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REVIEW ARTICLE

microRNAs regulation and its role as biomarkers in diseases*

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Abstract

MicroRNAs (miRNAs), approximately 21 to 23 nucleotides (nt) in length, belong to a set of small non-coding RNA molecules that were not thought to be functional until the recent decades. miRNAs play important roles in many diseases such as various kinds of cancers and immune disorders. Many studies have focused on the relationship between miRNAs and diseases. miRNAs are significant mediators in human growth and development and in the genesis and development of diseases. Almost 30% of the activity of protein-coding genes is forecasted to be regulated by miRNAs in mammals, and some miRNAs are regarded as potential therapeutic targets for various diseases. In this review, we outline some functions of miRNAs, especially those related to diseases.

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According to the central dogma of molecular biology, DNA is transcribed into messenger RNA (mRNA), and proteins are synthesized from mRNA via translation. However, in the recent decade, the complexity of the transcriptome has been appreciated further. An increasing number of unknown non-coding RNA species, including small RNAs, small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA), have been discovered. Small RNAs include microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNA (piRNAs). These diverse RNA species further our understanding of the regulation of DNA, RNA, and protein. Most non-coding RNA species play crucial roles in regulation (Table 1). The diverse regulatory functions of miRNAs in the cell cycle and in cell proliferation and differentiation have been identified by a large number of studies. This review outlines miRNA biogenesis and the essential roles of miRNA in various diseases, especially cancer. In addition, the diagnostic and therapeutic application of miRNAs, e.g., as disease biomarkers, and the development of new drugs targeting miRNA are discussed.

microRNAs (miRNAs)

miRNAs (also known as small molecular RNAs), approximately 21 to 23 nucleotides in length, are RNA molecules that are widely distributed in eukaryotes; these miRNA can regulate gene expression. The evolution of miRNA is relatively conservative and it belongs to a class of non-coding RNAs that are transcribed from DNA but are not further translated into proteins. miRNAs target messenger RNA (mRNA) with a specific combination to inhibit gene transcription and play a significant role in the regulation of gene expression, cell cycle, biological development, etc. [1–2]. The biogenesis of miRNA has been extensively studied. miRNAs are initially transcribed from intragenic or intergenic regions by RNA polymerase II as variable-length transcripts, usually between 1 kb and 3 kb in size, called long primary RNAs (pri-microRNAs) [3–5]. The pri-microRNA is then processed by nuclear RNase III enzyme Drosha together with DGCR8 (DiGeorge syndrome critical region gene 8), which is a double-stranded RNA binding domain (dsRBD) partner of Drosha, into short –70-nucleotide RNA hairpin structures called precursor microRNAs (pre-microRNAs). This pre-microRNA hairpin is then exported out of the nucleus into the cytoplasm with the help of RanGTP-dependent Exportin 5 [6–7].

In the cytoplasm, the pre-microRNA is processed by Dicer, another RNase III enzyme, into a mature double-stranded miRNA of variable length (–22 nucleotides)

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Table 1 The role of some non-coding RNA

tRNA (transfer RNA)	Translation
siRNA (small interfering RNA)	RNA silencing
microRNA (microRNA)	RNA silencing
snRNA (small nuclear ribonucleic acid)	RNA splicing
snoRNA (small nucleolar RNA)	Guide chemical modifications of other RNAs
piRNA (Piwi-interacting RNA)	Gene silencing in retrotransposons and other genetic elements in germ line cells
gRNA (guide RNA)	RNA editing

[8–9] (Fig. 1). TRBP, the dsRBD partner of Dicer, releases a 19–24-nucleotide fragment from the pre-microRNA hairpin. The miRNA plus-strand is usually degraded, and the separated strand of the mature miRNA is loaded onto the RNA-induced silencing complex (RISC), which is an effector complex comprising miRNA, Argonaute protein 1 to protein Argonaute 4, and other protein factors [10]. Argonaute protein contains a PIWI domain that binds to the 5′ end of the miRNA; hence, it is important for the recognition of specific target mRNAs that result in post-transcriptional repression or degradation of the target mRNA depending on the pairing complementarities [11–12].

