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REVIEW

MicroRNAs and Their Relationship with Diseases

MikroRNA'lar (miRNA) ve Hastalıklarla İlişkileri

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Abstract

Taking part in the noncoding RNA group, microRNAs (miRNAs) are approximately 22 nucleotides in length RNA molecules. The first studies on miRNAs focused on Caenorhabditis elegans, and the first miRNA gene lin-4 was discovered. To date, there are more than 5000 identified miRNAs, which are involved in the transcription and post-transcription regulation of gene expression and also play a role in several important biological events such as metabolism, cell differentiation, proliferation, and apoptosis. The increases and decreases in the levels of miRNAs have been associated with cancer, autoimmune, neurodegenerative, cardiovascular, and some respiratory diseases. In recent years, experimental studies have indicated that they act as oncogens or tumor suppressor genes in cancer development and that miRNAs in the bloodstream can be a good biomarker for cancer diagnosis and prognosis. In this review, the diagnostic–therapeutic uses of miRNAs and their relationship with diseases have been summarized.

Keywords: Biomarker; Cancer; Disease; miRNAs; Treatment

Although approximately 80% of the human genome is transcribed, only a small amount is converted into protein,[1] the rest forms noncoding RNAs (Fig. 1).[2] In terms of their length, noncoding RNAs are classified into two categories: the ones shorter than 200 nucleotides were named small noncoding RNA (sncRNA), and those larger than 200 nucleotides were named long noncoding RNA.[3] Taking place in the category of sncRNAs, microRNA (miRNA) molecules have a length of approximately 22 nucleotides.[4] mRNAs have crucial functions in the regulation of gene expression through the inhibition of translation by binding to mRNAs or post-transcription via mRNA degradation.[5–7]

The first studies on miRNA focused on the nematode Caenorhabditis elegans (C. elegans), and the first miRNA gene lin-4 was discovered in 1993.[8,9] It took many years to discover another miRNA, and the name miRNA has been used since 2001.[10] To date, more than 5000 miRNAs have been identified in humans.[11] miRNAs play a role in such significant biological processes as cell differentiation, proliferation, and apoptosis.[12] Their associations with various human diseases, including cancer, are well-known. miRNAs have also been indicated as playing the role of tumor suppressor gene and oncogene for cancer.[13]

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mRNA Biogenesis

miRNAs are formed in three stages. Initially, the transcription of primary miRNAs (pri-miRNAs) from miRNAs occurs. In the second step, pri-miRNAs are converted into precursor miRNAs (pre-miRNAs) in the nucleus, and finally, mature miRNAs are formed in the cytoplasm.[14] miRNA genes are transcribed by RNA Polymerase II in the cell nucleus and form a long miRNA (pri-miRNA) in the hairpin structure.[15] Following the cut of the hairpin structure by the RNAse III family member Drosha and its cofactor, "DiGeorge critical syndrome region 8 (DGCR8)," approximately 70 nucleotides long "pre-miRNA (pre-miRNA)" is formed.[16] Transported from the nucleus to the cytoplasm by Exportin 5 and cleaved by Dicer, the pre-miRNA forms a double-stranded miRNA with 21–24 nucleotides.[17] One of the double strands of this RNA molecule is broken;[18] the other forms a complex with the guide strand RISC (RNA-induced silencing complex). By base pairing, the miRNAs included in RISC bind to mRNA, which causes translation inhibition or mRNA degradation (Fig. 2).[19,20] miRNAs bind to the 3′ UTR (untranslated region) of mRNA or the ORF (open reading frame) region of mRNA. The position of the miRNA complex's complementary binding to mRNA differs; binding to the 3′ UTR region is defective-incomplete complementarity and results in the suppression of translation. Binding to the ORF region is perfect-complete complementarity and results in the destruction of mRNA by Argonaute2.[21]

Each of the miRNAs can regulate the expression of more than one mRNA, and mRNAs can be targeted by more than one miRNA.[22]

