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Micro-RNA in Health and Disease

Research Article

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Abstract

Micro-RNAs (miRNA) are functional, non-protein coding RNA molecules that are approximately 22 nucleotides in length and their transcriptions provided by intron or exon regions of the genome and non-protein coding regions of RNA genes. miRNAs inhibit translation of protein and destroy mRNA. Although approximately 2500 human miRNA types have been identified so far, quite little is known about their biological functions. In some studies, it is shown that miRNA expression levels are important for many biological processes such as cell proliferation, differentiation, apoptosis, organogenesis and metabolism. Recent studies have pointed out that miRNAs have been used as diagnosis and prognosis biomarkers in many human diseases including cancer, cardiovascular disorders, cerebrovascular disorders and metabolic disturbances.

Keywords: Noncoding RNA; miRNA; Biogenesis of miRNA.

Abbreviations: miRNA: Micro RNAs; T2DM: Type 2 Diabetes Mellitus; ORFs: Open Reading Frames; MSCs: Mesenchymal Stem Cells; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein; VCAM-1: Vascular Cell Adhesion Molecule 1; AMI: Acute Myocardial Infarction; cTnI: Cardiac Troponin I; STEMI: ST-Segment Elevation Myocardial Infarction; CK-MB: Creatine Kinase-MB; PD: Parkinson's Disease; ND: Neurodegenerative Diseases; AD: Alzheimer's Disease.

Introduction

Micro RNAs (miRNA) are small noncoding, endogenous, single stranded RNAs usually consisting of 18-25 nucleotides that regulate gene expression through repression or degradation of targeted mRNAs at the post transcriptional level [1]. According to a miRBase online database (http://microrna.sanger.ac.uk/, update on June 26, 2014), more than 2500 microRNAs have been found in human tissues [2]. It is estimated that about 30–50% of protein-coding genes are regulated by miRNAs [3]. The expression of miRNA is controlled by different mechanisms including the level of methylation of DNA and histones [4, 5]. Disrupted expression of miRNAs participating in cell process is related to many diseases, such as obesity, hyperlipidemia, atherosclerosis, type 2 diabetes mellitus (T2DM) and cancer through regulation of multiple genes [6].

A Historical Overview of miRNA Research

miRNAs were discovered in 1993 by Lee and colleagues in the nematode Caenorhabditis elegans. In these organisms, the down regulation of LIN-14 protein was found to be essential for the progression from the first larval stage (L1) to L2. Furthermore, the down regulation of LIN-14 was found to be dependent on the transcription of a second gene called lin-4. Interestingly, the transcribed lin-4 was not translated into a biologically active protein. Instead, it gave rise to two small RNAs approximately 21 and 61 nucleotides in length. The longer sequence formed a stem-loop structure and served as a precursor for the shorter RNA [7]. Later this group, along with Wightman et al., found that the smaller RNA had antisense complementarity to multiple sites in the 3' UTR of lin-14 mRNA. The binding between these complementary regions decreased LIN-14 protein expression without causing any significant change in its mRNA levels. These

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two studies together brought forth a model wherein base pairing occurred between multiple lin-4 small RNAs to the complementary sites in the 3' UTR of lin-14 mRNA, thereby causing translational repression of lin-14 and subsequent progression from L1 to L2 during *C.* elegans development [8]. This novel mode of regulating gene expression was first thought to be a phenomenon exclusive to *C.* elegans. In 2000, two separate groups discovered that a small RNA, let-7, was essential for the development of a later larval stage to adult in *C.* Elegans [9, 10]. More importantly, homologs of this gene were subsequently discovered in many other organisms, including humans [11]. The period that followed was marked by a deluge of information wherein multiple laboratories cloned numerous small RNAs from humans, flies, and worms. These RNAs were noncoding, around 19 to 24 nucleotides in length, and derived from a longer precursor with a stem-loop or fold-back structure [1]. Many were found to be evolutionarily conserved across species and exhibited cell-type specificity. The recognition and confirmation of the existence of these small RNAs, now termed mi-RNAs, led to intense research aimed at identifying new members of this family. This resulted in the discovery of multiple miRNAs across different species of plants and animals. A miRNA registry, named miRBase, set up in 2002 serves as the primary online repository for all potential miRNA sequences, annotation, nomenclature, and target prediction information [12, 13]. The current release (miRBase 20) contains 24 521 entries representing hairpin precursor miRNAs that express 30 424 mature miRNA products in 206 species. The biological significance of a vast majority of annotated miRNAs, however, remains unknown and requires functional validation.

