

The Role of MicroRNAs in Human Diseases

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Abstract

MicroRNAs (miRNAs) are short RNA molecules which bind to target mRNAs, resulting in translational repression and gene silencing and are found in all eukaryotic cells. Approximately 2200 miRNA genes have been reported to exist in the mammalian genome, from which over 1000 belong to the human genome. Many major cellular functions such as development, differentiation, growth, and metabolism are known to be regulated by miRNAs. Proximity to other genes in the genome and their locations in introns of coding genes, noncoding genes and exons have been reported to have a major influence on the level of gene expressions in eukaryotic cells. miRNAs are well conserved in eukaryotic system and are believed to be an essential and evolutionary ancient component of gene regulatory networks. Therefore, in recent years miRNAs have been studied as a likely candidate for involvement in most biologic processes and have been implicated in many human diseases.

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Background

Since the first draft of human genome was published in February 2001, many new discoveries have been made which have elucidated the complexity of the human genome and subsequently the human proteome. In the past decade, application of genomics and proteomics technologies for early detection of diseases have demonstrated that many types of diseases can be diagnosed at an early stage which would be helpful in initiation of treatment protocols at an earlier time point in the clinic. We have previously reported the application of proteomics technologies for early detection of ovarian cancer^(1, 2, 3), prostate cancer⁽⁴⁾, lymphatic vascular system⁽⁵⁾ and drug-induced cardiac toxicities⁽⁶⁾. Other genomics and proteomics technologies have been employed in a variety of other diseases

in the past decade^(7, 8).

As a result of human genome studies and the discovery of less than 25,000 genes in the human genome, a shift has occurred in the focus of research from mRNAs to noncoding RNAs as a major regulator of human genome. The presence of noncoding RNAs and its role in many human diseases make these molecules important mediators which have to be understood in medical research. We have recently reviewed the role of noncoding RNAs in cancer⁽⁹⁾ and in the present article extend this review in a more comprehensive way to include many other types of diseases that are now known to occur in humans.

In early 90's, it was discovered that two small RNAs (instead of a protein) were the product of *lin-4*, a gene controlling the timing

of larval development of *Caenorhabditis elegans* (*C. elegans*)⁽¹⁰⁾. Later studies revealed that the longer RNA (70 nucleotides) was the precursor of the shorter RNA (22 nucleotides) which is now known as a member of the class of microRNA (miRNA) genes⁽¹¹⁾. By targeting specific mRNAs for degradation and/ or translational repression, microRNAs (miRNAs), a novel class of endogenous, non-coding RNAs (ncRNAs) plays an important role in controlling gene expression⁽¹²⁾. Originally it was thought that *lin-4* gene expression was restricted to *C. elegans*, due to lack of homology with other species. However, in the year 2000 the miRNA gene (*let-7*) (product of *lin-4* gene precursor) was discovered to target *lin-41* (a protein coding gene) in many species⁽¹³⁾. Since then large amounts of microRNAs have been identified in mammals⁽¹⁴⁾.

Members of ncRNAs include microRNAs (miRNAs) and small nucleolar RNAs (snoRNAs) that are known to have well preserved functions in various species. The conservation of ncRNAs' activities in mediating the binding of RNA-enzymes to target RNA complexes results from their specific hybridization to other nucleic acids in the cell and their targeting ability of different cellular targets⁽¹⁵⁾. Such specific functions are thought to limit sequence co-variation and tendency to evolution⁽¹⁶⁾. As the human genome and its functions are rapidly being deciphered, the roles of miRNAs are becoming more evident in specific cellular functions. For example, miRNAs and a large set of ncRNAs including: Air, H19, Ipw, NTT, Tsix and XIST in mammals (known as “gene regulators”) have been proposed to have different functions ranging from imprinting to inactivation of X-chromosome in mammals⁽¹⁷⁾.

The biogenesis of miRNAs (Figure 1) involves multiple steps and specific cellular machinery⁽¹⁸⁾. miRNAs are encoded as short inverted repeats having a double-stranded RNA (dsRNA) stem loop about 70 bp long and are found in both introns and intergenic clusters in the genome⁽¹⁸⁾. RNA polymerase

II is responsible for the synthesis of the introns and exons of both protein-coding and non-coding transcripts from where miRNAs are derived⁽¹⁹⁾. In the nucleus, miRNAs are transcribed as primary pri-miRNA transcripts and then are processed to form the precursor pre-miRNA stem loop structure before transportation into the cytoplasm [where they are cleaved by the Dicer RNAase III endonuclease and produce mature miRNA (21-23 nucleotides)]⁽²⁰⁾.

MicroRNAs in Human Genome

Many major cellular functions such as development, differentiation, growth, and metabolism are regulated by miRNAs and approximately 2200 miRNA genes have been reported to exist in the mammalian genome⁽²¹⁾. One third of the human genome is estimated to be regulated by miRNAs⁽²²⁾. The precise mechanisms 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⁽²³⁾. 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^(24, 25). It is estimated that about 50% of miRNAs expressed in the genome are transcribed from non-protein-coding genes and the remaining miRNAs are coded in the introns of coding genes⁽²¹⁾.

