REVIEW

MicroRNAs: A new paradigm towards mechanistic insight of diseases

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Abstract: In 1993 miRNAs were discovered during a research on *Caenorhabditis elegans* conducted by Victor Ambros and Gary Ruvkun. The gene lin-4 that played important role in development in *C. elgans* was observed not encoding any protein but a very small RNA molecule of just 22 nucleotides. Main objective of this review is to highlight the significance of miRNAs in regulating the expression of many genes, which are either directly or indirectly involved in many diseases. One of the major causes of illness and death in developed countries of the world is cardiovascular disease. Some of the miRNAs have certain role to play in heart that are not specified for heart. So miRNAs have been found to be in other tissues like fibroblasts, endothelial cells and smooth muscle cells that are part of physiological study of cardiovascular system. Adult heart has limited capacity of regeneration therefore lost cardiomyocytes due to myocardial ischemia or infarction can result in low performance of heart. miRNAs have been shown to play a role in apoptotic regulation of cardiomyocytes *in vivo*. Many studies have shown that miR146a and 155 are up regulated in peripheral blood mononuclear cells, synovial fibroblasts, synovial fluid and Th-17 cells from rheumatoid arthritis patients as compared to healthy persons. Several types of miRNAs are playing important roles in type 1 diabetes mellitus including miR-375 and miR-375 with intolerance to glucose and decreased beta cells account due to impaired proliferation. Up regulation of miR-125a in WAT of type 2 Diabetes mellitus have been observed. miRNAs have proved to be the important regulators of cytokines and growth factor expression. Thus, suggested as a good biomarker and target of therapy. miRNA profiling techniques have revealed the role of miRNAs in Multiple sclerosis.

Keywords: MicroRNAs, treatment, diagnosis, diseases.

INTRODUCTION

In 1993 miRNAs were discovered during a research on *Caenorhabditis elegans* conducted by Victor Ambros and Gary Ruvkun. The gene lin-4 that played important role in development in *C. elgans* was observed not encoding any protein but a very small RNA molecule of just 22 nucleotides. This RNA molecule repressed translation of lin-14 gene during development by annealing to its 3'UTR sequence (Lee *et al.,* 1993, Wightman *et al.,* 1993). Then in 2000, a second small RNA molecule was discovered being the member of miRNA population (Reinhart *et al.,* 2000, Slack *et al.,* 2000). Now hundreds of miRNAs have been discovered. To date 533 miRNAs have been reported in humans in database (miRBase, Wellcome Trust Sanger Institute).

Small number of miRNAs have been doubted to be the regulators of more than one third of total human genes. This suggests that a very small number of cellular processes are regulated by miRNAs in terms of their expression of genes regulating these processes. It is now known that miRNAs are naturally abundant and conserved non-coding RNAs. Targeting the mature mRNA to repress translation is the main scheme of attack which is known as RNA interference (RNAi) (Bartel, 2004; Esquela-Kerscher and Slack 2006).

RNAi or RNA silencing was first described in 1990 in a popular flowering plant. When a gene was inserted in petunia plant genome, it showed stimulating effect on purple pigment gene and inhibited the homologous genes expression. This was then termed as homology-dependent gene silencing. Modulation of central dogma at post-transcriptional level by RNAi machinery was shown by Andrew Fire and Craig Mello in 1998 were awarded Nobel Prize in 2006 in medicine and Physiology for their remarkable piece of work.

Fire and Mello injected single stranded sense and antisense RNA along with double stranded RNA in *C. elegans* and noted their phenotypic effect. Injected dsRNA showed a loss of mRNA expression while single stranded RNAs showed no or very little negative impact on mRNA expression. It was concluded that dsRNA caused the loss of mRNA leading to the change in phenotype. But it was not clear that whether the silencing was acting through transcriptional or post transcriptional

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mechanism. Montgomery *et al.,* (1998) answered this question showing that silencing acts at post-transcriptional level.