The Biogenesis of miRNAs

The biogenesis of miRNAs (Figure 1) involves multiple steps and specific cellular machinery [14]. Each one of the multiple steps that compose miRNA biosynthesis seems to be remarkably well coordinated. Drosha initiates the processing by specific cropping of the stem-loop precursor in the nucleus [15]. The resulting structure, precursor miRNA (pre-miRNA), seems to be a signature motif for all dsRNAs that are involved in small-RNA pathways. Exportin-5 recognizes this signature motif and exports pre-miRNAs to the cytoplasm through nuclear pores on a GTP–GDP gradient [16, 17]. Following export, pre-miRNA is handed over to another RNase III enzyme, Dicer, that dices the pre-miRNA into a miRNA duplex that is further unwinded giving rise to the mature functional miRNA molecule.

miRNAs in Human Genome

miRNAs regulate many major cellular functions such as development, differentiation, growth, and metabolism and approximately 2500 miRNA genes have been reported to exist in the mammalian genome [18]. One-third of the human genome is estimated to be regulated by miRNAs [19]. The precise mechanism involved in the miRNA transcription is not known but proximity to other genes in the genome and their locations in introns of coding genes, noncoding genes and exons are reported to influence their expression [20]. In the genome, miRNAs are organized in clusters and share the same transcriptional regulatory units and are independently expressed if they have their own promoters [21, 22].

Most recent sequence analyses of the human genome demonstrates that the protein coding genes may be as low as 25,000 [23]. Although the exact number of the protein coding genes in the human genome is not known, the 25,000 figure is at least 3-4 times lower than the figure believed in late 1980's. What these new data reveal is that a large segment of the human genome consists of non-coding protein genes. Further sequence analysis indicates that the Open Reading Frames (ORFs) comprise less than 2%, repetitive sequences around 46% [24, 25] and non-coding parts of protein-coding genes (introns, 5' and 3'-UTRs) an estimated 25–27% of the 3.2 billion bases in the human genome [26].

miRNAs and Human Diseases

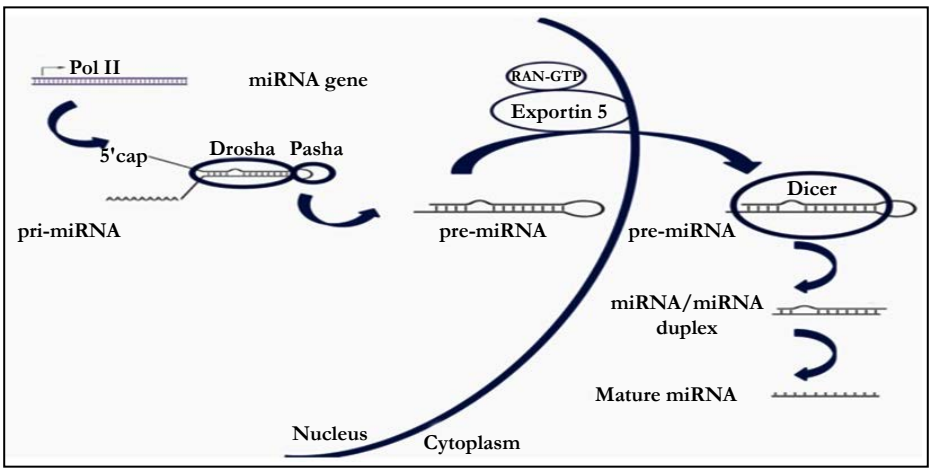
miRNAs have been demonstrated to play a major role in a wide range of developmental processes including metabolism, cell proliferation, apoptosis, developmental timing, and neuronal cell fate [27-29]. Other regulatory roles include neuronal gene expression [30], brain morphogenesis [31], muscle differentiation [32], and stem cell division [33].