In higher eukaryotic organisms, almost the entire genome (97%) is transcribed as non-coding RNA (ncRNA) which consist of rRNA, tRNA, introns, 5' and 3' untranslated regions, transposable elements, intergenic regions, and microRNAs^(12, 26). Recently, it has been suggested that mammalian miRNAs are derived from DNA repeats and transposons⁽²⁷⁾. Such reports have lead the scientific community to re-evaluate the functional role of transposons, especially because it appears that the specific sequences of transposons can play a major role in the developmental processes and epigenetic variations^(28, 29). Furthermore, it has

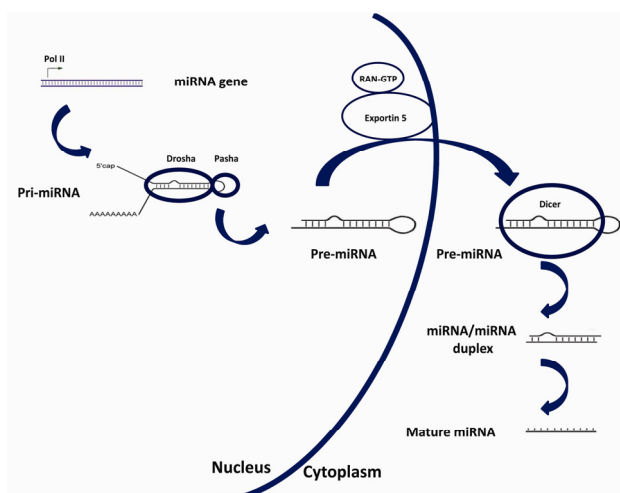


Figure 1. The biosynthesis pathway for miRNAs

been recently demonstrated that miRNAs can be derived from processed pseudogenes⁽³⁰⁾, which were once believed to have no cellular functions (Figure 2).

Most recent sequence analyses of the human genome demonstrates that the protein coding genes may be as low as 25,000⁽³¹⁾. 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 analyses indicate that the Open Reading Frames (ORFs) comprise less than 2%, repetitive sequences around 46%^(32, 33) and non-

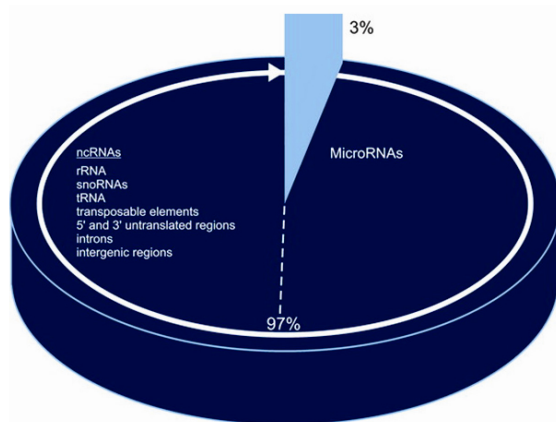


Figure 2. Coding and non-coding DNA in human genome

coding parts of protein-coding genes (introns, 5' and 3'-UTRs) an estimated 25–27%⁽³⁴⁾ of the 3.2 billion bases in the human genome.

MicroRNAs in Other Genomes

In addition to their major presence in the human genome, microRNAs have been shown to be involved in regulation of genes in higher eukaryotes⁽³⁵⁾. The rapid growth of research in the field of miRNAs is observed in the number of entries in the miRNA registry (version 1), with only 218 entries in 2002 and about 6500 entries in 2008 (version 11)^(36, 37). The sequence analyses of genomes in eukaryotes indicate that simple unicellular organisms, invertebrates and mammals have 10-40%, 70-90% and 98% of their genomes composed of noncoding DNA regions, respectively⁽³⁴⁾.

The cellular functions of miRNAs appear to vary in eukaryotes, including regulation of leaf and flower development in plants⁽³⁸⁾ and modulation of differentiation of hematopoietic cells in mammals⁽³⁹⁾. The fact that many micro RNAs' sequences are conserved among distantly related organisms indicates that miRNAs are involved in basic cellular processes⁽⁴⁰⁾.

MicroRNAs in Human Diseases

MicroRNAs 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^(15, 41 - 44). Other regulatory roles include neuronal gene expression⁽⁴⁵⁾, brain morphogenesis⁽⁴⁶⁾, muscle differentiation⁽⁴⁷⁾, and stem cell division⁽⁴⁸⁾.

The role of miRNAs as a major source in the development of cancer is still very much unappreciated⁽⁴⁹⁾. But altered patterns of miRNAs in cells have been shown to be responsible for changes that cause cells to make a decision to turn malignant⁽⁵⁰⁾.