RNAi has also been found in many organisms like fruit flies, plants and zebrafish. It was observed that RNAi silencing was observed when mammalian cells were exposed to short (21 nucleotide) ds RNAs (Elbashir *et al.,* 2001). These small dsRNAs were termed as small interfering RNAs (siRNAs) who act as expression blockers of particular mRNA by base pairing(Parrish *et al.,* 2000). In a cell dsRNA is cut into small pieces of 21-25 nucleotides and these RNAs are named as microRNA being an important component of RNAi guided gene silencing (Lee *et al.,* 1993).

Biogenesis of miRNAs and target recognition

Synthesis of miRNA involves transcription by RNA polymerase II to make pri-miRNA, processing into precursor miRNA and maturation of precursor into a mature function miRNA (Beezhold *et al.,* 2010). This long pri-miRNA can be characterized by stem-loop structure formation. Microprocessor molecules frill pri-miRNA precursor through an enzyme known as Drosha to produce a 60-100 nucleotide long pre-miRNA. Thus, formed pre-miRNA moves from nucleus to cytoplasm. The transport involves the RanGTP-dependent process when pre-miRNA binds to exprotin-5 proteins. On arrival to cytoplasm, it is cleaved through an enzyme known as Dicer. The activity of Dicer enzyme produces much more smaller RNA, miRNA which is 22 nucleotide long.

In RNA interference Dicer finally produces 22 nucleotide long siRNA but some Dicer like enzymes particularly Dicer-like1 (DCL-1) complicate miRNA processing in nucleus. Thus, miRNA is a genome encoded siRNA. miRNA targets mRNA while siRNA makes defense against viruses or transposons which makes them different from each other. There is present an additional class of siRNAs known as transacting siRNAs transcribed from genome as polyadenylated dsRNA precursors. These precursor dsRNAs produce a set of phased siRNAs which silence the gene expression. A miRNA has two strands known as guide and passenger strands. They get separated from each other and guide strand binds to its probable target through sequence complementarity. The guide strand contains RISC complex and passenger strand sometimes becomes the part of RISC complex or discarded (Zhou *et al.,* 2010).

A RISC complex with its guide miRNA strand is known as miRISC complex which results in translational repression of target mRNA by steric hindrance of ribosome. The mechanism through which miRNAs find their probable target are still not very clear or fully understood (Bartel, 2009). Whatever the role of miRISC complex plays to repress translation or induces active mRNA, degradation can depend not only on sequence complementarily but also the nature of Ago protein. miRNA will silence the gene expression through miRISC complex. Although partial complementation is for sure stable thermodynamically but target host attachment tends to be modulated and aided by some other factors like target specific binding proteins or even secondary structure of target RNA, or co-localization of host-target RNAs in cell chambers. Accessibility of target sequence is one important factor for miRNA binding to its target RNA. Sometimes target sequence can form a duplex with its own sequence or it may be covered by some RNA-binding protein. It is evident that first 2-8 nucleotides at 5' end are of great importance in target specificity. This particular sequence is known as seed sequence but still has not clear role in target recognition because sometimes there is no need of seed sequence in target recognition. Target location within the target mRNA varies but many of the reports locate them in 3'UTR. miRNA has a significant effect on 3'UTR region as this region is necessary for translation and contains many of the regions that are regulating the stability and localization of mRNA. One of the reason stated is that 3'UTR region is not translated into protein thus translation machinery cannot dislodge annealed miRNPs. It is also noteworthy that several miRNAs may regulate single mRNA and single miRNA may interact and regulate many of the target mRNAs.