MicroRNA's deficiencies or excesses have been linked to some other clinically important diseases ranging from myocardial infarction to autoimmune diseases [34].

miRNA as a Therapeutic Modality

miRNAs work by highly specific binding to the complementary

Figure 1. The Biosynthesis Pathway for miRNAs.



site on the mRNA target and are considered new therapeutic strategies. Specific oligomers, called antagomirs, have a complementary sequence to a specific miRNA and ultimately compete with the target mRNA to bind to miRNA. This concept has shown promise in cell culture models as well as initials *in vivo* experiments. For example, Krutzfeldt et al., demonstrated that miRNA antagomirs were successfully delivered *in vivo* and had higher stability showing target modulation in specific tissues where particular miRNAs were expressed. For example, miR-122 antagomir in the liver showed up-regulation of several genes targeted by miR-122 [35]. Conversely, it is possible to restore miRNAs that are often down-regulated in cancer by external delivery using suitable carrier systems. One of the key issues for this modality is to target the specific sites or tissues of interest. Efficient delivery systems for *in vivo* delivery of miRNA are highly desirable and several are currently under investigation. There are also emerging studies involving restoration of tumor suppressive miRNAs in tumor by *in vivo* delivery [36].

miRNAs in Obesity

Obesity is a chronic medical condition resulting from increased fat mass and energy storage in adipose tissue, genetic and environmental predispositions, increased calorie uptake, and decreased physical activity, which leads to an adverse effect on health [37]. Adipose tissue is a major contributor to the pathophysiology of obesity. In recent years, there has been substantial attention paid to the role of miRNAs in regulating adipogenesis and obesity [38]. miRNAs can enhance or suppress adipogenic differentiation of mesenchymal stem cells (MSCs) and mature adipocyte differentiation by regulating transcription factors and signaling pathways related to adipogenesis [39]. These miRNAs play important roles in physiologic and pathophysiological conditions which participate in cell differentiation, proliferation, apoptosis, hematopoiesis, limb morphogenesis, and important metabolic pathways, such as insulin secretion, triglyceride and cholesterol biosynthesis, and oxidative stress [40, 41]. Among these, it is shown that miR-103, miR-107, and miR-143 accelerate fat cell development [42]. miR-935, miR-4772, miR-223, and miR-376b are reporters of diet-induced obesity [43]. Mice lacking miR-378 are resistant to obesity and exhibit enhanced mitochondrial fatty acid metabolism and elevated oxidative capacity in insulin target tissues [44]. miR-221, miR-28, and miR-486 are associated with BMI, percentage fat mass, waist, and regional fat distribution [45].

miRNAs in Hyperlipidemia and Atherosclerosis

Hyperlipidemia, a chronic disorder with high levels of triglycerides (TG, hypertriglyceridemia), total cholesterol (TC, hypercholesterolemia), and low-density lipoprotein cholesterol (LDL-C) and a decreased level of high-density lipoprotein cholesterol (HDLC) [46].

Atherosclerosis is a complex multifactorial disease triggered and maintained by a low-level chronic inflammation of the arterial wall [47]. The onset of atherosclerosis includes a dysfunction of endothelial cells, caused by a variety of external stimuli (e.g. hypertension, reactive oxygen species, or modified low-density lipoprotein (LDL) cholesterol). The damaged endothelium consequently begins to express more adhesive molecules, for example, vascular cell adhesion molecule 1 (VCAM-1), leading to promoted adhesion and infiltration by immune system cells [47]. Hyperlipidemia is a well-accepted risk factor in the development of atherosclerosis [48]. Severe hyperlipidemia promotes the progression of atherosclerosis and its end-points, that is, myocardial infarction or stroke, as shown in patients with familial hypercholesterolemia who suffer a myocardial infarction or stroke at a very early age [49, 50].

Several genes and cytokines have been identified as risk factors for atherosclerosis [51, 52] and recent studies have suggested that miRNAs may play a role in regulating the atherosclerotic process [53, 54]. Expression of 1 to 900 microRNAs potentially associated with atherosclerosis was investigated in different studies. Cipollone et al reported that five miRNAsd miR-100, miR-127, miR-145, miR133a, and miR-133bd were over expressed in symptomatic plaques [55]. Among these five miRNAs, miR-145 and miR133a were further shown to modulate stroke-related proteins *in vitro*. Li et al., demonstrated that the levels of miR-21, miR130a, miR-27b, let-7f, and miR-210 increased significantly in the sclerotic intimal samples compared with normal intimal samples from the same patients with atherosclerotic obliterans [56], whereas miR-221 and miR-222 decreased significantly. Furthermore, significant increases in miR130a, miR-27b, and miR-210 expression were observed in the serum. Another study reported that the expressions of miR-21, miR-34a, miR-146a, miR-146b-5p, and miR-210 were significantly upregulated in human atherosclerotic arteries versus nonatherosclerotic arteries [57]. Fichtlscherer et al., demonstrated that the circulating levels of miR-126, miR-17, miR92a, miR-145, and miR-155 were significantly reduced in patients with coronary artery disease compared with healthy controls. In contrast, miR-133a and miR-208a levels tend to be higher in patients with coronary artery disease [58].

