

Micrnas are Not That Small to Ignore

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ABSTRACT

MicroRNAs (miRNAs) are small, noncoding RNA molecule that negatively regulates gene expression by causing either degradation or translational inhibition of their target mRNAs. These miRNAs are key regulators of various biological processes such as differentiation, maturation and maintenance of immune homeostasis. Furthermore, deregulated expression of miRNA has now been shown to regulate several disease processes by regulating tumorigenesis, angiogenesis, apoptosis and metastasis in cancer and other diseases such as rheumatoid arthritis, diabetes and cardiovascular diseases. This review article summarizes the present status of miRNA research, with major emphasis on the roles of miRNAs in the development of various human diseases.

Keywords: MicroRNA, diabetes, cardiovascular disease, cancer

1. INTRODUCTION

MicroRNAs (miRNAs) are small non-coding RNAs (~22 nt), which are involved in the regulation of gene expression. These miRNAs negatively regulates gene expression at the posttranscriptional level by binding to the 3'UTR of target mRNAs through base pairing, resulting in either target mRNAs cleavage or causing translation inhibition (Ambros *et al.*, 2004; Bartel, 2004). According to recent studies, in humans, more than 500 miRNAs have been identified and it is predicted that the total number may exceed up to 1000 (Bentwich *et al.*, 2005; Griffiths-Jones *et al.*, 2008). Despite the large number of identifying miRNAs, the target mRNAs and the biological function have been attributed to only a few of them (Bhardwaj *et al.*, 2010). Growing evidences suggest that miRNAs play significant roles in several biological processes like differentiation, cell proliferation, embryonic development, cell proliferation and apoptosis (Esquela-Kerscher and Slack, 2006). With the continuous influx of studies on miRNAs, it is now becoming evident that these miRNAs exhibit differential expression in several human diseases, including cancer (Calin and Croce, 2006; Esquela-Kerscher and Slack, 2006) and play important roles in the development of other disease processes such as cardiovascular disease

(Latronico *et al.*, 2007), schizophrenia (Hansen *et al.*, 2007; Perkins, 2007), renal function disorders (Amrouche *et al.*, 2011), fragile-X mental retardation syndrome (Provost, 2010), diabetes (Dehwah *et al.*, 2012), hepatitis (Murakami *et al.*, 2010) and obesity (Dehwah *et al.*, 2012). Considering the growing number of studies relating miRNAs and various diseases this review article will focus more on newly identified miRNAs in disease (**Table 1**) and will discuss about their role and its significance in diagnostics and prognostics. Furthermore, this study will provide a deeper insight about the role of recently identified miRNAs.

1.1. miRNAs in Cancer

Cancer is considered as one of the major health problem worldwide (Jemal *et al.*, 2011). According to an estimate, one in 4 deaths in the United States occurs because of cancer. Development of cancer occurs when normal cells in the body start developing in an abnormal growth fashion. In most of the cancers, genes responsible for maintaining growth gets apparently expressed or activated, thus causing uncontrolled growth of the cancer cells. During the past few years, expression signatures of miRNAs in many human cancers have been identified (Calin and Croce, 2006) and several lines of incidences suggest that these miRNAs play significant role in the