Discovery of miRNA

Victor Ambros and Gary Ruvkun discovered the first miRNA in 1993, when they were studying a gene named *lin-4* in *Caenorhabditis elegans*; they confirmed that it controlled developmental timing in the worm by binding partially to the 3' untranslated region (UTR) of *lin-14* mRNA [13–14]. In the following years, *lin-4* did not receive much attention and it was regarded an oddity in worm genetics, until a second small regulatory RNA, named *let-7*, was discovered in the worm [15]. These odd discoveries attracted the interests of Victor Ambros, David Bartel, and Thomas Tuschl; they began to look for other small RNAs in different organisms, and found a large number of miRNAs in *C. elegans, Drosophila* embryos, and human HeLa cells [16–17]. Subsequently, the first studies to report that miRNA dysregulation could cause human disease were published. Later, researchers found that miR-15a and miR-16-1 were deficient or downregulated in several cases of B cell chronic lymphocytic leukemia (CLL) [18], which led to an increase in the number of studies evaluating the function of miRNAs. For example, miR-155, the first human oncogenic miRNA to be identified, was found to be upregulated in hematological malignancies and in inflammatory responses of macrophages [19–21]. miR-146a/b, miR-132, and miR-155 are upregulated in the human monocytic cell line THP-1 following stimulation by LPS [22]. Eventually, several studies investigating

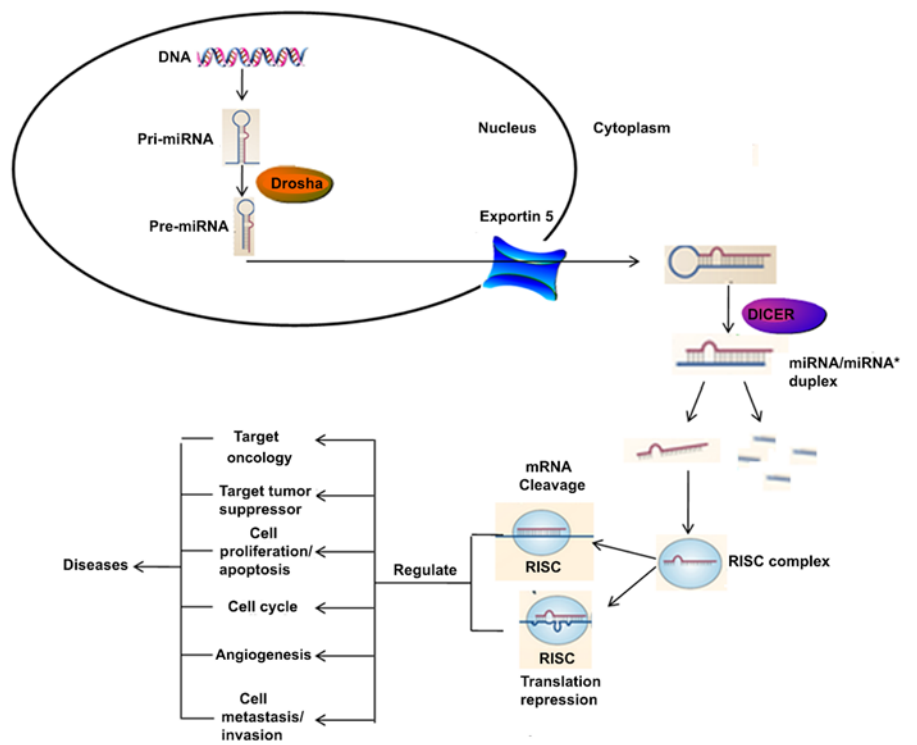

Fig. 1 The formation and function of microRNA

Table 2 Tissue-specfic miRNA expression signatures

Expression pattern	MicroRNA
Enriched in brain	miR-12a, miR-125b, miR-128, miR-132, miR-139, miR-7, miR-9, miR-153, miR-124a, miR-124b, miR-135, miR-149, miR-183, miR-190, miR-219
Enriched in lung	miR-18, miR-19a, miR-24, miR-32, miR-130, miR-213, miR-20, miR-141, miR-193, miR-200b
Enriched in spleen	miR-99a, miR-127, miR-142a, miR-142s, miR-151, miR-189, miR-212
Enriched in liver	miR-122a, miR-152, miR-194, miR-199, miR-215
Enriched in heart	miR-1b, miR-1d, miR-133, miR-206, miR-208, miR-143
Enriched in kidney	miR-30b, miR-30c, miR-18, miR-20, miR-24, miR-32, miR-141, miR-193, miR-200b
Enriched in haematopoetic tissues	miR-181, miR-223, miR-142
Ubiquitously expressed	miR-16, miR-26a, miR-27a, miR-143a, miR-21, let-7a, miR-7b, miR-30b, miR-30c

the different aspects and roles of miRNA were undertaken. Owing to these studies, we now have a deeper cognition of the functions of miRNA.

