MICRORNA AND DISEASES

Abstract

MicroRNAs (miRNAs)is a small non – coding regulatory RNA that binds to target mRNAs leading to translational repression resulting in gene silencing. All eukaryotic cells have miRNA. They approximately are of 21-25 nucleotides in length. MicroRNAs plays critical roles in the regulation of diverse biological processes such as embryonic development, differentiation, cell proliferation, cell death, metabolism and immunity. It has also been implicated that miRNAs plays significant roles in cellular signalling network as well as cross-species gene expression variation and transcription factor co-regulation. Abnormal miRNA expression results in a variety of human diseases. Also mutation of miRNAs, dysregulation of miRNA, dysfunction of miRNA causes numerous diseases. They are found to be associated with variety of cancers, brain, neuronal and muscular disorders, heart disease, autoimmunity, inflammation, fertility dysfunction and many other disease conditions including diabetes and retinal diseases. In recent years, miRNAs are being studied for its involment in biologic process and also for its association with various diseases in humans which can be used for diagnostic as well prognostic biomarkers and also as drug response predictor.

Keywords: microRNA, translational repression, gene silencing.

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I. INTRODUCTION

MicroRNAs belongs to the class of endogenous, non coding RNAs (ncRNAs) which plays an important role in controlling the expression of gene that targets specific mRNAs for breakdown process or supression of translation process. Their length is 21-25 nucleotides approximately .They regulate gene expression at the post-transcriptional level by base- pairing with complementary sequences in their target mRNA.[1] Degradation of mRNA or suppression of translational process is done by complementary base pairing that is again dependent on the complementarity degree of miRNA – mRNA. Degradation of mRNA results due to high sequence complementarity. Also, suppression in the translation process of mRNA can be attributed as a result of central mismatches. miRNA dependent gene expression at present is an active area of biologic research. Research in miRNA in recent years let to the discovery of approximately 17000 miRNAs in different species out of which 1000 belongs to the human genome. miRNAs regulates major cellular functions of development of cells, differentiation of cells, cell growth as well metabolism.

II. MIRNAS AND HUMAN DISEASES

With the discovery of human miRNAs, the role of miRNAs in various human diseases were studied extensively. It was seen that miRNAs pattern expression are tissue specific defining the physiological nature of the cell.[2] MicroRNAs plays vital role in proliferation of cell, cell death, immunity, cellular metabolism, neuronal gene expression etc. So any abnormal expression of miRNAs will affect the normal physiological process proportionately that results in a variety of pathological conditions and even malignant conditions.

III. MICRORNAS IN CANCER

Development of cancer may also be attributed to miRNAs dysregulation. Various human cancers is either due to the upregulation or down regulation of miRNAs . Many studies showed the presence of deregulated miRNAs in the plasma and serum of cancer patients which is absent in healthy individuals showing that miRNAs can be used as biomarkers for the detection and also to evaluate prognostic result of cancer.[3] Over expression of miRNA can act as oncogenes by tumour suppressor genes down regulation or regulator of cellular processes by the process of cellular differentiation or cell death process. The role played by the circulating miRNAs in malignant condition is by excercising its control over the oncogenes by acting through tumour suppressor miRNAs and also functions as tumor suppressors by acting on oncomiRs. In B – cell chronic lymphocytic leukemia(B_CLL) patients, there is deletion of miRNA genes miR15 and miR16 frequently in more than 50% of the B-cell chronic leukaemic condition. Interestingly, because of the presence of two intracellular miRNAs, in some B-CLL patients without miR-15 and miR-16 deletion, there is down regulation of miR-15 and miR-16. Abnormal miRNA expression is associated with manifestation of various types of malignant outcomes. Breast cancer is also one of the most common cancer among women that results from disregulation of miR-125b, miR-145, miR-21 and miR-155. In patients with lung carcinoma, miR-155 upregulation and let-7a down regulation is associated with bad outcome**.** The miRNA associated with malignancy is classified into tumor suppressors and oncogenes due to different clinical manifestation. Tumor suppressors miRNAS are miR-15, miR-16 and let-7. miRNAS that acts as oncogenes are miR-21 as well as miR-155. Anti – apoptotic gene bcl-2 expression is suppressed by miR-15 and miR-16 and leads to cell death in malignant cells. Antimalignant properties by let-7 family members is because of their ability to suppress the manifestation of oncogene. Thus each miRNA is unique in each own way having different manifestations in different cancers. Approximately, 50% of the genome related with malignancy have translocation or amplification in the miRNA coding genes. Any error in the transcription process of pri-miRNA causes miRNAs alterations and causes malignancy.