development and progression of cancer (Sotiropoulou *et al.*, 2009). Growing studies also reveal that the aberrant expression of miRNAs is associated with the stage and metastasis of cancers (Shimono *et al.*, 2009). These miRNA may function as either tumor promoters (oncomirs) or tumor suppressors (anti-oncomirs) (Bhardwaj *et al.*, 2010). Thus, miRNAs may play important roles in cancer development, progression, prognosis and diagnosis. The expression profile of miRNA in multiple cancer types including Chronic Lymphocytic Leukemia (CLL) (Moussay *et al.*, 2011), breast (Schooneveld *et al.*, 2012), colon (Piepoli *et al.*, 2012), lung (Wang *et al.*, 2012), pancreatic (Srivastava *et al.*, 2011), prostate (Hassan *et al.*, 2012), cancers and glioblastomas (D'Urso *et al.*, 2012), reveal that a large number of miRNAs are aberrantly expressed in various cancers. In CLL, expression of miRNAs, miR-15a and miR-16 was downregulated (Hanlon *et al.*, 2009). Bcl2, an anti-apoptotic protein is expressed at very high levels in CLL and is considered as an important survival factor of the cancer cells. Down regulated expression of miR-15a and miR-16-1 maintains the enhanced levels of BCL-2 and thus confers apoptosis resistance in CLL (Cimmino *et al.*, 2005). In another study, miR-16 is shown to suppress the growth of prostate cancer cells by regulating the expression of CDK1 and CDK2, which are associated with cell cycle control and proliferation (Takeshita *et al.*, 2010). Another study on miRNA in Lymphoma has shown that miR-17-92 cluster is upregulated in lymphomas. Their study demonstrated that the miR-17-92 cluster can enhance tumorigenesis by inhibiting apoptosis (Croce, 2008). Furthermore, several studies also show that this cluster is overexpressed in a wide array of cancers including breast, colon, lung, prostate and pancreatic endocrine. Among others oncogenic miRNAs, miR-21 has been shown to promote apoptosis through activation of caspases in human glioblastoma cells (Chan *et al.*, 2005). In breast cancer cells, silencing of miR-21 inhibited cell growth *in vitro* and *in vivo* by causing downregulation of Bcl-2 and induction of apoptosis (Si *et al.*, 2007). MiR-155 is overexpressed in many cancers including B-cell lymphomas, Burkitt lymphoma, Hodgkin's lymphoma and breast, lung, colon and thyroid cancers. Its expression was significantly correlated with poor survival in pancreatic cancer patients (Greither *et al.*, 2010). A study performed on mice also identified that mice overexpressing miR-155 are able to develop B-cell malignancy (Costinean *et al.*, 2009). A recent study conducted by Srivastava *et al.* (2011) and coworkers identified a tumor suppressor miRNA in pancreatic cancer. Their study demonstrated that miR-150 exerts its tumor suppressor function by directly targeting an oncoprotein MUC4 (Srivastava *et al.*, 2011). In lung and

colon cancer cells Let-7 family members of miRNAs are downregulated and that correlates with the shortened postoperative survival in lung cancer patients (Takamizawa *et al.*, 2004). Studies on miR-125a and miR-125b suggest that their expression is either downregulated or lost in breast cancer (Scott *et al.*, 2007). These miRNAs exert their function by regulating the oncogenes ERBB2 and ERBB3. Furthermore, miR-143 and miR-145 are frequently downregulated in colorectal and breast cancers as well as B-cell malignancies suggesting their involvement in cancer (Luo *et al.*, 2011; Akao *et al.*, 2007). With the huge influx of data, it cannot be overruled that there may be many other miRNAs which are involved in cancers development and progression that need to be explored.

1.2. miRNAs in Cardiovascular Diseases

Cardiovascular diseases are the major cause of mortality in developed countries. Therefore extensive studies have been done to develop novel diagnostic and therapeutic strategies to fight with the devastating outcome of these diseases. Several recent investigations suggest that miRNAs regulate various processes including angiogenesis, cardiogenesis, endothelial and myocyte growth, contractility and cardiac rhythm (Latronico *et al.*, 2007; Elton *et al.*, 2011; Care *et al.*, 2007) and studies also indicate involvement of these miRNAs in the pathogenesis of various cardiovascular diseases. Therefore, miRNAs have been considered as a potential target for therapeutic intervention. The expression of specific miRNAs is altered in diseased hearts and vessels as well as in stroke (Bonauer *et al.*, 2009; Rink and Khanna, 2010) and experiments of gain- and loss-of-function in mice have shown that miRNAs regulates multiple forms of cardiovascular disease (Care *et al.*, 2007; Rooij and Olson, 2007). In cardiac hypertrophic condition some miRNAs are downregulated, their forced expressions prevents cardiac myocyte hypertrophy. Furthermore, miR-21 which is an overexpressed miRNA in hypertrophic animal and human hearts, repression of this miRNA inhibits hypertrophic hearts *in vitro* (Cheng and Zhang, 2010). A study on rats has shown that inhibiting miR-21 exerts negative effect on the neointimal lesion formation in rat artery after angioplasty, thus suggesting the importance of miRNAs as regulators in the development of proliferative vascular diseases. The possible implication of miRNAs in the cardiovascular system is also supported by the findings that depletion of the miRNA-processing enzyme Dicer causes defects in angiogenesis, vessel formation and cardiac development (Kuehbachner *et al.*, 2007; Suarez *et al.*, 2007; 2008).