MicroRNAs are now recognized to play a pivotal role in the regulation of certain processes related to development in all eukaryotes and because of their potential role as

agents controlling cell growth and differentiation, they have been proposed to be good candidates for cancer therapy^(51, 52).

MicroRNAs' deficiencies or excesses have been linked to a number of other clinically important diseases ranging from myocardial infarction to autoimmune disease. Single point mutations in miRNA or its target or epigenetic silencing of miRNA transcription units is a mechanism by which the functions of miRNA in cell are affected⁽⁵³⁾. Great discoveries and rapid progress in the past few years on miRNAs provide the hope that miRNAs will in the near future have a great potential in the diagnosis and treatment of many diseases. In the following pages, the role of miRNAs as important new regulatory molecules in different human diseases will be reviewed⁽⁵⁴⁾.

MicroRNAs in Cancer

It is now well documented that up-regulation or down-regulation of miRNAs occurs in various human cancers⁽⁹⁾. Over-expressed miRNAs may function as both oncogenes (through down-regulation of tumor-suppressor genes) and/ or regulator of cellular processes such as cell differentiation or apoptosis^(55, 56).

Unique miRNA expression profilings have been demonstrated for many types of cancer. A list of such profiles for reproductive cancers (breast, ovary, and endometrioid adenocarcinoma) and colon, hematological cancers (AML, ALL, CML, CLL), esophagus, gastrointestinal, lung, bladder, and thyroid tumors are shown in tables 1 and 2, respectively⁽⁹⁾. It

has been predicted that microRNAs will have a great potential to be used in diagnosis and treatment of cancer in the near future (Tables 1-3).

Endothelial cells are known to play a major role in the angiogenesis process. In recent studies^(57 - 59) the mirRNA expression pattern (known for its tissue and cell type specificity) in endothelial cells has been demonstrated to include let-7b, miR-16, miR-21, miR-23a, miR-29, miR-100, miR-221, and miR-222. The regulation of miRNAs during patho-physiological processes has been suggested to help uncovering the role of miRNAs in vascular cells. For example in two recent reports^(60, 61), the regulation of miRNAs in vascular cells in response to serum and hypoxia have been studied. In one study⁽⁶⁰⁾ the pro-angiogenic miR-130a is expressed at low levels in quiescent HUVEC and is up-regulated in response to foetal bovine serum. In another study⁽⁶¹⁾ hypoxia was shown to induce miR-210 expression in endothelial cells. The overexpression of miR-210 was reported to be associated with the enhanced formation of capillary-like structures whereas inhibition of miR-210 expression was linked to decreased tube formation and migration⁽⁶²⁾.

miR-221 and miR-222 are among the highly expressed miRNAs in HUVEC that exhibit anti-angiogenic effects⁽⁵⁹⁾. Similar observations were reported⁽⁵⁷⁾ for the anti-angiogenic function of miR-221 miR-222 in endothelial cells. This study also showed that the overexpression of miR-221 and miR-222 also indirectly reduces the expression of the endothelial Nitric Oxide Synthase (eNOS)⁽⁵⁷⁾

Table 1. miRNAs in reproductive cancers⁽⁹⁾

Cancer type	miRNA	Up/Down Regulation
Breast	miR-21, miR-155, miR-23, and miR-191	Up
	miR-205, miR- 145, miR-10b, and miR-125b	Down
Ovary	miR-200a, miR-200c, and miR-141	Up
	miR-199a, miR-140, miR-145, and miR125bl	Down
Endometrioid adenocarcinoma	miR-205, miR155 miR 200a, 200b, 200c	Up
	miR-193a, 193b	Down

Table 2. miRNAs in cancer ⁽⁹⁾

Cancer type	miRNA	Up/Down Regulation
Colon	miR-let 7g, miR-21, miR-20a, miR-17- 19 family, miR 31, miR 135, miR-181b, and miR 200c	Up
	miR-34, miR-let7, miR 143, miR 145, miR-133b, and miR- 126	Down
AML	Has- miR- 191, 199a, miR 155	Up
CML	miR-17-5p, miR-173p, miR- 18a, miR-19a, miR-19b-1, miR- 20a and miR- 92a-1	Up
CLL	miR-21, miR 150, miR-155	Up
	miR- 15a, miR16, miR-29, miR143, miR-45, miR-30d, miR- let 7a, miR-181a	Down

Nitric oxide (NO) is an important molecule in regulating endothelial cell growth ⁽⁶³⁾, migration ⁽⁶⁴⁾, vascular remodeling ⁽⁶⁵⁾, and angiogenesis ⁽⁶⁶⁾ and its impaired bioavailability is the cause of diseases including: atherosclerosis and ischemic cardiomyopathy ⁽⁶⁷⁾. Recently it was demonstrated that eNOS also plays a major role in the mobilization and functional activity of stem cells ^(68 - 70); therefore, designing miRNAs to target eNOS is thought to regulate vasculogenesis ⁽⁶²⁾.