Micro RNAs and the cardiovascular system

Functions of miRNA have not been understood fully but there are certain tissues that give the evidence of their presence in living body. Heart is one of these types of tissues (Beuvink *et al.,* 2007, Kloosterman and Plasterk 2006). Some of the miRNAs have certain role to play in heart that are not specified for heart (Townley-Tilson *et al.,* 2010). So miRNAs have been found to be in other tissues like fibroblasts, endothelial cells and smooth muscle cells that are part of physiological study of cardiovascular system. Many of the miRNAs in these tissues are regulated by stress that cardiovascular system faces (Sayed *et al.,* 2007. Matkovich *et al.,* 2010). So it become more evident that cardiac stress responses also involve miRNA expression. A few of the miRNA molecules like miR-128, 302, 367 and 499 are supposed to be purely heart specific miRNAs but they are still needed to be confirmed. One of the miRNA miR-208 is known as heart specific playing regulation of functional and developmental processes of cardiac system. Recent studies have shown that during heart injury these heart specific miRNAs can enter the blood stream making it easier to diagnose heart damage (Wang *et al.,* 2010; Ji *et al.,* 2009). About 25% of miRNA expression consists of skeletal muscle mir-1, 133A, b and miR-206. They are collectively known as miomiRs19. Highly expressed miRNAs in skeletal muscle and cardiac tissue include mir-1, 133a and 133b. Only miR-206 is expressed in skeletal muscles (Kim *et al.,* 2006).

Micro RNAs in cardiovascular diseases

Zhao *et al.*,, 2005 showed that miR-1-1 and miR-1-2 are specific to heart and skeletal muscle precursor cells while miR-1 is regulating ventricular cardiomyocytes. Over-expression of MiR-1 in mouse developing heart produced a small pool of cardiomyocytes (Zhao *et al.,* 2005). Similarly, Kwon *et al.,* 2006 observed miR-1 in Drosophilla modeling the cardiogenesis. Chen *et al.*, 2006 reported miRNA-1 as myogenesis promoter and miR-133 along with miR-1 as myoblast proliferators (Chen *et al.,* 2006). vanRooij *et al.,* 2006 characterized cardiac stress and injury by increased size of cardimyocytes and static number of myocyte (Edwards *et al.,* 2010). More than 12 miRNAs were deregulated during cardiac hypertrophy and failure was shown through microarray analysis (van Rooij *et al.,* 2006). However, miR-195 has shown increased expression during hypertrophic growth of rat cardiomyocytes culturing (van Rooij *et al.,* 2006; Edwards *et al.,* 2010).

One of the major causes of illness and death in developed countries of the world is cardiovascular disease. Gene expression profiles of many genes are one of the most important evidence of heart pathology. Cardiac gene expression is controlled at transcriptional level involving the association of transcription factors and regulatory enhancers leading to gene expression activation (Olson, 2006). Multiple enhancers specify the specific gene expression patterns of cardiac gene expression making it a complex process. One of the cardiac gene expression regulators are miRNAs at transcription level. Recent researches on miRNAs have revealed the significant role of miRNA in heart diseases. Certain processes like cardiovascular development, cardiac fibrosis and arrhythmia have been found to be associated with miRNAs (Liu and Olson 2010; Jiang *et al.,* 2010; Wang *et al.,* 2010).

Cardiac development

Dicer is one major enzyme for miRNA processing. Creating mutations in this enzyme is one way to study the need of miRNA in vertebrate development. Many of the research workers have shown loss of Dicer through Dicer gene disruption in mice leading to lethal effects to embryo before body axis formation due to loss of pluripotent cells (Bernstein *et al.,* 2003) or impaired embryonic angiogenesis (Yang *et al.,* 2005). Impaired angiogenesis also caused insufficient corpus luteum and infertility in mice due to low level expression of Dicer1 (Otsuka *et al.,* 2008). Cre recombinase was used to create mutation in Dicer enzyme to study the role of miRNA in heart development. Cre recombinase production is under the control of a regulator known as Nkx2.5. Activated from E8.5, Nkx2.5 plays its part during heart patterning and differentiation. Embryonic lethality at E12.5 resulted from some developmental defects like pericardial edema, underdeveloped ventricular myocardium. Zebrafish embryo showed these phenotypes consistently when their Dicer was induced with defects (Giraldez *et al.,* 2005). Adult mice died due to lack of Dicer in myocardium showing cardiac hypertrophy and reactivation of fetal cardiac genes programing (da Costa *et al.,* 2008). Rao *et al.,* 2009 produced a mice affected with deletion in muscle specific deletion in DiGeorge syndrome critical region gene 8 (DGCR8) by using muscle creatine kinase (MCK)-Cre mice and of DGCR8 conditional floxed allele. DGCR8 is another important part of miRNA synthesis.

