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miRNAs, cancer, and unconventional miRNA functions

Ibrahim Bozgeyik*

*[1]Department of Medical Biology, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey

*Corresponding author : i.bozgeyik@gmail.com
Orcid No: https://orcid.org/0000-0003-1483-2580

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Abstract: MicroRNAs are non-protein-coding RNA molecules that control and fine-tune gene expression at the post-transcriptional level by negatively regulating their target genes. MicroRNAs mature into 22-nucleotide-long RNA transcripts that negatively regulate gene expression by inducing either inhibition of translation or degradation of mRNAs. Increasing evidence suggests that distinct signatures of microRNAs are a feature of human cancers. MicroRNA expression patterns have been linked to tumor development, progression, and response to therapies, implying that they could be used as prognostic and diagnostic biomarkers. Moreover, based on a growing body of research indicating that microRNAs may serve as tumor suppressive or tumor promoter functions, miRNA-based therapy against cancer has lately been utilized, either alone or in conjunction with current targeted strategies. One of the advantages of microRNA-based therapeutics is that they can target numerous components of signaling circuits involved in cell differentiation, proliferation, and survival. In this review, the current available evidence about miRNAs and their diagnostic, prognostic, and therapeutic potential will be discussed. miRNAs may play chief roles in the development and progression of human cancers, offer great advantages in differential diagnosis, and can be therapeutically targeted.

Keywords: Cancer; miRNA; non-coding RNAs; miPEP; unconventional miRNA functions

1 Introduction

Previously, most of the human genome was considered "junk DNA" and transcription at these sites was considered transcriptional noise or waste. On the contrary, scientific developments over the last two decades have shown that "junk DNA" encodes active RNA transcripts that are not converted into proteins but are functional (Esquela-Kerscher and Slack 2006; Mattick 2003; Zaratiegui et al. 2007). The discovery of these non-coding RNAs has allowed scientists to better understand complex molecular mechanisms. In 1993, Lee et al., by a chance, identified the lin-4 transcript, a small non-coding RNA that repress lin-14 protein synthesis (Lee et al. 1993). These short non-coding RNAs were later annotated as microRNAs in the early 2000s (Lee et al. 2004). These findings are the first to demonstrate the existence of functional non-coding transcripts. Later, rapid progress in the analysis of the human transcriptome with the development of advanced technological methods enabled the identification of numerous non-coding RNA transcripts involved in the control of key regulatory pathways.

Although many methods have been proposed for classifying non-coding RNAs, they are most often categorized based on their size (Nagano and Fraser 2011). Depending on their size, non-coding RNAs are classified into two main categories as long non-coding RNAs (lncRNAs) and short or small non-coding RNAs (sncRNAs) (Dozmorov et al. 2013; Nagano and Fraser 2011). Small non-coding RNAs are less than 200 nucleotides long and they include microRNAs (miRNAs), 5S and 5.8S ribosomal RNAs (rRNAs), piwi-interacting RNAs (piRNAs), short interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs) (Dozmorov et al. 2013; Nagano and Fraser 2011). Also, long non-coding RNAs are longer than 200 nucleotides and they comprise natural antisense transcripts (NATs), long intergenic non-coding RNAs (lincRNAs), transcribed ultra-conserved regions (T-UCRs), competing endogenous RNAs (ceRNAs) and ribosomal RNAs (rRNAs) (Dozmorov et al. 2013; Nagano and Fraser 2011; Ponting et al. 2009).

Cumulative evidence strongly suggests that non-coding RNA molecules play fundamental regulatory functions in many vital cellular mechanisms, including proliferation, cell growth, differentiation, and cell death (Calin and Croce 2006; Reddy 2015; Visone and Croce 2009). Coordinated regulation of these molecules is essential for the proper maintenance of cellular hemostasis. However, defects in the

regulation of non-coding RNAs are directly involved in the development of many pathological problems, especially cancer (Calin and Croce 2006; Esquela-Kerscher and Slack 2006; Wapinski and Chang 2011).