MicroRNAs in Cardiovascular Disease

The homeostasis of the vascular system depends on the functionality of endothelial cells and coordinated regulation of angiogenesis, vasculogenesis, and vessel regression. Little is known about the regulatory machinery at the gene expression level during neovascularization and vascular remodeling ⁽⁶²⁾. However, the discovery of microRNAs in recent years has made it evident that these RNA molecules have an important function in regulation of heart function ⁽⁷¹⁾ and mammalian cardiovascular system in general ⁽⁷²⁾.

The miRNA expression levels have been linked to deregulation of developmental processes and disease states, such as cardiac hypertrophy and failure. Many miRNAs are expressed in a tissue-cell-specific manner ⁽⁷³⁾ and in adult cardiac tissue, miR-1, miR-16, miR-27b, miR-30d, miR-126, miR-133, miR-143, and the let-7 family are abundantly

expressed ⁽⁷⁴⁾. Studies have shown that three miRNAs (miR-1, miR-133, and miR-208) are highly expressed in the heart ^(23, 75) and are important regulators of heart development and myocyte differentiation ^(72, 76 - 78). Recently, deregulated expression of miR-1 and miR-133 were reported in human heart failure ^(71, 79, 80).

Cardiac Failure

Severe cardiac remodeling with detrimental outcomes can result from disturbances in the physiological stimuli to the heart ⁽⁸¹⁾. One of the major responses of the heart to such stimuli is an extensive tissue remodeling known as pathological hypertrophic growth. Although the precise mechanisms involved in cardiovascular biological functions are not known, an increasing number of studies suggest that miRNAs are important regulators of cardiovascular growth, proliferation, cell differentiation, and apoptosis.

Cardiac hypertrophy in humans is a major determinant of mortality and morbidity in cardiovascular diseases. Because miRNAs are important regulators for the differentiation and growth of cardiac cells, they are hypothesized to have an important role in cardiac hypertrophy and heart failure ⁽⁸²⁾. Indeed, several recent reports have found aberrant expression of miRNAs in diseased hearts and vessels. miR-23a, miR-23b, miR-24, miR-195, miR-199a, and miR-214 were upregulated during cardiac hypertrophy (Table 4),

Table 3. miRNAs in cancer ⁽⁹⁾

Cancer type	miRNA	Up/Down Regulation
Esophagus		
	miR-194, miR- 192, miR-200c	Up
	miR- 203	Down
Gastrointestinal		
	miR-106b- 25	Up
	miR-15b, miR- 16	Down
Lung		
	has-mir-21 and has-mir- 205, miR- 17-92	Up
	has-mir-126*, miR-let 7, hsa-let-7a-2, let-7f-1	Down
Bladder		
	miR-2 23, miR- 26b, miR- 221, miR- 103-1, miR-185, miR-23 b, miR- 203,miR 17-5p, miR-23, miR- 205	Up
	miR-29c, miR-26a, miR-30c, miR- 30e-5p	Down
Thyroid tumors		
PC	miR- 146 b, miR- 221, miR- 222, miR- 181b, miR- 155, miR- 224	Up
AC	miR-30d, miR-125b, miR- 26a, miR- 30a- 5p	Down

and their over-expression in cardiomyocytes *in vitro* caused an induction of hypertrophic growth. Interestingly, miR-24, miR-125b, miR-195, miR-199a, and miR-214 were similarly upregulated in the tissue of patients with end-stage failing human hearts ⁽⁷⁴⁾.

Cardiac arrhythmias are still considered a serious health problem because of their sudden, unpredictable and potentially fatal nature. In human hearts with coronary heart disease and the rat model of myocardial infarction, it has been shown that the muscle-specific miRNA (miR-1) is upregulated in ischaemic heart tissue ⁽⁶¹⁾. Furthermore, the results of this study show that the injection of mature miR-1 exacerbates arrhythmogenesis, whereas inhibition of miR-1 by an antisense inhibitor suppresses arrhythmias. When the genes for the ion channels GJA1 and KCNJ2 were silenced, these proteins were shown to be important in mediating the miR-1-induced arrhythmogenic effect ⁽⁶¹⁾. The investigation into the role of miRNAs as a novel class of gene regulators in cardiovascular disease is a new frontier for research and it is hoped that the next decade will bring a greater understanding to their functions in cardiovascular biology ⁽⁸²⁾.

MicroRNAs in Inflammatory Disease

Inflammation is an essential component of host defense system and a major response to infection and injury, which is believed to contribute to multiple acute and chronic diseases ^(83,84). Recently a number of studies have investigated the role of miRNAs in vascular inflammation and leukocyte activation and their infiltration into the vascular wall. Indeed, a recent study ⁽⁸⁵⁾ provides the first evidence that miRNAs control vascular inflammation.