Table 1. List of MicroRNAs and their expression associated with various diseases

miRNA	Diseases	Expression	Reference
miR-15a and miR-16-1	CLL	Downregulated	(Hanlon <i>et al.</i> , 2009)
miR-17-92	Lymphomas	Upregulated	(Croce, 2008)
miR-21	Breast cancer	Upregulated	(Si <i>et al.</i> , 2007)
miR-150	Pancreatic cancer	Downregulated	(Srivastava <i>et al.</i> , 2011)
miR-21	Hypertrophy	Upregulated	(Cheng and Zhang, 2010)
miR-1	Ischemic heart, Arrhythmogenesis	Upregulated	(Tang <i>et al.</i> , 2009)
miR-34a, miR-200a and miR-520, let-7f, miR-371 and miR-517/517	Alzheimer's disease	Upregulated	(Maes <i>et al.</i> , 2009)
miR-144, miR-146a, miR-150 and miR-182	Impaired fasting glucose and Type 2 Diabetes	Upregulated	(Karolina <i>et al.</i> , 2011)
miR-25	Diabetic neuropathy	Downregulated	(Fu <i>et al.</i> , 2010)
miR-146a, miR-155, miR-132 and miR-16		Upregulated	(Pauley <i>et al.</i> , 2008)
miR-124a and miR-15a	Rheumatoid arthritis	Downregulated	(Wittmann and Jack, 2011)
miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195 and let-7f	ulcerative colitis	Upregulated	(Dalal and Kwon, 2010)
miR-19b and miR- 629	Crohn's colitis	Downregulated	(Wu <i>et al.</i> , 2010)
miR-146a	Systemic lupus erythematosus/lupus	Downregulated	(Ceribelli <i>et al.</i> , 2011)

In a rat model of myocardial infarction and in human hearts with coronary heart disease, miR-1 was significantly unregulated in ischemic heart tissue (Tang *et al.*, 2009; Brattelid *et al.*, 2011). Several studies have shown the significance of miRNAs in cardiac function and maintaining its structure. MiR-1, miR-133, miR-208, miR-21 and miR- 221/222 are associated with cardiac growth, erythropoiesis, angiogenesis, proliferation (Latronico *et al.*, 2007; Bauersachs *et al.*, 2007). Overexpression of mature miR-1 increases the severity of arrhythmogenesis and its downregulation suppress arrhythmias (Tang *et al.*, 2009; Brattelid *et al.*, 2011; Latronico *et al.*, 2007; Latronico and Condorelli, 2009). All these evidences thus support the potential of miRNAs in the development of cardiovascular diseases.

1.3. miRNAs in Neurodegenerative Diseases

Neurodegenerative Diseases (NDs) are the diseases which result from many genetic and environmental factors. Several lines of evidence suggests the role of miRNAs in causing neurodegeneration or neuroprotection. In the current situation, with the emergence of miRNAs it is now considered that miRNAs play significant role in several mammalian brain-related biochemical pathways, including neuroplasticity and stress responses and contributes to various neurological disorders in humans, like fragile X syndrome (Caudy *et al.*, 2002), Alzheimer's Disease (AD) (Hebert *et al.*, 2010). The correlation between