Distribution of miRNA

In the last 10 years, an increasing number of studies have focused on miRNA research and discovery. miRNAs are highly conserved and are ubiquitous in both animals and plants. Almost 30% of the activity of protein-coding genes is predicted to be regulated by miRNAs in mammals, and this aspect is being intensively researched upon in many fields. Different tissues have been found to exhibit distinctive patterns of miRNA expression. In addition, some miRNAs are ubiquitously expressed (Table 2) [23].

miRNA and diseases

As seen in Fig. 1, miRNAs play pivotal roles in many biological processes such as cell growth, apoptosis, gene regulation, angiogenesis, cell cycle, and cancer cell metastasis/invasion. Therefore, miRNAs are associated with numerous human diseases. Dysregulation of miRNAs causes many diseases including various types of cancer and immune disorders. miRNAs can serve as promising therapeutic targets for several diseases because of their oncogenic functions, and potential therapies targeting miRNAs include miRNA silencing, antisense blocking, epigenetic modification, DNA copy number change, and genetic mutations [24]. A useful strategy for tumor suppression involves the overexpression of miRNAs that suppress tumor growth and development. Thus, miRNAs are significant mediators of human physiology and disease and are crucial to early detection and prognosis of the disease and treatment-related decision-making.

miRNAs and cancer

Studies on miRNAs majorly focus on their potential role in tumor development. The function of miRNAs is similar to that of oncogenes or tumor suppressor genes, which are closely related to tumor development. First, research on worms and fruit flies confirmed that miRNA function to regulate cell proliferation and apoptosis, which suggests that they are closely associated with hyperplastic diseases such as cancer. Second, many miRNA genes have been confirmed to be located in areas along with the variation of the tumor in the genome. Third, compared with normal tissue, tumor tissue or tumor cell lines exhibit widespread abnormal expression of regulatory miRNAs. Studies have found that mutations, deletions, and imbalance of post-transcriptional regulation, modification of DNA methylation in the promoter region of genes encoding miRNAs, and abnormal protein binding can cause abnormal expression of miRNAs.

Approximately more than 50% of human miRNA genes are located in cancer-associated regions or at chromosome fragile sites, which are susceptible to gene deletion, amplification, and mutations. In addition, abnormal expression of miRNA has been observed in many human cancers. Negative regulation of tumor growth by miRNAs has been observed in pancreatic cancer [25], breast cancer [26], prostate cancer [27], liver cancer [28], colon cancer [29–30], and ovarian cancer [31]. Amplification of the miR-17–92 cluster in human B-cell lymphomas and upregulation of miR-155 in Burkitt's lymphoma have also been reported as examples of associations of oncogenic miRNA with human cancers [19, 32–33]. Different tumor tissues have markedly different miRNA expression spectra, with respect to the quantity and richness of miRNA expression. Another important aspect of the association of miRNAs with cancer is that the expression of some miRNAs is upregulated in some cancers, while in others, the expression of miRNAs may be downregulated, which indicates that miRNAs may be oncogenic or act as tumor suppressors. For example, in breast cancer, miR-10b [34], miR-21 [35], miR-22 [36], miR-27a [37], miR-155 [38], miR-210 [39], miR-221 [40], miR-222 [40], miR-328 [41], miR-373 [42], and miR-520c [42] were found to be upregulated, while let-7 [43], miR-7 [44], miR-9-1 [45], miR-17/miR-20 [46], miR-31 [47], miR-125a [48], miR-125b [49], miR-146 [50], miR-200 family [51–52], miR-205 [52], miR-206 [53], and miR-335 [54] were found to be