In this study, miR-126 was demonstrated to inhibit the expression of vascular cell adhesion molecule 1 (VCAM-1), which is required to mediate leukocyte adherence to endothelial cells. In macrophages, miR-155 has been shown to be induced by cytokines such as TNF α and IFN- β ^(86, 87) and contribute to physiological granulocyte/ monocyte expansion during inflammation ⁽⁸⁸⁾. Furthermore, miR-155 is reported to be required for B and T lymphocyte and dendritic cell function ^(89, 90). At the gene level, the transcription factor Pu.1 has been identified as a direct target of miR-155 in B cells ^(62, 90).

Table 4. miRNAs in human diseases

Disease type	miRNA	Up/Down Regulation	References
Cardiac hypertrophy			
	miR-23a, miR-23b, miR-24, miR-195, miR-199a, and miR-214	Up	74
Down syndrome			
	miR-99a, let-7c, miR-125b-2, miR-155 and miR-802	Up	133
Alzheimer			
	miR-9, miR-128a, miR-125b	Up	140
Rheumatic arthritis			
	miR-155, miR-146	Up	156
Systemic lupus erythematosus			
	miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR 342, miR-299-3p, miR-198 and miR-298	Up	165
	miR-196a, miR-17-5p, miR- 409-3p, miR-141, miR-383, miR- 112, and miR-184	Down	
Psoriasis			
	miR-203	Up	183

Another study ⁽⁹¹⁾ has demonstrated that miR-181 is involved in regulation of haematopoietic lineage differentiation and several miRNAs have been reported to regulate B-cell differentiation, including the miR-17-92 cluster and miR-150 ^(92 - 94). During monocyte differentiation, the transcription of miR-424 has been shown to increase and regulate the translation of the transcription factor NFI-A involved in monocyte/ macrophage differentiation ⁽⁹⁵⁾. Moreover, miR-146 is found to be induced in macrophages by several microbial components and proinflammatory cytokines ⁽⁹⁶⁾. Finally, the myeloid-specific miR-223 is reported to be involved in regulation of granulocyte differentiation and activation during inflammation ^(62, 97). The role of miRNAs in regulation of every major cell type important in modulation of the immune system indicates that they can be potentially used in immune therapies.

MicroRNAs in Neurodevelopmental Disease

MicroRNAs are highly expressed in human and other mammalian brains relative to other organs ^(98 - 100). The results of high-throughput sequencing experiments suggest that the

number of miRNAs expressed in human brain should be over 1000, although currently this number stands at about 550 in all humans ⁽¹⁰¹⁾. The expression of miRNAs in brain changes during brain development. Therefore, some miRNAs are expressed more abundantly during early development in the mammalian brain, and some are expressed less during later development ^(102, 103). The changes in miRNA expression levels in brain during development may represent biochemical signals for cell fate determination, apoptosis and/or cell division programming ⁽¹⁰⁴⁾. Studies ⁽¹⁰⁵⁾ have shown that some miRNAs are differentially expressed in neuronal nuclei, and/or different cell populations in brain ⁽¹⁰⁶⁾.

Because miRNAs are known to be dynamically regulated in neurogenesis and brain development ^(107, 108), it is believed that miRNAs are also involved in neural development and play an important role in mediating neuronal plasticity. One of the major common traits linking many of the neurodevelopmental disorders [*e.g.* intellectual disability, autism, Attention Deficit Hyperactivity Disorder (ADHD) and epilepsy] is that disease onset occurs during periods of maturation and development ⁽¹⁰⁹⁾. Therefore, it is very likely

that miRNAs contribute significantly to the pathogenesis of neurodevelopmental disorders at the molecular level⁽¹¹⁰⁾.

As for the role of non-coding RNAs (especially mirRNAs) in human brain, it is speculated that these molecules may help the generation of complexity required for brain functions from approximately 25, 000 human protein-coding genes^(106, 111, 112).

A. Fragile X syndrome

Fragile X Syndrome (FXS) is the first genetic disorder linked to the miRNA pathway^(113 - 115). The clinical manifestations of FXS include: learning disabilities, severe cognitive or intellectual disabilities and delays in speech and language development⁽¹¹⁶⁾. The fragile X mental retardation-1 (*FMR1*) gene is associated with a massive unstable CGG trinucleotide repeat expansion within the gene's 50 untranslated region (50-UTR)^(117 - 119).

The functional FMR1 gene product, Fragile X Mental Retardation Protein (FMRP), belongs to a small and highly conserved RNA-binding protein family^(120 - 124) and functions as a suppressor of target mRNA translation via binding of non-coding RNA structures within the UTRs of target mRNAs^(110, 125 - 128).

Recombinant human FMRP has been shown to be able to act as an acceptor for Dicer-derived miRNAs, and significantly, endogenous miRNAs are found associated with FMRP in both flies and mammals^(113 - 115). This interaction is presumed to regulate translation of target mRNAs and demonstrates the involvement of miRNA machinery in inducing the genetic Fragile X syndrome.