2 MicroRNAs

MiRNAs are non-protein-coding RNA molecules that control and fine-tune gene expression at the post-transcriptional level through negative regulation of their target genes (Esteller 2011). MiRNAs mature into 22-nucleotide-long RNA transcripts. A growing mass of evidence indicates miRNAs have central tasks in various dynamic cellular mechanisms such as growth, differentiation, apoptosis and, proliferation (Melo and Esteller 2011; Ruan et al. 2009). More than 60% of human genes are thought to be controlled by miRNAs (Esteller 2011). While some participate in the control of specific target molecules, others can act as principal regulators of a signaling pathway, allowing important miRNAs to control the levels of hundreds of genes at once, and several sorts of miRNAs to work together to regulate their targets (He and Hannon 2004; Mendell 2005). A growing body of evidence suggests that deregulated expression of microRNAs is an important contributor to the development and progression of many diseases, including immune system disorders, diabetes, neurodegenerative diseases, and cancer (Garzon et al. 2009; Melo and Esteller 2011; Ruan et al. 2009).

2.1 Genomic localization, biogenesis, and mechanisms of action of miRNAs

MiRNA genes have been shown to be conserved across species (Rodriguez et al. 2004). They can be found in exons, introns, and intergenic regions of protein-coding genes (Rodriguez et al. 2004). The majority of intronic or exonic miRNAs are oriented in the same direction as the host gene, indicating that they are co-transcribed (Rodriguez et al. 2004). The latter group of miRNAs are synthesized from gene deserts or intergenic regions containing independent transcription elements (Rodriguez et al. 2004). The RNase III enzymes, Drosha and Dicer, are involved in miRNA biogenesis. Biogenesis of miRNAs first begins with the production of the primary miRNA transcript (pri-miRNA) by RNA polymerase II (Bartel 2007). The pri-miRNA is further cleaved by the enzyme Drosha, a double-strand DNA-specific ribonuclease, in the nucleus (Bartel 2007). As a result of this enzymatic cleavage, a 70-100 nt long precursor miRNA (pre-miRNA) transcript is produced (Bartel 2007). The pre-miRNAs are subsequently transported to the cytoplasm from the nucleus by the Exportin-5-RanGTP protein and undergo a second cleavage in the cytoplasm. This second cleavage reaction is catalyzed by the Dicer enzyme. As a result, mature microRNAs with an average length of 22 nucleotides are formed (Bartel 2007). TRBP and Argonaute 2 proteins aid mature miRNAs to interact with their target mRNAs.

2.2 MiRNA-mediated gene silencing

To perform their regulatory functions, miRNAs cooperate with members of the Argonaute proteins to assemble into miRNA-induced silencing complexes (miRISCs) (Ameres and Zamore 2013). Post-transcriptional silencing of mRNAs containing sequences partly or completely complementary to miRNA genes is mediated by these complexes. (Ameres and Zamore 2013; Jonas and Izaurralde 2015). Target mRNAs with excellent complementarity are degraded by enzymatically active AGO proteins (Ameres and Zamore 2013; Jonas and Izaurralde 2015). In mammals, however, mRNA often form partial complementarity with miRNAs, making AGO protein destruction impossible (Ameres and Zamore 2013; Jonas and Izaurralde 2015). Moreover, only AGO2 is catalytically active in humans, while other members including AGO1, AGO3 and AGO4 proteins are not active (Ipsaro and Joshua-Tor 2015). Where degradation is not possible, AGO recruits some additional proteins to mediate silencing (Fabian and Sonenberg 2012; Huntzinger and Izaurralde 2011). In this case, silencing of mRNA is achieved through a collection of translation suppression, deadenylation, decapping, and 5′-to-3′ degradation (Fabian and Sonenberg 2012; Huntzinger and Izaurralde 2011). In this mechanism, the GW182 proteins, which are among the most well-studied AGO-related proteins, play a critical role (Fabian and Sonenberg 2012; Huntzinger and Izaurralde 2011). These proteins act as scaffolds between the AGO proteins and the downstream effector complexes. It has been revealed that the degradation of mRNAs by miRNA-mediated silencing is catalyzed by enzymes of 5′ to 3′ mRNA degradation pathway (Jonas and Izaurralde 2015). In the 5′-to-3′ mRNA decay pathway, mRNAs are deadenylated at first by sequential action of the PAN2-PAN3 and CAF1–CCR4–NOT deadenylase complexes (Wahle and Winkler 2013). Deadenylated mRNAs are further subjected to mRNA decapping by decapping protein 2 (DCP2), which necessitates the assembly of extra cofactors. In metazoans, these factors are DCP1 (decapping protein 1), EDC3 (enhancer of decapping 3), EDC4 (enhancer of decapping 4), PATL1 (PAT1-Like Protein 1), and DDX6 (DEAD box protein 6) proteins. Ultimately, deadenylated and decapped messenger RNAs are degraded by exoribonuclease 1 (XRN1) (Jonas and Izaurralde 2015). Argonaute proteins, GW182 proteins, decapping factors, and XRN1 localize to P-bodies (also known as mRNA-processing bodies). However, the functional relevance of this localization is still a mystery (Jonas and Izaurralde 2015).