downregulated. In chronic lymphocytic leukemia, miR-21 [55] and miR-155 [55] are upregulated, while miR-15 [18], miR-16 [18], miR-29b [56], miR-29c [56], miR-34a [56], miR-143 [57], miR-145 [57], miR-181b [56], and miR-223 [56] are downregulated. In lung cancer, the miR-17-92 cluster, miR-21, miR-106a, and miR-155 are upregulated, while miR-1, the let-7 family, miR-7, miR-15a/miR-16, and the miR-29 family are downregulated [44, 58–61]. miR-221 and miR-222 are upregulated in prostate cancer, while the miR-15a-miR-16-1 cluster, miR-101, miR-127, and miR-449a are downregulated [32–44]. As for hepatocellular carcinoma, the miR-17-92 cluster, miR-21, miR-143, and miR-224 are upregulated, while miR-1, miR-101, and miR-122a are downregulated [28, 62–66]. Early studies in the field of neurobiology have shown that the tissue-specific abundant expression of miR-124 and miR-9 in the brain is regulated during brain development or during development of neurons and astrocytes in culture [67–68]. The spatial expression patterns of several miRNAs in human brain samples has revealed that miR-124 appears to be widely expressed in differentiated neurons, while miR-9 is more prominently expressed at an earlier stage in proliferating neuronal precursors [67, 69]. In addition, miRNA regulation has showed its significance in glioma development. miR-21 was found to be overexpressed in high-grade gliomas [70–71]. In addition, Chen [72] found that miR-107 inhibits glioma cell proliferation, migration, and invasion, and indicated that it could be a potential therapeutic target for glioma. Another study [73] showed that osthole could restrain the proliferation of human glioma cells and promote their apoptosis by upregulating the expression of miR-16 and downregulating the expression of MMP-9. Furthermore, through a study evaluating the expression of selected miRNAs (miR-16, -17, -19a, R-20a, -140, and -184) in an independent set of low-grade and secondary glioblastoma multiforme samples, the grade-associated regulation of these miRNAs was confirmed [74].

Role of miRNAs in the immune system

Since miRNAs are associated with the regulation of multiple genes, it is true for miRNAs involved in immune function. miRNAs have been shown to be associated with the proliferation of quiescent naïve T cells and effector T cells capable of differentiation that produce various cytokines during an effective immune response, as a result of their progressive differentiation owing to a marked change in gene expression profiles during and after infection, where they are expected to influence fundamental cellular processes [75–77]. Several miRNAs appear to be vital players in immunity. For example, miR-155, which has a specific role in inflammatory stress, has been identified as a key player in the biology of lymphocytes [21, 78]. miR-155 was found to be oncogenic after mice expressing miR-155 in B cells developed lymphoma [79]. Moreover, miR-155 also plays a significant role in Alzheimer's disease by regulating T-cell functions during inflammation [80]. Another finding about miR-155 was that it could promote dendritic cell migration toward sites of ATP release, accompanied by inflammasome activation [81]. Members of the human miR-146 family have been identified as vital inflammatory inducers that regulate Toll-like receptor (TLR) signaling by a negative feedback mechanism [82]. miR-146a has been observed to regulate the innate immune response as a negative regulator of the expression of the NF-κB components IRAK1 and TRAF6, which encode key adapter molecules downstream of Toll-like receptors, by interfering with the NF-κB pathway [21–22, 83–84]. In addition, the miR-146 family was found to be involved in regulating lipid metabolism during inflammation through test the expression of the downstream factors of MyD88-Traf6 pathway, pro-inflammatory genes, after knocking down miR-146a and miR-146b expression [82]. miR-150 is highly upregulated during the development of mature T and B cells and is crucial to their terminal stages of differentiation [85–86]. miR-181 was preferentially expressed in B cells and its ectopic expression in hematopoietic progenitor cells during lineage differentiation led to a doubling of the number of cells of the B-lymphoid lineage [87].

miRNA-based clinical applications

Clinical research studies are currently focused on an increasing number of miRNAs. The miRNA-based classification of tumors seems to be more accurate than the mRNA expression profile-based classification of tumors [88]. Moreover, miRNAs could become useful tools in cancer diagnosis and prognosis and be effective therapeutic targets. Their applications in clinical practice mainly focus on two aspects: (1) First, their use as biomarkers of disease. miRNA profiles are potentially useful as early detection, classification, prognostic, and predictive biomarkers. As early detection biomarkers, they indicate the onset of a disease and often play a role in the disease. (2) Second, their use as attractive therapeutic targets. Various studies are underway worldwide to tap the potential of miRNAs for use as disease biomarkers. From http://www.clinicaltrials.gov/, a service of the U.S. National Institutes of Health, we found some pre-clinical trials evaluating the use of certain miRNAs as biomarkers of a particular disease (Table 3).

