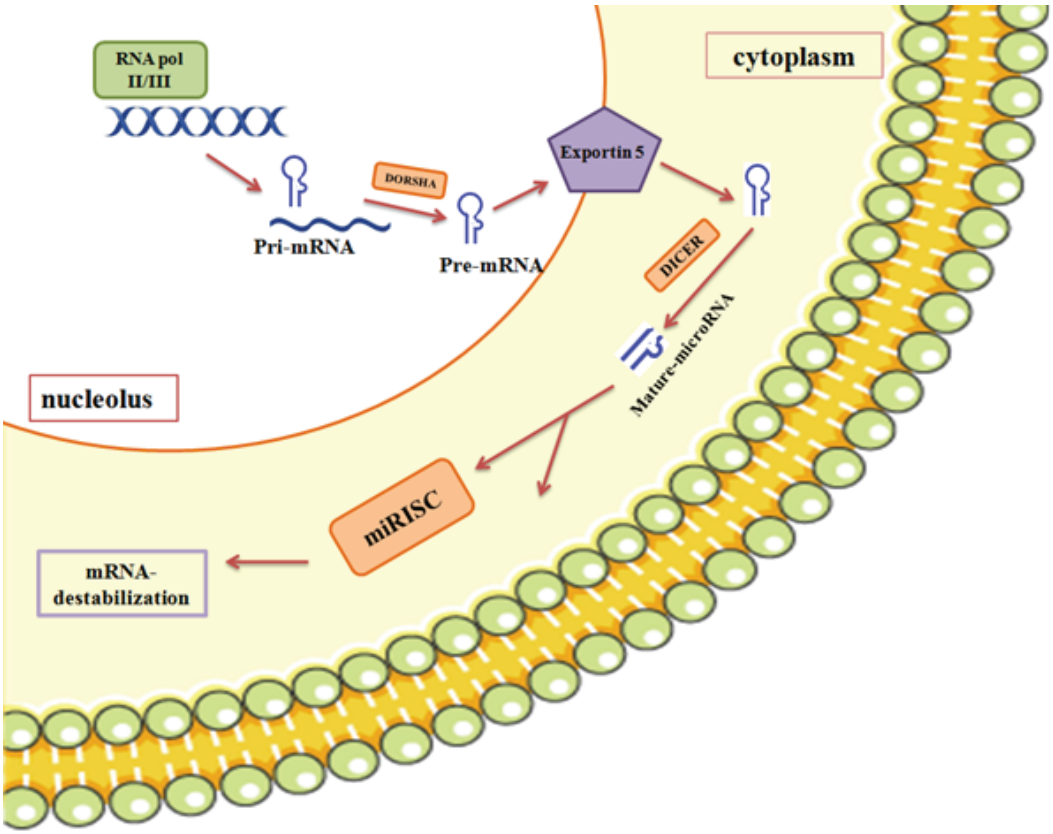

Figure 2: MicroRNA biogenesis and regulation. The pri-mirNA is capped, polyadenylated, and then cleaved in the nucleus and identified as a precursor mirNA (pre-mirNA). Then, Dicer (RNase III enzyme) cleaves the double stranded mature RNA duplex by RISCs and guides the translation of mature mirNA.

3. A Potential Role for MicroRNA Expression in Cancer

Most types of cancers have characteristics including the lack of cellular identity, enhancement of proliferation ability, and loss of the cell death regulatory system(22-24).Studies carried out in different organisms have indicated that mirNAs are involved in several of these cellular processes, suggesting that they play a critical role in carcinogenesis. Several reports have firmly established that mirNAs are expressed in cancer tissues and normal. Further, that they are located in tumor-associated genomic sites or in fragile regions (22). Amplification, deletion, and translocation of mirNA genesin tumor cells may lead to mirNA copy number variation (25). Research has demonstrated an absence of the mir-16 and mir-15a genes in the 13q14 chromosomal region of B-cell chronic lymphocytic leukemia (B-CLL) patients (26). In lung cancer, the genes mir-143 and mir-145 in the 5q33

region are mostly omitted leading to reducedmirNA expression (27).However, mir-17–92 gene amplification was found in lung tumor and B-cell lymphomas (BCL).In addition, over expression of this gene cluster was also observed in T-cell acute lymphoblastic leukemia (T-ALL)(28).Aberrant expression of several transcription factors (TFs) can be the key cause of mirNA dysregulation in tumor cells such as p53 and c-Myc(29).O'Donnell and colleagues in 2008 showed that c-Mycis overexpressed in several neoplasms to control cell apoptosis and proliferation, elevate expression of oncogenic mir-17–92, and induce binding of E-box elements. Furthermore, c-Myc up regulated the activity of the TF regulated mirNAs involved in cancer suppression including let-7, mir-15a, mir-26 and mir-30 (30).Recent evidences have shown that mirNAs combined with chemotherapeutic agents can be used a new strategy for next-generation malignancy treatment (31-33).

In breast cancer, similar to lung cancer,the down regulation of let-7a was linked with poor prognosis and invasion(34). In addition, *mir*-21, *mir*-25, and *mir*-221 have been identified to be associated with solid cancer such as papillary thyroid carcinoma (PTC). Volinia et al.in 2006 carried out a genome-wide *mir*Nome study that included stomach, colon, prostate, and breast cancers and found that solid tumors over expressed *mir*NAs such as iR-17–5p, *mir*-21, *mir*- 20a, *mir*-92,*mir*-106a, and *mir*-155. Some evidences indicated that *mir*-20 and *mir*- 106 can target the transforming growth factor b receptor II and retinoblastoma genes, respectively(34). On the other hand, there are significant differences in *mir*NA expression between normal and CLL B cells(35). Karube etal.in 2005 showed that low mRNA expression of Drosha and Dicer was associated with lung cancer with a remarkable prognostic potential on the survival of surgically treated cases and was implicated in reduction of genomic instability and transformation inhibition (36, 37). Argonaute genes such as AGO3, AGO1, and AGO4 are located in 1p34–35 and were found to be mutated in Wilms tumors and correlated with neuroectodermal tumors (38).Further research indicated that *mir*NA inhibition could be essential in designing-drugsfor disorders such as tumors.