Regeneration and apoptosis of Myocardial cells

Adult heart has limited capacity of regeneration therefore lost cardiomyocytes due to myocardial ischemia or infarction can result in low performance of heart. miRNAs have been shown to play a role in apoptotic regulation of cardiomyocytes *in vivo*. They also have been found to play a crucial role in stem cell differentiation and fate (Xu *et al.,* 2009). Here are some of the miRNAs playing roles in apoptosis of cardiomyocytes.

MiR-199a has been shown to be down regulated in cardiomyocytes in hypoxic conditions by posttranscriptional mechanisms (Rane *et al.,* 2009). The down regulation of miR-199a depressed the expression level hypoxia-inducible factor -1. This hypoxia-inducible factor-1 is one of the most important transcription factors to induce the gene expression during hypoxia (Rane *et al.,* 2009). The down regulation of miR-199a also led to the depression of Sirtuin-1. Sirtuin 1 is responsible for down regulation of prolyl hydroxylase 2. The role of this hydroxylase is to hydroxylate hypoxia-inducible factor-1 to induce its degradation (Rane *et al.,* 2009).

miRNA-195 belongs to miRNA-15 family who has been found to be a target of consistent upregulation during cardiac failure and ischemia. Its overexpression leads to cardiac hypertrophy and dilated cardiomyopathy (van Rooij *et al.,* 2006). Exact role of miRNA-15 is still unclear in heart other studies have shown this miRNA family to induce apoptosis by Bcl-2 down-regulation (Wang *et al.,* 2009).

Different ion channels like sodium, calcium, potassium, and gap junction proteins like connexin43 are the regulators of polarization and depolarization of cardiac cells during contraction and relaxation of heart respectively. These ion channels are targeted by different types of miRNAs like miR-1 and 133 thus playing a crucial role in cardiac conduction and onset of arrhythmias. Zhao *et al.,* 2007 showed that adult miR-1-2 knockout mice have shown alterations in ECGs. These alterations include decreased heart rate, short PR interval and wide QRS complexes. The mice died because of cardiac arrhythmia. These alterations were seemingly because of elevated miR-1 expression target Irx5. miR-1

expression target Irx5 is a regulator of Kncd2 potassium channel important for repolarization (Zhao *et al.,* 2007). miR-1 is upregulated in coronary artery disease. Overexpression of miR-1 aggravated and antagonize miR-induced knockdown relieved arrhythmogenesis on MI most likely via regulation of connexin43 and potassium channel Kir2.1 subunit (Yang *et al.,* 2007). Moreover, miR-1 regulated calcium signaling by targeting B56a subunit of protein phosphatase PP2A (Terentyev *et al.,* 2009).

Fibrosis

The formation of excess fibrous connective tissue in an organ or a tissue during repairing or reaction is termed as fibrosis (Birbrair *et al.,* 2013). Fibrosis can be reactive, benign or pathological condition. If fibrosis is caused by an injury then it is called as scarring fibrosis and if it results from single cell line then a fibroma. Fibrosis brings the deposition of more connective tissues to destroy the function of an organ or tissue.