aberrant expression of miRNA and neurological diseases can be best explained with the fragile X disease. In patients suffering from this disease, there is loss of Fragile X Mental Retardation 1 Protein (FMRP) and that impairs Dicer and RISC functions which are required for miRNA-mediated synaptic plasticity and dendritic development (Maes *et al.*, 2009). There are other experimental evidences which also suggest that if miRNA processing is altered by inactivating Dicer in *Drosophila* that also prevents dendritic development (Maes *et al.*, 2009) and enhances polyglutamine and tau-induced neurodegeneration (Hebert *et al.*, 2010). Loss of midbrain Dopaminergic Neurons (DNs) which is a Parkinson's disease-like phenotype, was observed in conditional Dicer knockout mice in post-mitotic midbrain, which suggested that miRNAs are essential for the terminal differentiation and/or maintenance of multiple neuron types, including midbrain DNs (Kim *et al.*, 2007). In a separate study miRNA profiling on AD affected brain and PBMC was performed and a specific signature was identified. Up-regulated expression of miR-34a, miR-200a and miR-520, let-7f, miR-371 and miR-517/517* was observed in the CSF and PBMC of AD patients. Of note, miR-520h is reported to be highly up-regulated in AD brain (Maes *et al.*, 2009) and its elevated expression in PBMCs of AD suggests that these miRNAs may play an important role in the systemic manifestations of the disease.

1.4. miRNAs in Diabetes

Diabetes is an autoimmune disorder and is often genetically inherited. So far more than 19 Insulin-Dependent Diabetes Mellitus (IDDM) susceptibility loci have been identified in humans. MiRNAs are linked to the regulation of different biological pathways associated and are now widely implicated with the diabetes. In a study, more than 27 miRNAs were observed to be located on 9 human IDDM loci and it was also revealed that some of the miRNAs may target autoimmune- and β -cell-related genes (Zhou *et al.*, 2008). In the diabetic rat model, an altered profile of miRNA expression in insulin target tissues was observed. A growing body of data suggests significant roles of miRNAs in insulin production, secretion and in glucose homeostasis and adipocyte differentiation. Karolina *et al.* (2011), performed an miRNA expression profiling in pancreas, liver, adipose and skeletal muscle and in blood samples from the T2D rat model as well as from Impaired Fasting Glucose (IFG) and T2D male patients and their investigation revealed that four miRNAs i.e. miR-144, miR-146a, miR-150 and miR-182 to be a potential signature miRNAs that distinguished IFG and T2D (Karolina *et al.*, 2011). According to published studies, role of several miRNAs like miR-124a2, miR-195, miR-15a, miR-15b and miR-16 have been identified in regulating pancreatic development (Baroukh *et al.*, 2007; Joglekar *et al.*, 2007). Up-regulation or down-modulation of miR-124a2 can cause either elevated or decreased insulin mRNA levels, respectively (Baroukh *et al.*, 2007). Notably, overexpression of miR-124a in MIN6 cell line was able to decrease glucose-stimulated insulin secretion (Lovis *et al.*, 2008). Krek *et al.* (2005) have shown that miR-375 and miR-124 may share common pathways in the regulation of insulin secretion (Krek *et al.*, 2005). Furthermore, overexpression of miR-410 elevates the level of glucose-stimulated insulin secretion in MIN6 cells (Hennessy *et al.*, 2010). MiR-7 and miR-9 have also been identified as important regulators of insulin secretion (Bravo-Egana *et al.*, 2008). The expression of miR-21, miR-34a and miR-146a was increased in the islets of non-obese diabetic mice during development of pre-diabetic insulinitis (Roggli *et al.*, 2010). Additionally, miR-126 was identified to be involved in the development of insulin resistance induced by mitochondrial dysfunction (Ryu *et al.*, 2011). In diabetic nephropathy, reduced level of miR-25 was seen in the kidney from both diabetic rats and high glucose-treated mesangial cells which indicate

that miR-25 may regulate NOX4 expression and function in diabetic nephropathy (Fu *et al.*, 2010).