MiRNAs in Cardiovascular Disease

In the cardiovascular system, miRNAs control the proliferation and differentiation of stem and progenitor cells, and the function of cardiac myocytes, pacemaker cells, endothelial cells and smooth muscle cells. miRNAs play a crucial role in cardiac development and regeneration. They are involved in cardiovascular pathophysiology and their expression is altered in various cardiovascular diseases [59].

miRNA-22 (miR-22) is one of the most abundant miRNA in the heart. Many studies have demonstrated that miR-22 plays critical roles in myocardial infarction and subsequent cardiac remodeling [60].

miR-208 is a cardiac-enriched miRNA and is found at much higher level during cardiac tissue injury [61]. So There was a good correlation between the changes in plasma miR-208 and cardiac troponin I (cTnI), a classical biomarker of acute myocardial infarction (AMI) [62].

miR-208a was absolutely identified to be expressed in the human heart. miR-208a was undetectable in plasma of healthy individuals or non-AMI patients (such as patients with acute kidney injury, chronic renal failure, stroke, or trauma), but it was easily detected in 90.9 % AMI patients and in 100 % AMI patients within 4 h of the onset of chest pain while cTnI was not yet affected, suggesting that miRNAs may leak into the bloodstream at an earlier stage of

myocardial injury (the biological peak of troponins is ~18 h after AMI). It is reasonable to speculate that circulating *miR-208a* has advantages over cTnI (or cTnT) in distinguishing pure AMI from patients with renal disease, stroke, and trauma [63].

In case of acute ST-segment elevation myocardial infarction (STEMI) patients, the levels of plasma *miR-208b* increased 3,000-fold compared to healthy controls within 12 h after infarction. Peak values of *miR-208b* were well correlated with peak cTnI and the ejection fraction, indicating a possible role for circulating *miR-208b* as a biomarker in diagnosis of STEMI or in prediction of long-term complications [64].

Plasma level of *miR-499* was obviously increased in all patients with AMI but it was below the limit of detection for acute coronary syndromes, congestive heart failure, and for all healthy controls. These results indicated that circulating *miR-499* might be a useful biomarker for the diagnosis of AMI [65].

In a rat AMI model, plasma level of *miR-133* a was increased at 1-3 h, peaked at 3-12 h, and decreased at 12-24 h after coronary artery ligation. In AMI patients, *miR-133* plasma level was substantially higher compared with healthy controls. A positive correlation was also reported between the elevated plasma miR-133 and cTNI. These results provided evidence that miR-133 is a powerful biomarker for the diagnosis of AMI [63].

The level of circulating *miR-1* was increased nearly 100-fold in AMI patients compared with healthy subjects and showed a positive correlation with serum creatine kinase-MB (CK-MB) level. In another separate clinical study, plasma miR-1 level was significantly higher in AMI patients compared with non-AMI subjects and the level was returned to normal on discharge following medication. Interestingly, the increased plasma miR-1 was not associated with age, gender, blood pressure, diabetes mellitus, or other established biomarkers for AMI including cTnI and CK-MB. Moreover, in a necrosis model of cultured cardiac cells, miR-1 was found to be released into the culture medium and was stable at least for 24 h. Collectively, these results strongly support that circulating miR-1 might be a novel sensitive biomarker for AMI diagnosis [66].

MiR-214, which increases in mouse and human tissue after myocardial infarction, exerts a protective effect during ischemia/reperfusion. Deletion of *miR-214* increases injury and mortality following myocardial infarction [59].

Cai et al., demonstrated that *miR-765* is overexpressed in failing hearts and is involved in contractile regulation [67]. Potous et al., revealed the role of *miR-126* in right ventricle (RV) failure associated with pulmonary arterial hypertension (PAH). Due to the methylation process, *miR-126* is downregulated in RV failure in PAH patients, causing decreased capillary density. Administration of *miR-126* mimics ameliorates microvascular density, improves RV function and diminishes fibrosis, whereas antagomir-mediated *miR-126* downregulation exacerbates RV failure [68]. Circulating miRNA-423-5p is also correlated with NT-pro BNP. Also, meticulous screening of 186 miRNAs uncovered four main miRNAs (miR-423-5p, miR-22, miR-320a, and miR-92b) significantly increased in the serum of HF patients. With the detection of the four miRNAs, a sensitive and specific score could be defined for assessing HF patients. The miRNA-score was closely related to several important prognostic parameters, including increased serum BNP, widening QRS, and dilatation of left ventricle and atrium [69, 70].