The activation and multiplication of fibroblasts in cardiac disease results in an appropriate secretion of extracellular matrix proteins and some interstitial fibrosis. Impaired cardiac tissue contractility and changed electromechanical characteristics are the results of fibrosis. Often these complexities lead to arrhythmias. Several miRNAs also face the change in their expression level. Some MI or other fibrotic pathologies play direct and indirect roles in cardiac fibrosis regulation. Liu *et al.,* showed that adult miR-133a double knockout mice developed severe fibrosis and heart attack (Liu *et al.,* 2008). MiR-133 might target connective tissue growth factor. Its downr egulation during heart disorder may result in increased expression and secretion of connective tissue growth factor from cardiac muscle cells. This stimulates extra cellular matrix synthesis in fibroblasts (Duisters *et al.,* 2009). miR-21 is up regulated in failing and hypertrophic myocardium perhaps due to fibroblast multiplication. miR-21 increases the survival of fibroblasts and fibrosis by inhibiting the sprout homolog 1 and activating consecutive extracellular receptor kinase-mitogen-activated protein kinase (Thum *et al.,* 2008). Van Rooij *et al.,* 2008 found that all members of miR-29 downregulate after myocardial infarction. This family is thought to target myriad genes involved in fibrosis for example collagens, fibrillins and elastins.

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a chronic inflammation of joints resulting in deformed and painful joints leading to loss of function. Some other organs other than joints may also show the similar symptoms. Underlying cartilage and bone may also be affected. The process of RA involves inflammation and fibrosis of capsule around joints (Shah and Ankur). RA can also induce inflammation in lungs, myocardium, pleura and whites of eyes. Symptoms and physical examination are clinical diagnostics but laboratory tests, X-rays and synovial fluid examination may add to the diagnosis (Majithia and Geraci, 2007).

Both types of treatments *i.e.,* medical and non-pharmacological are aimed to treat inflammation and damage. Physical therapy, splints, braces, and dietary changes, painkillers and anti-inflammatory drugs are adopted but they cannot control the progression of the disease (Majithia and Geraci, 2007). RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year (Scott *et al.,* 2010). RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year (Scott *et al.,* 2010). In 2013, it resulted in 38,000 deaths up from 28,000 deaths in 1990 (Global Burden of Disease 2013).

Many studies have shown that miR146a and 155 are upregulated in peripheral blood mononuclear cells (Pauley *et al.,* 2008) synovial fibroblasts (Stanczyk *et al.,* 2008), synovial fluid (Murata *et al.,* 2010) and Th-17 cells from RA patients as compared to healthy persons (Niimoto *et al.,* 2010). An important issue for RA pathogenesis is impaired apoptosis of synovial fibroblasts but miRNA dependent regulation of apoptosis is rarely known. Recent researches have shown that miR-34a and miR-34a* are involved in the apoptotic pathways regulation. Their expression is enhanced by demethylation of miR-34a* enhances the apoptosis in FasL and TRAIL stimulated synovial fibroblasts (RASFs). On the other hand, overexpression of mature strand of miR-34a protects the cells from FasL- mediated apoptosis but without having any effect on TRAIL-induced cell death (Niederer *et al.,* 2012).

Another miRNA related to RA is miR-124 involved in cell proliferation. This miRNA targets and regulates CDK2 and monocytes protein-1 thus, proving itself an important regulator of synovial inflammatory milieu in RA (Nakamachi *et al.,* 2009). In another case, miR-346 have been found to be regulated in RA fibroblasts-like synoviocytes (Alsaleh *et al.,* 2009). This miRNA regulates IL-8 release. In RA patients synovial fibroblasts is up-regulated and its elevated levels enhance the secretion of MMP-1 and IL-6 through NF-x B pathway.

In another research, increased levels of miR-363 and lower levels of miR-498 were noted. Let-7a were found to be down regulated in PBMCs in RA (Pauley *et al.,* 2008) whereas, miR132 and 16 were up regulated. Up-regulation of miR-155 expression in PBMCs and fibroblast-like synoviocytes in RA patients showed a protective role against inflammation due to the ability miR155 to offset the expression of IKBKE (Long *et al.,* 2013). Murata *et al.,* 2013 found miR24 and miR-125a-5p

as a RA diagnostic marker. Another marker miR-140 was downregulated in human articular chondrocytes showing its involvement in cartilage development and modulation in IL-1 response (Miyaki *et al.,* 2009). miRNA-323-3P is upregulated in synovial fibroblasts (Xu *et al.,* 2013).