3 MiRNAs and cancer

Previously, it was thought that only defects in tumor promoter and tumor suppressive genes play a role in the formation of cancer (Rajasegaran et al. 2021). However, with the discovery of miRNA molecules, diagnostic, prognostic, and therapeutic approaches against cancer gained a new dimension (Rajasegaran et al. 2021). Accumulating evidence indicates that these small RNA molecules are highly deregulated in human cancers. In tumor tissues, certain microRNAs (OncomiRs) are elevated, while other miRNAs (tumor suppressor miRNAs) are downregulated. (Dalmay and Edwards 2006; Ruan et al. 2009). Low levels of tumor suppressive miRNAs and enhanced expression of tumor promoter miRNAs contribute to main hallmarks of cancer such as sustained proliferation and growth, disruption of death mechanisms, modulation of immune surveillance, invasion, and metastasis(Calin and Croce 2006; Rajasegaran

et al. 2021). The first findings between cancer and miRNAs were found in studies of patients with chronic lymphocytic leukemia. Calin, G. A. et al. reported that the genomic region encoding mir-15a and mir-16-1 is frequently deleted or translocated in patients with B-cell chronic lymphocytic leukemia (CLL) (Calin et al. 2002). As a result, the expression level of the anti-apoptotic BCL-2 (B-cell lymphoma 2) protein, which is the target of these miRNAs, increases and apoptosis is suppressed (Calin et al. 2002). Because miRNAs play such an active role in tumorigenesis, mimicking the functions of tumor suppressive miRNAs or inhibiting the functions of tumor promoter miRNAs offers a strong therapeutic potential (Petrocca and Lieberman 2009).