B. Rett syndrome

The X-linked dominant Rett syndrome (RTT)⁽¹²⁹⁾ is a progressive neurodevelopmental disorder and one of the most common causes of mental retardation and involves de novo mutations in MECP2 gene known to cause aberrations in the DNA methyl-CpG-binding protein, MeCP2^(110, 130). Interestingly, it has been demonstrated that in postnatally cultured rat neurons, miR-132 directly repress

the expression of MeCP2. This observation may indicate that the role of miRNA is important in regulation of MeCP2 as a mechanism by which normal neuronal development and synaptic maturation in the postnatal brain is maintained⁽¹³¹⁾. The role of MeCP2 in direct regulation of the expression of miRNA genes and the role of miRNA(s) in the pathogenesis of RTT is still being determined.

C. Down syndrome

Down Syndrome (DS) results from triplication of all or part of human chromosome 21 and affects 1 in 700 newborns and is manifested with variable phenotypes such as congenital heart defects, craniofacial abnormalities and cognitive impairment⁽¹³²⁾. Recently, bioinformatic analyses of chromosome 21 have revealed that five miRNAs (miR-99a, let-7c, miR-125b-2, miR-155 and miR-802) are encoded on this chromosome. Interestingly, all five miRNAs have been shown to be overexpressed in fetal brain and heart tissues from DS individuals, suggesting a role in the cognitive and cardiac defects observed in DS (Table 4)^(110, 133).

In general, individuals with DS exhibit lower blood pressure and lower angiotensin II type 1 receptor (AGTR1) protein levels than those without DS. Recent study⁽¹³⁴⁾ has reported that miR-155 downregulates AGTR1, a human gene associated with hypertension; thus providing potential evidence that miRNAs contribute to the DS phenotypes.

D. Alzheimer's disease

Dysregulated miRNA expression has been reported in the brain of Alzheimer patients⁽¹³⁵⁾. Specific miRNAs have been demonstrated to be linked to the pathogenesis of Alzheimer's Disease (AD). For example, loss of miR-29 cluster has been shown to be associated with increased (beta-amyloid precursor protein-converting enzyme) BACE1/beta-secretase expression in sporadic AD patients⁽¹³⁶⁾. Furthermore, miR-298 and miR-328 have been identified to directly interact with the 30-UTR of the BACE1 transcript that is involved in b-amyloid production⁽¹³⁷⁾. Recently, the miR-20a family (i.e. miR-20a,

miR-17-5p and miR-106b) has been demonstrated to regulate the expression of Amyloid Precursor Protein (APP) raising the possibility of a role for these micro RNAs during AD development^(138, 139).

DNA arrays were employed to analyze and evaluate the expression of a subset of 12 miRNAs in the AD hippocampus in comparison with non-demented controls and fetal brain^(140, 141). The results of the expression profiling showed that miR-9, miR-128a and miR-125b are elevated in AD hippocampus (Table 4)⁽¹⁴⁰⁾. In another study⁽¹⁴¹⁾, cultured human fetal brain-derived primary neural (HN) cells were shown to be induced for production of Reactive Oxygen Species (ROS) in presence of metal salts such as aluminum and iron sulfates. Simultaneously, these cells were demonstrated to have increased expression of miR-9, miR-128 and to a lesser extent miR-125b, suggesting that ROSs influence AD brain through pathways specifically mediated by miRNAs. Further clarifications of the role of miRNAs in development of AD remain to be elucidated in the future.

E. Huntington's Disease

Huntington's Disease (HD) is a neurodegenerative disease resulted from CAG expansion in the gene encoding the protein huntingtin (Htt). The manifestations of HD include cognitive defects and motor control impairment which lead to neuronal dysfunction characterized by progressive loss of cortical and striatal neurons⁽¹⁴²⁾. How this process is regulated is not precisely known; however many potential miRNA targets have been predicted in the brains of HD sufferers. In the cortex of the mouse model of HD (R6/2), out of the seven target miRNAs which were found to be expressed after 40 cycles of qPCR, four microRNAs (mir-29a, mir-124a, mir-132 and mir-135b) displayed significant reduction in expression⁽¹⁴³⁾.

Interestingly, among the dysregulated miRNAs found in the cortex of the mouse model of HD, mir-124a and mir-132 are known for their important neuronal-specific

activity. These results indicate that widespread and significant dysregulation of target miRNAs takes place in the brains of R6/2 animals. In tissue samples from human unaffected individuals ('WT') and HD-sufferers ('HD'), target miRNAs, mir-29a, mir-124a, mir-132 and mir-330 have been detected but not shown to be significantly over or under expressed at any specific pathologic state in HD⁽¹⁴³⁾.

Some investigators have suggested that the results from mouse and human samples cannot be compared because they are taken from different regions and are from different species. Although no experimentally validated target mRNAs have been reported for the miRNAs in the brain of HD patients, transcriptional dysregulation of miRNAs in human HD cortex has been shown and further studies are needed to establish the association between miRNAs and HD in the clinic.