Role of miRNA in Diabetes Mellitus

Diabetes mellitus (DM) is a group of chronic metabolic diseases characterized by insulin deficiency and/or insulin resistance that leads to elevated blood glucose levels as well as abnormal fat and protein metabolism [68]. The number of people with diabetes mellitus is projected to rise to 439 million globally, which represents 7.7% of the total adult population of the world's adults several microRNAs are involved in - cell development and function, insulin secretion [71], and insulin resistance in the liver, skeletal muscle, and adipose tissue, which play an important role in glucose homeostasis and the pathogenesis of diabetes [72]. Altered microRNA expression also affects the progression of diabetic complications in the kidney, retina, and peripheral nerves. As each microRNA has the potential to regulate multiple genes in biological processes that include cell proliferation, differentiation, apoptosis, and development, it has been confirmed that the dysregulation of microRNAs affects many pathological pathways in diabetic complications [73, 74]. Decreased circulating miR-126 was a significant predictor of DM. miR-15a, miR-29b, miR-126, and miR-223 were decreased in the subjects with DM [75, 76]. In pancreatic -cell, islets, enriched miR-375 was increased in subjects with T2DM and modulated -cell function through several physiological mechanisms. miR-375 inhibits insulin secretion and transcription, maintains -cell mass, proliferation, and regeneration, and promotes embryonic pancreas development [77].

Role of miRNA in Cancer

Since the early stages of miRNA research, cancer has been the most prominent of human diseases with a clear role for miRNA regulation. The first evidence came from a study by Calin et al., in which they demonstrated a frequent deletion of miRNA genes miR15 and miR16 among 65% of B-cell chronic lymphocytic leukemia patients [78]. The deregulation of miR-125b, miR-145, miR-21, and miR-155 expression was associated with the increased risk of breast cancer [79]. In addition, up-regulation of miR-155 and down-regulation of let-7a were correlated with poor survival of lung cancer patients [80]. Yu et al., reported low miRNA-34a levels in human bladder cancer tissues. Therefore, miRNA-34a is potential anti-angiogenic and anti-metastatic therapeutic target in bladder cancer patients [81]. Smits et al., showed that miRNA-101 inhibited proliferation, angiogenesis and migration of glioblastoma cells [82]. Moreover, Tang et al., showed that miRNA-101 was downregulated in nasopharyngeal carcinoma tissues and cell lines. They further showed that overexpression of miRNA-101 suppresses angiogenesis and lung metastasis [83]. miRNA-135a is a tumor suppressor, which is reported to be downregulated in human prostate and gallbladder cancers [84, 85]. Cheng et al., reported that miRNA-135a levels were downregulated in gastric cancer tissues and cell lines. They showed that miRNA-135a inhibited gastric cancer angiogenesis and metastasis [86].

miRNA Regulation on Immunity

MicroRNAs critically influence the development and responses of the immune system, but the contributing biological mechanisms

are poorly characterized [87]. miRNA-155 is among the first miRNAs to be identified to play diverse roles in immunity and inflammation. It is generally believed that miRNA-155 is a multifunctional miRNA [88]. miRNA-155 has also been reported to regulate antigen presentation [89] and to regulate toll-like receptor (TLR) and cytokine signaling negatively. Rodriquez et al., showed that miR-155 is required for normal functioning of B and T lymphocytes, as well as dendritic cells [90]. Overexpression of the miR-17-92 cluster and miR-181 enhanced B-cell proliferation, while miR-150 regulated B-cell differentiation [91]. When overexpressed, miR-181 has been shown to decrease T-cell numbers [94], but enhance T-cell receptor signaling [90]. When T cells are activated, the miRNA expression profiles are altered [92, 93].