3.1 MiRNAs as tumor suppressive genes

As stated above, many miRNAs are localized in cancer-related genomic areas and thus they play important roles in cancer formation by acting as tumor promoter or tumor suppressive genes (Frixa et al. 2015). Similar to genes that code for proteins, miRNAs can also show tumor suppressive effects (Garzon et al. 2009). Thus, loss of function of miRNAs can initiate malignant transformation of a normal cell or contribute to the oncogenic process (Garzon et al. 2009). Loss of miRNA expression might be due to diverse mechanisms, such as mutation, genomic deletion, alterations in miRNA processing and/or epigenetic silencing (Garzon et al. 2009). For instance, it was determined that the expressions of let-7 family of miRNAs are diminished in multiple kinds of cancer (Garzon et al. 2009). Let-7 family members targets the expression of well-recognized tumor promoter genes such as the Ras family (Johnson et al. 2005). Additionally, latest studies have enabled the identification of many miRNAs with tumor suppressive functions. microRNA-34a is one of the well-known tumor suppressive miRNAs. miR-34a was recognized as a direct transcriptional target of p53 and is known to induce G1 cell cycle arrest, senescence, and apoptosis in response to DNA damage (Saito et al. 2015). Like miR-34a, Ma et al. established that miR-361-5p showed tumor suppressive properties in breast cancer as well as colorectal and gastric cancers (Ma et al. 2017). Moreover, miRNA-329 prevents tumor growth and cell proliferation while facilitating apoptotic death of gastric cancer cells by negatively regulating KDM1A (Cai et al. 2017). MiRNA-211 expression was also shown to be highly reduced in cervical cancer cell lines and tissues compared to controls, and overexpression of miRNA-211 suppressed the expansion and metastasis of cervical cancer cells through modulating ZEB1 (Chen et al. 2017). MiRNA-193a-3p is another miRNA known for its tumor suppressor properties. It has been shown that it is downregulated in colorectal cancer patients and increased expression of miRNA-193a-3p represses expansion and invasion of colorectal cancer cells (Takahashi et al. 2017). Also, miRNA-195 has been shown to be frequently downregulated in melanoma patients. Functional analyzes have shown that miRNA-195 exerts an anti-proliferative effect on human melanoma cancer cells by suppressing Prohibitin 1, which plays an active role in the RAS-RAF-MEK-ERK pathway (Cirilo et al. 2017). In addition to these findings, members of miR-29 family of miRNAs were reported to be downregulated in patients with CLL, AML, cholangiocarcinoma, lung, and breast cancers (Calin et al. 2005; Garzon et al. 2008; Iorio et al. 2005; Mott et al. 2007; Yanaihara et al. 2006). Moreover, overexpression of miR-29b provoked apoptosis in lung cancer and cholangiocarcinoma cell lines and weakened tumorigenic properties in the lung cancer mouse xenograft model (Fabbri et al. 2007; Mott et al. 2007). Anti-apoptotic MCL-1 and TCL-1 oncogenes are two identified targets of miR-29b (Mott et al. 2007; Pekarsky et al. 2006). There is also increasing evidence that miR-139 is frequently suppressed in various human malignancies. Although miR-139 is encoded in the intronic region of the phosphodiesterase 2A (PDE2A) gene, no correlation was found between these two in carcinogenesis (Shen et al. 2014). miR-139 was reported to be directly activated in cells expressing wild type p53 gene during DNA damage (Cao et al. 2016) and silenced by Polycomb repressive complex-2 (PRC2) and RNA Polymerase 2 Subunit M (POLR2M) (Cao et al. 2016; Stavast et al. 2022).

3.2 MiRNAs as oncogenes

Accumulating body of evidence also revealed that many miRNAs show tumor promoter functions. MiR-155 was one of the first oncomiRs discovered and its gene expression level was found to be markedly elevated in various cancers as lung cancer, pancreatic cancer, breast cancer, B-cell lymphoma and Hodgkin's lymphoma. In addition, miR-155 was shown to downregulate TP53INP1 (Tumor protein 53-induced nuclear protein 1) expression (Hemmatzadeh et al. 2016). Another oncogenic miRNA that accelerates tumor formation is miR-21 (Garzon et al. 2009). miR-21 is upregulated in many hematological malignancies such as CLL and AML, as well as breast, lung, prostate, colon, liver, stomach, pancreatic and glioblastoma cancers (Garzon et al. 2009). miR-21 triggers the metastasis and invasion of cancerous cells by suppressing tumor suppressor proteins including PTEN (phosphatase and tensin homolog), PDCD4 (programmed cell death 4) and TPM1 (tropomyosin 1) (Garzon et al. 2009). Moreover, overexpression of miR-21 has been shown to suppress apoptosis of glioblastoma cells (Chan et al. 2005). In addition, suppression of its expression in breast, liver, and glioblastoma cancer cells suppresses cell proliferation, triggers caspase activation, and increases apoptotic cell death (Chan et al. 2005; Frankel et al. 2008; Meng et al. 2007). The miR-17-92 miRNA gene cluster (including miR-19a, miR-19b-1, miR-17, miR-18a, and miR-92-1, miR- 20a) is recurrently amplified in many solid tumors and hematological malignancies, including lung, colon, breast, pancreatic, prostate, gastric cancers and lymphomas (Garzon et al. 2009). These miRNAs trigger proliferative signaling and invasion in cancer cells and suppress apoptosis (Garzon et al. 2009). Interestingly, c-myc, a tumor promoter gene which is commonly stimulated in cancer, transactivates the miR-17-92 miRNA cluster.