4. *mir*NA Approach in Cancer Diagnosis and Treatment

Various studies have demonstrated the significant roles played by *mir*NAs in tumorigenesis and have explored their possible use as therapeutic biomarkers and their impact onthe prognosis of human cancer(39).*mir*NAs can directly target cancer cells and aid in the treatment ofother disorders(40). AnRT-qPCR study revealed that *mir*NAs can be used to distinguish ErbB2(HER2)-positive from ErbB2(HER2)-negative and HER2-positive from HER2-negative breast tumors in biopsies(41). Overexpression of some *mir*NAs can decrease the expression levels of tumor suppressors or additional genes

involved in cell differentiation and, therefore, lead totumor development by stimulating angiogenesis, proliferation, and metastasis,i.e., these *mir*NAs function as oncogenes(42). Most researchers are focusing on non-invasive and inexpensive methods fordiagnosis including assessment of plasma, serum, saliva, and urine for detection of *mir*NA levels.Welch and colleagues in 2007 indicated that *mir*-34a is involved in neuroblastoma celltumorigenesis as a potential tumor suppressor (43). Cochettietal in 2016 demonstrated that let-7i, *mir*-195, and *mir*-26a were elevated in the serum of patients with prostate tumor compared to those with benign prostate hyperplasia(Table 1 shows microRNA abnormality in tumorigenesis) (44).In addition, circulating *mir*-141 and *mir*-375 levels were found to be associated with metastatic prostate cancer and could be used as a prognostic biomarker. Bianchi et al showed that *mir*-28, *mir*-30, *mir*-92, *mir*-140, and *mir*-451 have uncontrolled expression in lung cancer (45). Moreover, *mir*-27, *mir*-158, and *mir*-200 were associated with metastatic colon cancer (46).

4.1. Genetic variation

Since 2004, different evidences have demonstrated that about half of the *mir*NAs are found in fragile sites and tumor susceptibility regions (47). Different studies involving mapping repetitive sequences, breakpoints and CpG islands have been performed to confirm the association of *mir*NA genes with fragile sites (48). In addition, certain mutations that result in changes in*mir*NA sequences might be involved in down-regulation of cancer suppressor genes and lead to oncogenesis. Thus, several genetic polymorphisms influence *mir*NA molecular pathways and processing of *mir*NA precursors (49).

4.2. Epigenetic alteration

Aberrant epigenetic processes a well-known feature of malignant cells and possibly happens in primary stage of cell cycles. Epigenetic alterations leading to DNA methylation and histone modification have been noted in particular cancers (49).Most studies have utilized chromatin remodeling therapy to address epigenetic change of microRNAs (50).

5. Conclusion

Diagnostic, predictive and therapeutic potentials of *mir*NAs have been significantly determined by various research studies. Numerous evidences suggest that *mir*NAs can act as tumor suppressive or oncogenes and can be incorporated into novel cancer therapies. Performing comprehensive and well-designed, retrospective and prospective

Table 1: MicroRNA abnormalities associated with tumorigenesis.

MicroRNA	Chromosomal location	cancer	Function	Expression	Ref
Let-7	11q24	colon, Lung, , breast, ovarian cancer	Tumor-suppressor	Down	(51)
mir-15/-16	13q31	CLL and prostate cancer	Tumor-suppressor	Down	(52)
mir-26a	3p22	liver cancer	Tumor-suppressor	Down	(53)
mir-29	7q32	AML, CLL, lung and breast	Tumor-suppressor	Down	(54)
mir-31	9p21.3	Breast, stomach, ovarian cancer	Tumor-suppressor	Down	(55)
mir-34	*mir*-34	Colon, ovarian, glioblastoma cancer	Tumor-suppressor	Down	(56)
mir-96	7q32.2	Pancreatic cancer	Tumor-suppressor	Down	(57)
mir-107	10q23.31	Colon and pancreatic cancer	Tumor-suppressor	Down	(42)
mir-126	9q34.3	Stomach and breast cancer	Tumor-suppressor	Down	(58)
mir-181c	19p13.12	Stomach cancer	Tumor-suppressor	Down	(59)
mir-196	17q21.32	Pancreatic cancer	Tumor-suppressor	Down	(60)
mir-10b	2q31.1	Breast, esophagus and glioblastoma cancer	Oncogene	up	(61)
mir-17/92	13q22	lung, colon, breast, cancer	Oncogene	up	(34)
mir-21	17q23.1	Lung, esophagus colon,liver,pancreatic, breast and glioblastoma cancer	Oncogene	up	(62)
mir-155	21q21	CLL, AML, breast, lung, colon cancer	Oncogene	up	(34, 63)
mir-181b	1q32.1	Liver cancer and myeloma	Oncogene	up	(64)
mir-196	17q21.32	Esophagus, glioblastoma and colon	Oncogene	up	(65)
mir-200a/b	1p36.33	Ovarian cancer	Oncogene	up	(66)
mir-221/-222	Xp11	lung cancer, hepatocellular carcinoma	Oncogene	up	(67)

studie swill enable better characterization of the potentials of *mir*NAs. Furthermore, studies on least invasive procedures comprisingblood, saliva and urine collection will help in the expansion of cost-effective and reliable *mir*NA-based technology for early cancer detection.

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Conflicts of Interest

None

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