miRNA and Cerebrovascular Disease

miRNAs are crucial for the development of the nervous system. Recent studies have demonstrated that some miRNAs play important roles in the occurrence and development of ischemic cerebrovascular diseases such as stroke [94]. miR-126 could facilitate the angiogenesis following ischemia. Van Solingen et al., [95] firstly confirmed that miR-126 could facilitate the angiogenesis following ischemia. Bonauer et al., [96] also found that miR-92a could significantly inhibit the angiogenesis *in vivo* and *in vitro*. In addition, there was evidence that showed that miR-21 may promote the proliferation of newly generated smooth muscle cells in the intima [97, 98] and downregulation of miR-222 could facilitate the migration and proliferation of endothelial cells, which may increase the angiogenesis in the plaques [99, 100]. Cell apoptosis is an important pattern of cell death after stroke and plays important roles in the pathological processes following cerebral stroke. Some miRNAs (such as miR-497, -15a, and -21) have been found to be involved in the cell apoptosis after stroke. Besides apoptosis, miRNAs are also associated with brain edema after stroke [101]. Neurodegenerative diseases (ND) such as Parkinson's disease (PD) and Alzheimer's disease (AD) have placed substantial social-economic burdens on countries with aging populations. Notably, recent progresses from studies elucidating miRNA functions in NDs have shed newlight on disease pathogenesis and may lead to novel treatment strategies. For example, a systemic miRNA profiling in peripheral blood mononuclear cells from PD patients revealed miR-30b, miR-30c, and miR-26a to be associated with the susceptibility of the disease [102].

Table 1. miRNA's Associated with Common Human Disease [103-106].

Diseases type	MiRNA
Metabolic Syndrome	miRNA -23a, miRNA -27a, miRNA -130, miRNA -195, miRNA -197, miRNA -320a, miRNA -509-5p
Obesity	miRNA -17-5p, miRNA -132
Type II Diabetes	miRNA -144, miRNA -150, miRNA -103, miRNA -146a, miRNA -182
Cardiovascular Disease	
AMI	miRNA-208a, miRNA -1, miRNA -133a, miRNA -133b, miRNA -499, miRNA -499-5p, miRNA -328, miRNA -1291, miRNA -663b, miRNA -223, miRNA -122, miRNA -375, miRNA -197, miRNA -223, miRNA -126
HF	miRNA-423-5p, miRNA -423-5p, miRNA -22, miRNA -320a, miRNA -92b, miRNA -499
AF	miRNA-150
Hypertension	miRNA -23b, miRNA -130a, miRNA -191, miRNA -451, miRNA -1246, miRNA -26a, miRNA-150
CAD	miRNA -126, miRNA -92a, miRNA -17, miRNA -145, miRNA -155, miRNA -135a, miRNA -147, miRNA -149, miRNA -31, miRNA -133a, miRNA -208a
Cancer	
Leukemia	miRNA -128a, miRNA -128b, miRNA -21, miRNA -150, miRNA -155
Breast Cancer	miRNA -125b, miRNA -145, miRNA -21, miRNA -155, miRNA -210
Lung Cancer	miRNA -155, let-7a, miRNA -21, miRNA -205
Gastric Cancer	miRNA -145
Hepatocellular Cancer	miRNA -21, miRNA -221, miRNA -224, miRNA -18
Prostate Cancer	let-7c, miRNA -125b miRNA -145
Pancreas Cancer	miRNA -21, miRNA -221, miRNA -222, miRNA -181a, miRNA -181b, miRNA -181d, miRNA -155, miRNA -196a
Ovarian Cancer	miRNA-200a, miRNA-141, miRNA-199a, miRNA-140, miRNA -145, miRNA -125b1
Uterine Leiomyoma	let-7, miRNA -21, miRNA -23b
Thyroid Cancer	miRNA-197, miRNA-346, miRNA-221, miRNA-222, miRNA-181b, miRNA -146b
Colorectal Cancer	miRNA-25, miRNA-92, miRNA-31, miRNA-96, miRNA -135b,
Cerebrovascular Disease	
Stroke	miRNA -125b-2, miRNA -27a, miRNA -422a, miRNA -488, miRNA -627, miRNA -290, miRNA -124, miRNA -10a, miRNA-182, miRNA -200b, miRNA -298
Alzheimer's disease	miRNA -29b-1, miRNA -29a, miRNA -9
Parkinson's disease	miRNA -30b, miRNA -30c, miRNA -26a, miRNA -133b, miRNA -184, let-7

miRNA; Micro RNA, AMI; Acute Myocardial Infarction; HF, Heart Failure; AF, Atrial Fibrillation; CAD, Coronary Artery Disease.

Conclusion

The effects of miRNAs on gene expression in different physiological processes and diseases have been determined. Recent studies shown that miRNA expression levels are important for many biological processes such as cell proliferation, differentiation, apoptosis, organogenesis and metabolism. So they serve as biomarkers and potential therapeutic targets and agents in various cancers and other diseases, e.g., cardiovascular disease, cerebrovascular disease and type II diabetes (table). Consequently it is thought that miRNAs will provided important benefits in the development of early diagnosis and treatment.

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