IV. MICRORNAS IN CARDIOVASCULAR DISEASE

miRNAs plays an important role in the regulation of cardiac cell differentiation and cardiac cells growth. They play vital role in heart failure and cardiac hypertrophy. Numerous studies have shown abnormal expression of miRNAs in many pathological conditions of both blood vessels and human heart. In hypertrophy of cardiac cells, there is upregulation of miR-23a, miR-23b, miR-24, miR-195, miR-199a and miR-214 . The critical condition of end stage failing heart is due to upregulation of miR-24, miR-195, miR-199a and miR-214 in the cardiomyocytes. It is seen that there is upregulation of myomiR family which includes miR-1, miR-133a, miR-208a/b and miR-499 shortly after myocardial infarction.[5] The muscle specific miRNA,miR-1 is present in both cardiac and skeletal muscles .When the muscle specific miR-1 is released in acute myocardial infarction,

there is necrotic death of cardiac myocytes. The level of miR-1 increases in acute MI and comes back to normal after treatment. Heart specific miRNAs are miR-208a, miR-208b and miR-499 and they belong to the miR-208 family. The α- cardiac muscle myosin heavy chain genes is encoded by miR-208a and the introns of β cardiac muscle myosin heavy chain genes are encoded by miR-208b and miR-499 respectively .The clinical outcome of ST-elevation in myocardial infarction is indicated by miR-133a level in the plasma of MI patients. More the elevated levels of miR-133a, more is the myocardial damage, more reperfusion injury and decreased chances of recovery of myocardium.

V. MIRNAS IN NERVOUS SYSTEM DISORDERS

miRNAs plays important role in the development of neural cells as well as nervous cell functions . They are involved in translational process, development of gene as well as gene regulation. Any abnormal expressions or dysfunctions of miRNAs causes numerous nervous system disorders like Parkinson's disease (PD), Alzheimer's disease (AD), myasthenia gravis (MG), epilepsy, multiple sclerosis (MS), gliobastoma (GBM)[6]. In Parkinson Disease, there is overexpression of miR-29a-3p , miR-103a-3p, miR-30b-5p and these overexpressed RNA can be used as biomarkers that can help in diagnosing this neuronal disease . Another important nervous system disorder is the Alzheimer Disease. This nervous system disorder is one of the most common cause of dementia. miR-107 is expressed poorly in the cortex of Alzheimer disease in both early as well as advanced stage of the disease. GBM is one of the most dangerous carcinoma of the brain in which miRNAs plays a crucial role in proliferation of cells, , invasion to surrounding areas ,cell death and angiogenesis. There is also involvement of miR-124, miR-132 and miR-155 in Myasthenia Gravis as well as Multiple Sclerosis. In many neurodevelopmental disorders, disease onset occurs during periods of maturation and development.Thus it is seen that miRNAs contribute significantly to the pathogenesis of neurodevelopmental disorders at the molecular level.

VI. MICRORNA AND IMMUNE RELATED DISEASES

Cellular miRNAs is associated with many immune related diseases such as systemic lupus erythematosus(SLE), typeI/II diabetes, non alcoholic fatty liver disease(NAFLD) and even multiple sclerosis(MS). In MS, the expression of mi-RNAs namely miR-34a, miR-155and miR-326 is increased and the degree of MS severity increases with increased expression of miR-326. Also, when there is decreased miR-146a expression, the risk of SLE also increases. In type 2 diabetes, apart from the numerous pathologies involved, the involvement of miR-144, miR-146a, miR-150 and miR-182 is seen when RNA expression profiling is done. Also in type 2 diabetes by targeting Caveolin-1, which is an important regulator of insulin receptor, miR-103 and miR-107 regulate both the glucose homeostasis as well as insulin sensitivity negatively. In many inflammatory process, miRNAs have vital role by regulating the pathways associated with the central mediator of inflammatory response, nuclear factor kappa beta(NF-κβ). Also, miR-155 and miR-146 are found to be associated with many immune related diseases.[7] All these highlights the role of miRNAs in inflammatory process and the development of immune related diseases.

VII. SUMMARY

Many types of miRNA are identified and their regulatory roles have been revealed both by in vitro and in vivo studies. Numerous human diseases have been linked with abnormal expression of miRNA. miRNAs are altered in various conditions of the most common cause of morbidity as well as mortality among humans including cardiovascular disease, disorders of nervous system, immune related disease as well as malignancy. Therefore, a great potential lies in identifying these disease specific molecules and integrating the role of miRNAs in the diagnosis of many diseases as well as to study the prognostic outcome which will help in the treatment modality of various pathological conditions.

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