Relationship of mRNAs with Diseases

mRNA expression patterns are peculiar to the tissue and define the physiological nature of the cell in several cases.[23,24] For instance, as for the heart of an adult individual, miR-1 is strongly expressed, whereas miR-1 has been observed not to be expressed sufficiently in the human brain, kidneys, lung, or colon.[25] The variable expression profiles of miRNAs between cells and tissues indicate the importance of miRNAs in maintaining tissue homeostasis. The increases and decreases in the levels of miRNAs have been associated with several diseases.[26] miRNAs are expressed in different profiles in brain, thyroid, breast, esophagus, liver, stomach, pancreas, colon, prostate, and ovarian cancers;[27,28] in nervous system diseases such as Alzheimer's disease (AD) and schizophrenia;[29] and in cardiovascular diseases.[30] There is still ongoing research on MiRNA in various diseases, and the obtained results are used to develop strategies of treatment.[31,32]

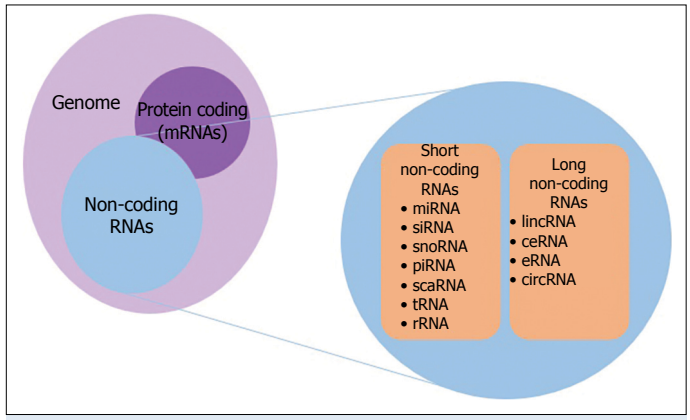

Figure 1. Classification of RNAs.[2]

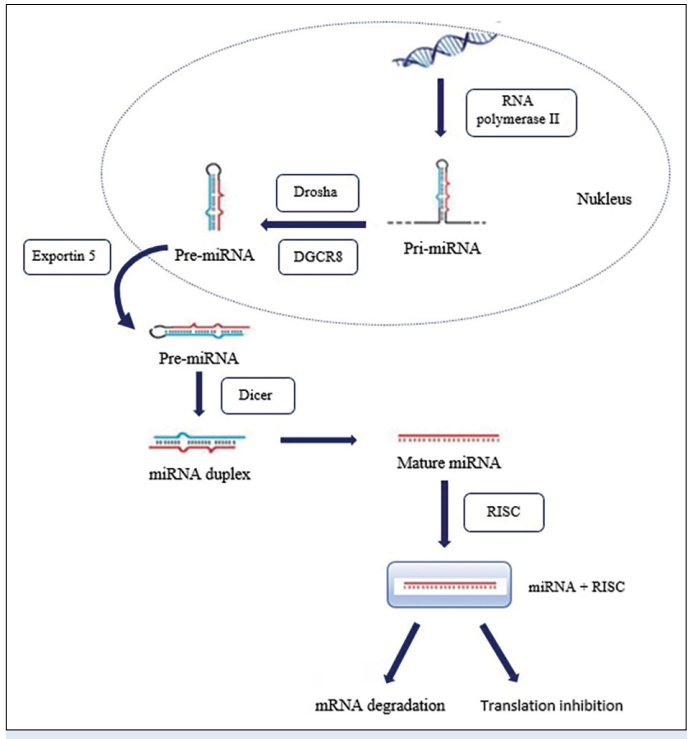

Figure 2. MicroRNA biogenesis.[19,20]

Relationship of MiRNA with Cancer

In the conducted studies, miRNAs were reported to be more effective than mRNAs in detecting human cancers and can be used as markers for the diagnosis and process of cancer.[33] Most miRNAs are located in cancer-related genomic regions or in easily cleavable regions.[34–36] miRNA is used so that the proliferation of cancerous tissues can be prevented, and these miRNAs can do it by targeting the antiapoptotic gene Bcl-2.[37]

miRNAs perform as tumor suppressors or oncogenic miRNAs. Although tumor suppressor miRNAs prevent tumorigenesis by suppressing oncogenes, oncogenic miRNAs

Table 1. Cancer-associated miRNAs

Cancer	miRNA	Reference
Breast	miR-125b, miR-145, miR-21, miR-155, miR-29a, miR-29b, miR-29c, miR-10b	[49–52]
Lung	miR-155, miR-28-3p, miR29, miR-30c, miR-92a	[40, 49, 50]
Colon	miR-92, miR-27b, miR-326, miR-158a, miR-21, miR-17-92	[43–45]
Liver	Let-7, miR-21	[43, 44]

miRNA: microRNA.