Diabetes mellitus

Diabetes also known as Diabetes mellitus is group of metabolic disorders characterized by high blood sugar levels for relatively a longer period. Symptoms include frequent urination, increased thirst and hunger. Further complications can result if Diabetes mellitus s not treated like accumulation of ketoacidosis and non-ketoic hyperosmolar comma (Kitabchi *et al.,* 2009). Further fetal complications include cardiovascular disease, stroke, chronic kidney failure, ulcers and eye damages.

Diabetes mellitus arises due to insufficient production of insulin by pancreas or the cells may be unable to sense insulin (Shoback *et al.,* 2011; Greenspan's basic & clinical endocrinology (9th ed.). There are mainly two types of Diabetes mellitus i.e., type 1 that results from pancreas failure to produce enough insulin. Type 1 Diabetes mellitusis also known as insulin dependent diabetes mellitus or Juvenile diabetes. The other type of diabetes mellitus is type 2 diabetes mellitus or insulin independent diabetes mellitus (NIDDM) or adult on-set diabetes. In this type of diabetes mellitus, the cells are unable to sense insulin properly.

Several types of miRNAs are playing important roles in type 1 diabetes mellitus. These miRNAs include miR-375 and miR-375 knockout mice showed intolerance to glucose and decreased beta cells account due to impaired proliferation (Poy *et al.,* 2009). This suggests the importance of miR-375 in normal glucose metabolism, alpha and beta turnover and adaptive beta cell growth response to increase insulin need during insulin resistance. Therefore, expression of miR-375 has an indirect impact on type 1 Diabetes mellitus. Many important miRNAs predicting beta cell devastation and regeneration in type1 diabetes mellitus diagnosed children (Nielsen *et al.,* 2012). Twelve miRNAs were found to be up regulated and some of them were associated with apoptosis and beta cells. A tissue specific miR-25 that controls glycemic levels in onset of T1D children may be a biomarker for tissue physiopathology and therapeutic target.

miR-375 regulates glucose-stimulated insulin secretion in a negative way, while its antagomiRs (small synthetic chemically engineered oligonucleotide used to silence endogenous miRNAs) enhance insulin secretion (Tang *et al.,* 2008). Myotrophin (Mtpn) is one target of miR-375. Myotrophin is a protein involved in the distal stage of insulin secretion in pancreatic β-cells but the regulating mechanism is still not clear. However, it has been proposed that this process of regulation is facilitated by NF-κB or its interaction with a protein known as CapZ (actin-capping protein) (Hennessy and O'Driscoll, 2008; Tang *et al.,* 2008). Mice with homozygous deletion of miR-375 showed hyperglycemia due to decreased total pancreatic beta cell mass and insulin levels (Poy *et al.,* 2007) thus increasing total pancreatic alpha cells, fed and fasting blood glucagon levels, gluconeogenesis and hepatic glucose output (Poy *et al.,* 2009).

In contrast, the pancreatic islets of obese (ob/ob) mice, a model of increased β-cell mass, exhibit increased expression of miR-375. Genetic deletion of miR-375 in ob/obmice further diminishes the proliferative capacity of the endocrine pancreas and results in a more severe diabetic phenotype (Poy *et al.,* 2009). This suggests that in addition to regulating insulin secretion, miR 375 plays an important role in pancreatic β-cell development.

Many different studies have identified miRNAs being regulated in adipose tissue from rat and human of T2D. miR-222, 27, 29a, 335, 125a have been found to be upregulated in two studies in T2D (Herrera *et al.,* 2010; Herrera *et al.,* 2009; Takanabe *et al.,* 2008). In cultured 3T3-L1 adipocytes, when cultured in high glucose concentration also showed upregulation of the three miRNAs 222, 27a and 29a (Herrera *et al.,* 2009).