F. Schizophrenia

Schizophrenia is a neuropsychiatric disorder that approximately affects 1 in 100 individuals in a general population⁽¹⁴⁴⁾. Schizophrenia is a heritable disorder^(145, 146) and Brain-Derived Neurotrophic Factor (BDNF) has been shown to play an important role in the regulation of the development and synaptic maintenance of a variety of neurons in the CNS including GABA and glutamatergic neurons^(147, 148). Furthermore, BDNF may regulate type 3 dopamine receptor (DRD3) expression during brain development^(149 - 151).

Recent bioinformatic investigations have indicated that two newly described miRNAs, hsa-mir-1 and hsa-mir-206, may target the 30-UTR of BDNF⁽¹⁵²⁾. This suggestion provides credence to the hypothesis that miRNA could regulate BDNF protein synthesis by interfering with BDNF mRNA translation during brain development.

MicroRNAs in Autoimmune Disease

Results from both cell culture and animal studies indicate that miRNAs have an important role in regulation of normal immune functions and prevention of autoimmunity.

What is not clear yet is the precise mechanism(s) by which miRNA dysregulation could lead to pathogenesis in an autoimmune disease. In the following sections some possible roles for miRNAs in regulation of two of the most significant autoimmune diseases [i.e. rheumatoid arthritis (RA)] and Systemic Lupus Erythematosus (SLE) will be reviewed⁽¹⁵³⁾.

A. Rheumatoid arthritis (RA)

In a recent study⁽¹⁵⁴⁾, an abnormal expression of miRNAs was reported in patients with RA. Specifically, two microRNAs (miR-155 and miR-146) were found to be expressed at a significantly higher level in synovial tissues and synovial fibroblasts isolated from patients with RA, relative to healthy controls (Table 4). Interestingly, the levels of both these miRNAs were found significantly upregulated in synovial fibroblasts from patients with RA following TNF/interleukin (IL)-1 β stimulation^(155, 156).

Evidence from mouse 3'-UTR mutational studies has implicated an interaction between miRNAs and TNF transcripts^(157, 158). In the near future, the identification of candidate miRNAs that target genes implicated in rheumatic disorders should increase our molecular understanding responsible for rheumatic disease. Furthermore, Inducible Costimulator (ICOS) was recently reported to be a target of miR-101⁽¹⁵⁹⁾, and ICOS-deficient mice are shown resistant to collagen-induced arthritis without any signs of joint tissue inflammation⁽¹⁵⁶⁾.

Pathogenesis of RA has been associated with the viral infections such as *Epstein-Barr Virus (EBV)*, chronic *Hepatitis C Virus (HCV)*, *HIV* and Kaposi's-sarcoma associated herpes^(160, 161). Variety of reports indicates that viruses have the ability to encode their own miRNAs and these viral-encoded miRNAs can control the expression of viral transcripts and suppress the host immune response during infection⁽¹⁶²⁾. For example, miR-UL112-1 expressed by the human cytomegalovirus has been demonstrated to target

the major histocompatibility complex class 1-related chain B⁽¹⁶²⁾. Also, miR-K12-11 encoded by the Kaposi's-sarcoma-associated herpes virus, has been reported to down-regulate the expression of numerous similar cellular target mRNAs⁽¹⁶³⁾. Therefore, it is possible that viral-encoded miRNAs by targeting different host proteins can induce inflammatory arthritis⁽¹⁵⁶⁾.

Three studies have demonstrated alteration of miRNA expression in RA patients compared to controls^(154, 155, 164). Specifically, increased miR-155 and miR-146a expression in RA synovial fibroblasts have been in comparison to those patients with Osteoarthritis (OA)⁽¹⁵⁵⁾.

B. Systemic Lupus Erythematosus (SLE)

SLE is a systemic inflammatory autoimmune disease with diverse clinical manifestations including photosensitivity, arthritis, glomerulonephritis, and neurological disorders. In a recent microarray analysis of miRNA expressions in SLE patients, seven miRNAs (miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112, and miR-184) were found downregulated and nine miRNAs (miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR-342, miR-299-3p, miR-198, and miR-298) upregulated compared to healthy controls (Table 4)⁽¹⁶⁵⁾. The miRNA profiling of kidney biopsies from lupus nephritis patients showed sixty six differentially expressed miRNAs (36 upregulated and 30 downregulated) when compared to healthy controls⁽¹⁶⁶⁾. Of course, further studies are required to determine if the differential expression of these miRNA in SLE patients are reproducible⁽¹⁵³⁾.

MicroRNAs in Liver Disease

The liver is composed of many cell types and each cell type may have a distinct miRNA expression profile. In recent years, an increasing understanding of miRNA functions in liver physiology and disease and identification and validation of miRNA targets have gained a lot of attention⁽¹⁶⁷⁾.