are inhibitors of tumor suppressor genes. The decrease of tumor suppressor miRNAs' expression leads to increased expression of oncogene and tumorigenesis. Oncogenic miRNAs, which increase in cancers, are called oncomIR.[38]

The relationship between miRNAs and cancer was first defined in a study by Calin et al.[39] Imn this study conducted in patients with chronic lymphocytic leukemia (CLL), miRNAs were observed to contribute to the cancerization process. CLL is a type of cancer characterized by the 13q14 deletion. This region had a deletion for more than half of B-cell CLL patients, and miR-16-1 and miR-15 were concluded to be located in this region owing to deletion analysis.[39] The first determined miRNAs having tumor suppressor function were the Let-7 family.[36] Targeting MYC and RAS oncogenes, which are highly expressed in several cancers, Let-7 prevents cancer development.[35] Unlike tumor suppressor miRNAs, oncogenic miRNAs function as antiapoptotic or enhance uncontrolled proliferation.[5] The first proposed miRNA as an oncogene is miR-155 and is located in the 21q21 chromosome region. MiR-155 was determined to have high expression in CLL and Hodgkin's disease, pediatric Burkitt lymphoma, and breast and lung cancers.[40] One study revealed that the levels of miR-155 and miR-125b in the serum of breast cancer patients were found to be useful in evaluating the chemotherapeutic response, diagnosis, and prognosis.[41,42]

miR-21 is the miRNA with the most common increase in human cancers.[11] The miR-21 gene functions as oncomIR, and mir-21 is characterized by invasion and metastasis. Such tumor suppressor genes as PDCD4 and PTEN1 have been determined as the targets of miR-21 (12). Additionally, in CLL; acute myeloid leukemia; and lung, breast, prostate, liver, pancreatic, stomach, and colon cancers, high expression of MiR-21 has been determined.[43,44] A high expression of MiR-17-92 members (miR-92-1, miR20a, miR-19b-1, miR-19a, miR-18a, and miR-17) that function as onchomirs in various solid tumors and cancer types (stomach, colon, breast, lung, pancreas, prostate, hematological malignancies, and lymphomas) was detected.[45] Also, reportedly, the miR-17-92 gene cluster supports angiogenesis by preventing apoptosis.[46–48]

Although a particular miRNA has an oncogenic function in some cancer types, the same miRNA can act as a tumor suppressor in other cancer types. To exemplify, miR-29, especially miR-29a/b/c, has been an oncogene in breast cancer. However, reportedly, the same miRNA-29 functions as a tumor suppressor gene in lung tumors (Table 1).[49,50] Besides their tumor suppressor and oncogene functions, miRNAs play a role in cell migration and metastasis. Although MiR-10b is highly expressed in metastatic breast cancer, it regulates cell migration and invasion positively.[51] The overexpression of miR-10b in nonmetastatic breast cancer cells has been confirmed to induce invasion and metastasis, and in this way, silencing miR-10b has been indicated as inhibiting metastasis in a mouse model of breast cancer.[52]

In a study that focused on prostate cancer, the role of miR-214 in prostate cancer cell survival/migration, cell cycle regulation, and apoptosis have been investigated, and in prostate cancer cells, the overexpression of miR-214 has been observed to inhibit cell proliferation and colony formation ability by inducing apoptosis. In the research, miR-214 was estimated to have the ability to act as a tumor suppressor in prostate cancer and be used potentially as a biomarker and therapeutic target.[53]

MiRNAs in Neurodegenerative Diseases

Parkinson's disease (PD), AD, and Huntington's disease (HD) are the most common neurodegenerative diseases associated with structural and functional loss of neurons in the central nervous system. The common features of these diseases are mitochondrial dysfunction and axonal transport disorder.[54] Most of the identified miRNAs (70%) have been reported to be expressed in the brain.[55,56] After different miRNA expressions in the brains of some patients with neurodegenerative diseases were detected, it was concluded that miRNAs might play a role in the pathophysiology of these diseases.[57]

miR-34, miR-124, and miR-132 are the most studied miRNAs for their role in memory function, and their expression is known to be misregulated in common neurological diseases.[58]

Table 2. miRNAs associated with neurodegenerative diseases

Disease	miRNA	Reference
Alzheimer's	miR-149, miR-342-3p	[64, 67]
Parkinson's	miR-30b, miR-30c and miR-26a, miR-133b, miR-34b, miR-34c	[60, 57, 61]
Huntington's	miR-29a, miR-124a, miR-132, miR-330, miR-9	[69, 70]

miRNA: microRNA.