Thus, suggesting an increased expression of these miRNAs may be involved in initial cellular response of adipocytes to hyperglycemia (Herrera *et al.,* 2009). He *et al.,* 2007 showed up regulation of miR-29 in insulin resistance 3T3-L1 adipocytes. They also showed that over expression of miR-29 family inhibits glucose uptake in 3T3 L1 adipocytes by inhibiting insulin signaling. Ling *et al.,* 2009 also showed the up regulation of miR-125a in WAT of type 2 Diabetes mellitus.

Bioinformatics has revealed many target mRNAs involved in glucose metabolism (Herrera *et al.,* 2009). miR-335 was found to be involved in adipocyte differentiation and maturation and to be increased in WAT of obese mice. This miRNA expression increases in WAT of GK (Goto-kakikazi) rats (Nakanishi *et al.,* 2009). An increase in miR-335 expression occurs with the differentiation of cultured pre-adipocytes to adipocytes. This rise in expression of miR-335 is also assisted by increase in expression of some differentiation markers like aP**2** (adipocyte fatty-acid-binding protein 2), PPARγ (peroxisome-proliferator-activated receptor γ) and FAS (fatty acid synthase) (Nakanishi *et al.,* 2009). This phenomenon could be linked to increase in size and number of adipocytes observed in obesity enabling the WAT to store more lipids and fatty acids (Nakanishi *et al.,* 2009).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating neurodegenerative disorder of central nervous system. Both environmental and genetic factors are thought to be involved in development of MS. The thought gets its support by genome wide association studies. Pathology of MS suggests autoimmune etiology and infiltration of T-cells, B-cells and macrophages in active MS. Autoreactive T-cells mediate the immune reaction in CNS. Theses T-cells move through blood brain barrier (BBB) to attack oligodendrocytes and myelin. Adaptive and innate immune systems impart in inflammation and tissue injury (Prat and Antel, 2005; Becher *et al.,* 2006). Altered cytokine profiles including TNF-α, IFN-γ, IL-17, IL-6, and IL-18 also contribute to demyelination, loss of oligodendrocytes and axon degeneration in MS (Lucchinetti *et al.,* 2000; Bjartmar *et al.,* 2003; Imitola *et al.,* 2005).

Furthermore, balance between pro and anti-inflammatory mechanisms also contributes to injury and repair. Many cytokines are involved in existence and differentiation of nerve cells, oligodendrocytes and oligodendrocyte progenitor cells. So, a narrow range of transcriptional and translational regulation is needed to honor such roles of cytokines and chemokines for central nervous system. Recently, miRNAs have proved to be the important regulators of cytokines and growth factor expression. Thus, suggested as a good biomarker and target of therapy.

In humans, miRNAs are playing an important role in modulation of innate immunity against viruses, bacteria and other pathogens. The development and regulation of adaptive immune system is also under the influence of miRNAs.

MS is an autoimmune disorder of nervous system caused by inflammatory and neurodegenerative processes leading to progressive disabilities (Compston and Coles 2008). miRNA profiling techniques have revealed the role of miRNAs in MS (Du *et al.,* 2009 Otaegui *et al.,* 2009; Keller *et al.,* 2009; Junker *et al.,* 2009; Sievers *et al.,* 2010; Santis *et al.,* 2010). miRNAs have been shown to play roles in Th-17 polarization and pathology of MS. miR-326, a Th-17 cell related miRNA has shown distinct role in MS severity. It has also been found to be involved in autoimmune encephalomyelitis (EAE) in mice. When silenced in vivo, miR-326 caused decrease in Th-17 cells and mild EAE whereas over expression resulted in increase in Th-17 cells and severe EAE (Du *et al.,* 2009). The significantly up regulated miRNAs like miR-18b, miR-599 and miR-493 were found in relapsing-remitting MS patients and healthy persons (Otaegui *et al.,* 2009). Microarray technology studies of miRNAs expression showed significant dysregulation of ten miRNAs (Keller *et al.,* 2009). miRNA expression profiles of miR-106b and miR-21 showed an upregulation of these miRNAs in all types of MS and miR-106b falls in miR-17-92 cluster category (Lindberg *et al.,* 2010).

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