1.5. miRNAs in Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a common systemic inflammatory disease. The disease is characterized by inflammation of synovial tissue, progressive cartilage destruction and bone erosion of affected joints (Srivastava *et al.*, 2011). RA is a major cause of disability and is even correlated with increased mortality in severe cases. It is now known that miRNAs are involved in the modulation of inflammatory process in the joints. Several studies demonstrate that in Peripheral Blood Mononuclear Cells (PBMC) of RA high levels of miR-146a, miR-155, miR-132 and miR-16, were observed (Pauley *et al.*, 2008). In a separate, study elevated expression of miR-146a in different cells and tissues of RA patients was observed, that suggest its association with the disease severity (Nakasa *et al.*, 2011). Also, miR-146a expression in RA positively correlated with the levels of TNF- α in both Peripheral Blood (PB) and Synovial Fluid (SF) (Nakasa *et al.*, 2011). Some groups have also provided their input and their data shows that miR-155 and miR-146a are up-regulated, while miR-124a and miR-15a are down-regulated miRNAs in the synovial membrane in RA (Wittmann and Jack, 2011). It was identified and reported that miR-124a regulates the cell cycle (Kawano and Nakamachi, 2011) and miR-155 regulates the metalloproteinases production (Leng *et al.*, 2011) of RA synovial fibroblasts. Furthermore overexpression of miR-15a expression induces apoptosis in these cells (Nagata *et al.*, 2009).

1.6. miRNAs in Inflammatory Bowel Disease

Crohn's Disease (CD) and Ulcerative Colitis (UC) are the two different types of idiopathic Inflammatory Bowel Disease (IBD) (Odze, 2003). This disease is the outcome of an altered immune response to environmental factors in genetically susceptible individuals and the aberrant gene and protein expression signatures. In a study on samples from colon biopsy miRNA microarray profiles was performed and their analysis revealed a distinct miRNA signature. Three miRNAs viz miR-192, miR-375 and miR-422b were downregulated in the UC tissues, whereas eight miRNAs viz miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195 and let-7f were significantly increased in active UC tissues (Dalal and Kwon, 2010). Profiling

done on samples of colon biopsies of 5 patients with chronically active CD and 13 control individuals revealed upregulated expression of miR-23b, miR-106 and miR-191 in tissues from patients with active CD, while miR-19b and miR-629 were downregulated in Crohn's colitis patients (Wu *et al.*, 2010). Studies also demonstrate that miRNA expression profiles correlates with the disease progression.

1.7. miRNAs in Systemic Lupus Erythematosus/Lupus

Systemic Lupus Erythematosus (SLE) is a chronic disease that causes inflammation, pain and swelling. Sometimes it is also called as "great imitator" because it can affect the skin, joints, kidneys, lungs, nervous system and other organs of the body. In SLE patients, expression of miR-146a expression is downregulated in PBMCs as compared to healthy controls. This decrease in miR-146a was associated with disease severity (Ceribelli *et al.*, 2011). Working on the line to get the more insight about involvement of miRNAs, an miRNA profiles in SLE patients, Idiopathic Thrombocytopenic Purpura (ITP) patients and healthy controls was performed that identified a group of 13 miRNAs exhibiting same expression pattern in SLE and ITP whereas, miR-184, miR-198 and miR-21 were observed to have a differential expression in SLE compared to controls (Dalal and Kwon, 2010). In case of ITP, Six miRNAs were downregulated but this downregulation was not observed in patients with SLE. In kidney biopsies taken from lupus nephritis patients, miRNAs are differentially expressed compared to controls (Te *et al.*, 2010).

1.8. Conclusion and Perspective

Growing evidences suggest that miRNAs play important role in a various developmental process including cell proliferation, cell cycle, cell differentiation, metabolism, apoptosis, developmental timing. These miRNAs are either down-regulated or overexpressed in various organs including lung, liver and kidney and exert diverse functions. Several studies have experimentally proved the links between miRNA and various disease conditions including cancer, cardiovascular diseases, arthritis, diabetes, Lupus. Additionally, identification of miRNAs in specific disease could provide impetus for the disease diagnosis, prognosis and evaluation of treatment response. Furthermore, targeting miRNAs may be a novel therapeutic approach in human diseases.

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