miRNAs have garnered considerable interest owing to their close association with many important diseases. As crucial targets for drug development, drugs corresponding to the miRNAs can be designed such that they achieve their therapeutic effect via the upregulation or downregulation of miRNAs or via silencing of miRNA expression. At present, molecular drug design based on miRNA is

Table 3 Pre-clinical trials of miRNAs as biomarkers used in diseases

Name of microRNA	Disease	Sponsor
MicroRNA 107	Alzheimer's disease	Shanghai Mental Health Center
Mir155	Biomarkers of sepsis (diagnostic and predictive value of circulating microRNAs during sepsis)	Changhai Hospital
Mir326	ESCC and NSCLC	China Medical University Hospital
Mir-29b	Oral squamous cell carcinoma	National Taiwan University Hospital
Mir-122	Chronic hepatitis C	National Taiwan University Hospital
Mir-29 family	Head-and-neck squamous cell carcinoma	National Taiwan University Hospital
Mir-10b	Astrocytoma; oligodendroglioma; oligoastrocytoma; anaplastic astrocytoma; anaplastic oligodendroglioma; anaplastic oligoastrocytoma; glioblastoma; brain tumors; brain cancer	National Taiwan University Hospital

still in its infancy. Many studies have mainly focused on simulating miRNAs to enhance the effectiveness of their role in targeting genes, or on designing small molecules as miRNA antagonists, such as miRNA antisense oligomeric nucleotides (anti-miRNA oligonucleotides, AMOs) and miRNA antagonism molecules (such as antagomirs).

The design of nucleic acid drugs in 2008 opened a new page of history in miRNA-based drug design. It should be noted that the first drug targeting miRNA was named miravirsen. The Danish pharmaceutical company Santaris Pharma announced that it would be the first to implement miRNA targets for drug clinical trials worldwide. Miravirsen is an antisense oligonucleotide with a locked nucleic acid (LNA)-modified oligonucleotide (SPC3649) complementary to miR-122. miR-122, expressed in the liver, is related to the replication of the hepatitis C virus (HCV) and to the regulation of cholesterol and lipid metabolism [89–90]. LNA nucleosides are a class of nucleic acid analogues in which an extra methylene bridge fixes the ribose moiety either in the C3'-endo or C2'-endo conformation. By locking the molecule, LNA oligonucleotides display unprecedented hybridization affinity towards complementary single-stranded RNA or double-stranded DNA [91–92]. In addition, they display excellent mismatch discrimination and high aqueous solubility. So-called LNA anti-miR constructs have been used successfully in several *in vitro* studies to knock down the expression of specific miRNAs [93–94]. According to the results of the phase I clinical trials of the drug, a dose-dependent effect of the drug on the reduction of HCV RNA levels was observed for an extended period, which was consistent with the results of the pre-clinical studies. According to the preliminary data obtained in phase II clinical trials, 18 individuals received miravirsen therapy, and six other individuals received a placebo treatment. No serious adverse reactions were observed, and the side effects included headache, diarrhea, and rhinitis; however, these side effects were moderate and infrequent [89].

Conclusion and future prospects

miRNAs have attracted considerable attention owing to their important role in cell differentiation, biological development, and in the development of various diseases. With further studies on the mechanisms underlying miRNA function and on the relationships between miRNAs and diseases by using the latest high-throughput technology such as miRNAs chips, our understanding of the network of gene expression and regulation in eukaryotic cells will reach a new and higher level.

Various studies have found that miRNAs are significant mediators in human physiology and disease and are crucial to early detection and prognosis of the disease and treatment-related decision-making. Although the study of miRNAs has made great progress, especially with respect to the function of miRNAs in cell differentiation, gene regulation, and disease control, currently, the study of miRNAs is still in its nascent stage, with many genes yet to be identified and the mechanisms underlying the functions of most genes yet to be elucidated. As for the clinical applications, several technical hurdles to miRNA research remain, e.g., the cost of miRNA profiling and the development of drugs targeting miRNA is still high. Moreover, it is still technically difficult to achieve long-term and stable silencing of miRNA expression.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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