A. Viral hepatitis

Viral genes encode miRNAs and these miRNAs have a regulatory effect on the viral protein-coding genes⁽¹⁶⁸⁾. Using computational approaches, *Hepatitis B Virus (HBV)* has been found to encode a candidate pre-miRNA, suggesting that *HBV* has the capacity to use viral miRNAs to regulate its own gene expression⁽¹⁶⁹⁾. miRNAs from the host cells may also play a role in regulating viral genes^(168, 170, 171). It has recently been reported that miRNA-122 facilitates the replication of *Hepatitis C Virus (HCV)* by targeting the viral 5' non-coding region⁽¹⁷²⁾.

Expression of a total of 30 cellular miRNAs in hepatocytes has been shown to be influenced by IFN- α/β or IFN- γ . Interestingly, in this study, eight of the miRNAs (miR-1, miR-30, miR-128, miR-196, miR-296, miR-351, miR-431 and miR-448) were shown to be upregulated which also have an almost perfect complementarity with HCV RNA genomes. This suggests that these miRNAs are capable of inhibiting HCV replication and infection⁽¹⁶⁷⁾.

B. Polycystic liver diseases

The polycystic liver and kidney diseases have heterogeneous etiologies and are caused by mutations in two genes, PKD1 and PKD2⁽¹⁷³⁾. Autosomal Recessive Polycystic Kidney Disease (ARPKD) can present in neonates with massive renal cysts and recent study by Lee et al, 2008, provides data to support a role for miRNA. In this study, it was demonstrated that levels of the miR15a was decreased in livers of patients with ARPKD. The findings in this study indicate that changes in miRNA expression contribute to the phenotypic changes found in cystic liver disease⁽¹⁷³⁾.

MicroRNAs in Skeletal Muscle Disease

The muscular dystrophies are a heterogeneous group of disorders involving degeneration of skeletal muscle. Recent studies provide evidence to support a role for miRNAs in the regulation of muscle development. The roles of miRNAs in myogenesis have been mainly from studies on

muscle-specific miR-1, miR-133 and miR-206⁽¹⁷⁴⁾. Recently unique miRNA signatures have been found in Duchenne muscular dystrophy^(175, 176).

It has been demonstrated that diagnosis of Facioscapulohumeral muscular dystrophy (FSHD) could be distinguished from Duchenne muscular dystrophy based on the level of miRNAs-381 and miRNAs-382 expressions in FSHD patients⁽¹⁷⁵⁾. Other studies have also shown a significant up-regulation of miRNAs-100, 103 and 107 in certain myopathies⁽¹⁷⁶⁾.

MicroRNAs in Skin Disease

The involvement of miRNAs in hair follicle morphogenesis, autoimmune and chronic inflammatory diseases affecting skin has been proposed^(177 - 181). Dermal fibroblasts are important cells involved in the wound healing process⁽¹⁸²⁾. Analysis of the potential involvement of miRNAs in regulating the transition to proliferation has been performed and a cluster of 33 miRNAs were reported to be involved in regulation of expression of target genes required for the entry of fibroblasts into the cell cycle and proliferation⁽¹⁷⁸⁾. A recent review has outlined the potential importance of miRNAs' involvement in wound angiogenesis and abnormal healing sequence in chronic wounds^(179, 183).

Psoriasis

Psoriasis is a chronic inflammatory skin disease and genetic and environmental factors are thought to be involved in pathogenesis of the disease. It is widely accepted that psoriasis results from impaired communications between the immune system and the structural cells of the skin^(180, 184, 185). The psoriasis-associated miRNAs have been identified in the skin and miR-203 was found to be expressed more than 100-fold higher in skin compared to other organs (Table 4). Expression analyses of psoriasis-associated miRNAs (miR-203, miR-146a, miR-21, and miR-125b) in cells that present in healthy and psoriatic skin (keratinocytes, dermal fibro-

blasts, melanocytes, and leukocyte/ immune cell subsets) have been shown to have a distinctive expression pattern⁽¹⁸³⁾. Such studies demonstrate that psoriasis-specific miRNA are involved in the the pathogenesis of psoriasis.

Perspective

One of the most exciting findings of human genome project has been the discovery of a major class of non-coding protein RNA molecules. The findings of human genome project have demonstrated that the DNA molecules previously known as "junk DNA", is now actively transcribed and code for miRNAs. Studies now provide evidence that miRNAs play a pivotal role in a variety of developmental processes and disease as reviewed in the present article.

miRNAs as a special class of non-coding RNAs can post-transcriptionally regulate gene expression in a negative manner; therefore, it is predicted to have a great potential in diagnosis and treatment of diseases in the future. For instance, in the last few years, several techniques such as miRNA silencing, antisense blocking and miRNA modification have been considered for potential therapeutic treatment of several types of cancers. As the role of miRNAs are further clarified and established in each disease, we will surely see new methods developed to address the diagnosis and treatment of major human diseases. This new knowledge appears to have a major role in the practice of personalized medicine in the near future.

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