3.3 MiRNAs in cancer treatment

Because of the oncogenic and tumor suppressor roles played by miRNAs in cancer expansion and advancement, mimicking the functions of tumor suppressive miRNAs or suppressing the functions of tumor promoter miRNAs emerges as an innovative approach in cancer treatment.

Today, there are pre-clinical and clinical studies that have been made or are being conducted for the use of miRNAs in the therapy of various health manifestations, including cancer (Li and Rana 2014). The use of miRNAs in cancer therapy has several benefits. Mature miRNA sequences are small and conserved among many vertebrate species (van Rooij and Kauppinen 2014). In addition, miRNAs often target many genes in cellular signaling pathways. Thus, therapeutic targeting of disease-associated miRNAs may allow targeting of the entire disease-associated pathway (van Rooij and Kauppinen 2014). Two basic methods have been used to modulate miRNA activity; the first is to restore miRNA activity using synthetic double-stranded miRNAs or viral overexpression vector, and the second is to inhibit miRNA activity using chemically modified antimiR oligonucleotides (Shah et al. 2016; van Rooij and Kauppinen 2014).

4 Unconventional functions of miRNAs

Numerous unconventional regulatory functions of miRNAs have also been reported. Primary transcripts of miRNAs have been found to encode small peptides with regulatory functions, termed miRNA-encoded peptides (miPEPs). Lauressergues et al. were the first to report that miRNAs encode for regulatory peptides. In plants, they have discovered that several pri-miRNAs, comprising pri-miR-165a of *Arabidopsis thaliana* (miPEP165a, 18 amino acids) and pri-miR-171b of *Medicago truncatula* (miPEP171b, 9 amino acids), codes for short regulatory peptides. These pri-miRNA-encoded oligopeptides have been identified to advance transcription of their own pri-miRNA, which increases the production of their respective mature miRNAs (Lauressergues et al. 2015). Although a direct physical interaction has not yet been demonstrated, increased expression of miRNAs has been shown to enhance Toll-like receptor (TLR) activity. Specifically, in lung cancer, miR-29a and miR-21 have been reported to activate the expression of TLR7 in humans. Let-7b has also been reported to directly stimulate the expression of TLR7 and exert a neurodegenerative effect (Lehmann et al. 2012). Another unconventional function of miRNAs is the upregulation of protein expression in response to cell cycle progression. During cell cycle arrest, certain miRNAs promote translation of their target mRNAs while repressing translation in proliferating cells. Specifically, miR-369 was shown to control the association of Argonaute (AGO) and Fragile X Mental Retardation-Related Protein 1 (FXR1) with the AU-rich elements (AREs) in tumor necrosis factor mRNA during cell cycle arrest to enhance translation (Vasudevan et al. 2007). Although the mitochondrial genome lacks miRNAs, Das et al. discovered that miR-181c translocates to mitochondria and represses expression of the mitochondrially encoded cytochrome c oxidase subunit 1 (mt-COX1) protein while increasing expression of mt-COX2 mRNA and protein content (Das et al. 2012). These findings further indicate that miRNAs also participate in the control of genes encoded by the mitochondrial genome to regulate mitochondrial dynamics. AGO-independent actions of miRNAs have also been reported. Eiring et al. identified that miR-328 acts as a molecular decoy for heterogeneous ribonucleoprotein E2 (hnRNP E2) to rescue translation of CEBPA mRNA. When miR-328 binds to hnRNP E2, releasing CEBPA mRNA from hnRNP E2-mediated translational repression (Eiring et al. 2010).

5 Conclusion

Although considerable efforts have been made for many years to identify biomarkers for cancer diagnosis and treatment, no biomarker has attracted as much attention as the potential of miRNAs. A substantial body of research shows that miRNAs have tremendous potential for the development of targeted cancer therapies since they can selectively bind to and repress the target gene. Currently available evidence indicates that suppression of oncogenic miRNAs or replacement of tumor suppressor miRNAs could be an innovative therapeutic strategy in cancer therapy. Furthermore, miRNA profiling of human cancer provides significant advantages for the discovery of effective therapeutic drugs and treatment planning. In further studies, more detailed studies on the clinical use of these molecules are needed.

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