Table 3. miRNAs associated with viral diseases

Disease	miRNA	Reference
HCV	miR-122	[77]
HIV-1	miR-28, miR-125b, miR-150, miR-223, miR-382	[79]

miRNA: microRNA; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

PD is defined by gradual loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in the midbrain and abnormal accumulation of Lewy bodies in neurons.[59] The studies on peripheral blood mononuclear cells taken from patients with PD have indicated that miR-30b, miR-30c, and miR-26a are associated with the susceptibility of the disease (Table 2).[60] Upon examining the studies, it has been reported that decreased miR-34b and miR-34c expression in the brain has various connections with changing oxidative stress and cell death in PD.[57] Additionally, miR-133b has been reported as necessary for the protection and regulation of dopaminergic neurons in the brain and contributing to the pathogenesis of PD.[61]

AD is a neurodegenerative disorder characterized by the death of brain cells of unknown origin.[62] As the pathological changes in AD, the formation of neurofibrillary tangles containing tau protein inside the cell and the accumulation of amyloid-beta (Aβ) plaques outside the cell have been defined.[63] In AD,[64] miR-342-3p and, in differentiating patients with multiple sclerosis (MS) from healthy controls, miR-145 have been predicted to be used as good diagnostic biomarkers.[65,66] In a study that investigated the relationship between miR-149 and BACE1 in AD, serum miR-149 expression was downregulated in AD patients, and it was concluded that miR-149 could be a potential diagnostic biomarker. It has also been indicated that the overexpression of miR-149 can suppress Aβ accumulation and increase neuronal viability by targeting BACE1 in AD model cells.[67]

HD is a neurodegenerative disease characterized by loss of cortical neurons and characterized by cognitive and motor disorders.[68] In a study on a mouse model of HD, miR-29a, miR-124a, miR-132, and miR-330 were reported to show decreased expression.[69] In the miRNA expression study, it was observed that the expression level of miR-9 decreased in patients with HD.[70]

There are two different methods to be used for miRNA-based therapies in neurodegenerative diseases. The first one is to use miRNA mimics (agonists) to restore suppressed miRNA levels in therapy, and the second is to inhibit miRNA function using anti-miRs (antagonists) to suppress overactive miRNA function.[71]

MiRNAs in Viral Diseases

Some disease-associated miRNAs are not of human origin but encoded by viruses. Viruses are pathogens that can cause not only chronic diseases but also deadly epidemics. The first virally encoded miRNAs were cloned from Burkitt's lymphoma cell line infected by the DNA virus Epstein–Barr virus (EBV).[72] Viruses not only use their own miRNAs, but they can interact with the host's miRNAs, also affecting the amount and distribution of miRNAs in host cells.[73] It has been determined that virus-encoded miRNAs directly regulate host immune system factors.[74] Some of the viruses mimic the host's miRNAs and gain control over cellular processes.[75] The other virus-encoded miRNAs are directed against viral mRNAs.[72] It has been indicated that hepatitis C virus (HCV) replication depends primarily on a host's cellular miRNA. Liver-specific miR-122 triggers HCV translation.[76] HCV replication can be stopped by inhibition of miR-122, and this makes liver-specific miR-122 a potential drug target against HCV infections.[77]

Various cellular miRNAs that disrupt various early stages of the HIV-1 life cycle and potentially target several HIV-1 helper genes have been identified.[78] For instance, human miR-382, miR-223, miR-150, miR-125b, and miR-28 can target the 3′ UTR of HIV-1 transcripts (Table 3).[79] Besides their direct effects on HIV-1 replication, miRNAs have important roles in regulating host innate immune defenses based on phagocytes such as macrophages.[80]

Table 4. miRNAs in autoimmune diseases

Disease	miRNA	Reference
Multiple sclerosis	miR-34a, miR-155, miR-326, miR-142-3p, miR-146a, miR-146b and miR326	[89, 90]
Type 1 diabetes	miR-21, miR-93	[92]
Type 2 diabetes	miR-144, miR-146a, miR-150, miR-182	[93]
Nonalcoholic fatty liver disease	miR-34a ve miR-122	[95]

miRNA: microRNA.

Coronavirus disease 2019 (COVID-19), which has affected the entire world, has been the cause of the deaths of many individuals and has infected millions more. In a study that investigated miRNA expression profiles in patients with COVID-19, miRNA expression was observed to be different in peripheral blood from patients with COVID-19 and healthy donors. In the study, miR-16-2-3p, miR-6501-5p, and miR-618 were found to be expressed higher in patients with COVID-19 than in healthy controls, and it was observed that miR-183-5p, miR-627-5p, and miR-144-3p in patients with COVID-19 were less expressed than in healthy controls.[81]

MiRNAs in Autoimmune Diseases

Research on the regulatory role of miRNAs in the immune system in recent years has indicated that miRNAs play a role in the hereditary and adaptive immune systems.[82] A study on the deletion of Drosha or Dicer enzymes in T cells has accentuated the importance of miRNA in T lymphocytes.[83,84] miRNAs that play a role in the development and differentiation of T cells have been identified as miR-181a, miR-182, miR-10a, miR-17–92, and miR-29a/b.[85] miRNAs that play the most active role in the immune system are miR-155, miR-146a, and miR-21. Except for these miRNAs, many of them also regulate the immune response.[82] The relationship between specific miRNAs and autoimmunity has been demonstrated by a study that involved miR-17–92 overexpression in mice. The mice with higher expression of miR-17-92 in lymphocytes developed lymphoproliferative disease and autoimmunity and died prematurely.[86]

The relationship between several immune-related diseases, including MS, systemic lupus erythematosus, type 1 diabetes (T1D)/type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD) with cellular miRNAs was indicated with the research. A large number of miRNAs were identified when the miRNA expression profiles of relapsing–remitting MS and healthy controls were compared.[66] MS is a central nervous system autoimmune disease and is multifactorial inherited.[87] It is known in its etiology that genetic factors, autoimmunity, vitamin D, smoking, and previous EBV infection play a role.[88] Increased miR-34a, miR-155, and miR-326 expressions have been reported in MS lesions.[89] It was predicted that the upregulation of miR326, miR-146a, miR-146b, miR-142-3p, and miR-21 could be used as a diagnostic marker in the etiopathogenesis of MS (Table 4).[90]

T1D is an autoimmune disease involving environmental and genetic factors that triggers the selective destruction of insulin-producing beta cells in the pancreas.[91] It has been indicated that miR-93 and miR-21 expressions decrease in peripheral blood mononuclear cells of patients with T1D.[92] Additionally, the miRNA expression profile identified miRNAs associated with type 2 diabetes, including miR-144, miR-146a, miR-150, and miR-182.[93]

In industrialized western countries, NAFLD is regarded as the most common cause of chronic liver disease.[94] miR-122 and miR-34a expressions in the pathogenesis of NAFLD have been reported to increase.[95] These miRNAs can be used as markers in the diagnosis and treatment of NAFLD.

MiRNAs in Disease Diagnosis and Treatment

Biomarkers are the biological indicators of diseases.[96] They aim to develop better clinical tests that improve the diagnosis or prognosis of diseases.[97] Thus, it poses an important position for the treatment of the following patient.[98] As for biomarkers, miRNAs have an advantage over proteins and metabolites. The first advantage is that miRNA biomarkers enable early diagnosis. Another advantage is that the low amount of miRNA biomarkers are amplifiable and can be detected by Real-time Quantitative Polymerase Chain Reaction.[97] miRNAs in such biological fluids as cerebrospinal fluid, tears, plasma, serum, saliva, urine, colostrum, and semen have been presented in the studies.[99] MiRNAs, which make it possible to obtain from tissue, serum, or plasma without the need for invasion, are more preferred due to fewer complications with such studies. Circulating miRNAs have been indicated as an important biomarker in the diagnosis and prognosis of diseases since they are abundant in the blood and they have a stable structure.[100]

Conclusion

Studies with miRNAs, which have become the focus of attention recently, have shown that miRNAs are associated with various types of cancer, cardiovascular diseases, and central nervous system diseases.

Identification of miRNAs that are crucial in diseases can contribute to the early diagnosis, the prognosis of the disease, and the application of new treatment models. Recent studies have reported that miRNAs can be used as a biomarker in the diagnosis of different diseases and provide improvements in the way of alternative treatment; however, studies on the identification of miRNAs and miRNA–disease relationships are insufficient, and hence, further studies are needed.

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