**Title:**

**The Role of mi (micro) RNAs as Biomarker of Different Health Conditions.**

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Abstract:

MicroRNAs (miRNAs) are the intron transcribed small non-coding oligoribonucleotides that regulates the process of gene expression at both transcriptional and translational level. The regulatory role of miRNAs is associated with most of the cellular, biological and physiological processes of a cell and an organism. Any alteration in the process of regulation is reflected as altered health conditions including cancer. Intracellular, extracellular (circulating/ exosomal) miRNAs in the developed disease condition have both predictive and diagnostic value as biomarkers. Evaluation of miRNA as biomarker is helpful in assessment of clinical conditions like cancer, diabetes, viral infections, alcoholism, obesity, neuronal disorder, renal and cardiovascular disorders. Further miRNA can also serve as therapeutics in the diseased state reversing the altered clinical conditions. In this chapter association of different miRNAs as biomarker in different health conditions has been summarised and the general prospect of use of miRNAs as diagnostics and therapeutics has been discussed. Further evaluation and validation of nano based miRNA molecular or lateral flow techniques can enhance its dual role as both diagnostics and therapeutics.

Key words: alcoholism: Biomarker: Cancer: Dicer: Drosha: : Diagnostic: Exportin: Micro RNA: Therapeutics:

**I. INTRODUCTION**

The major fraction of the RNA world consists of messenger (m), transfer (t) and ribosomal (r) RNAs are involved in coding the regular functioning of cells. The noncoding proportionate consisting of microRNAs (mi), small interfering RNAs (si) are observed to rule the RNA era for the last few decades. First miRNA discovered in *Caenorhabditis elegans* (Lee et al., 1993) was 22 ribonucleotide long lin*-4* miRNA gene, that is partially complementary to [3' UTR](https://en.wikipedia.org/wiki/3%27_UTR) of the *lin-14* mRNA. The *lin-4* miRNA binds to the UTR segment and represses *lin-14* gene expression involved in process of larval development. Subsequently [*let-7*](https://en.wikipedia.org/wiki/Let-7_microRNA_precursor) mi RNA was discovered that represses *lin-41* gene in *C. elegans* involved in later developmental stage transition ( Reinhart et al., 2000). Gradually the miRNAs discovered were found to be 12 to 28 ribonucleotide entity involved in regulation of gene expression mechanism associated with different physiological processes in wide range of cells and tissues. The miRNAs constituting about 1%–3% of the mammalian genome (Bartel et al., 2004) were found to be associated with various vital biological processes like growth, differentiation, reproduction, lactation, pregnancy etc. Any imbalances in the genesis and regulatory mechanism usually reflects as disease condition in both humans and animals (Bartel et al., 2004; Wang and Sen, 2011). Transcribed as pre-miRNA mostly from the introns (small extent from exons) of the genes (Selbach M et al., 2008: Rodriguez A et al., 2004) with characteristic hairpin stem loop, they undergo polyadenylation followed by splicing with the help of drosha protein through microprocessor complex (Berezikov E et al., 2007; Ali PS et al., 2012; Auyeung VC et al., 2013; Conrad T et al., 2014). The pre-miRNAs also undergo nuclear editing (Murchison EP et al., 2004; Ohman M et al., 2007; Kawahara Y et al., 2008; Winter J et al., 2009) by the enzyme ADARs ([adenosine deaminases](https://en.wikipedia.org/wiki/Adenosine_deaminase) acting on RNA) and cytoplasmic editing by enzyme Dicer (Murchison EP et al., 2004; Lund E et al., 2006). However, the functional miRNA interacts with the target mRNA through [RNA-induced silencing complex](https://en.wikipedia.org/wiki/RNA-induced_silencing_complex) (RISC) inhibiting the process of translation. So, the non-coding micro RNAs are basically involved in gene silencing during the process of transcription and post-transcriptional gene expression regulation (Wang and Sen, 2011; Qureshi A et al., 2014; Bartel et al., 2018). This short oligoribonucleotides usually gets paired with complementary mRNA sequences either cleaving it into fragments or shortening the poly(A) tail. Thus, destabilizing the mRNA structurally and hindering the process of translation in cells (Bartel et al., 2009; Fabian et al., 2010). Apart from disruption of translation initiation miRNAs were also supposed cause hinderance in the process of histone modification and DNA methylation at the site of promoters dysregulating the process of functional gene expression (Hawkins PG et al., 2008; Tan Y et al., 2009; Bazzini AA et al., 2012; Djuranovic S et al., 2012). The dysregulated gene expression associated with various biological processes gets altered and reflected in clinical form as diseases.

**II. ASSOCIATION OF mi-RNA WITH DIFFERENT HEALTH CONDITIONS**

1. **miRNA as biomarker in cancer:**

Cancer is the disease with abnormal cellular proliferation associated with dysregulated angiogenesis, adhesion, apoptosis, causing its initiation, progression and metastasis (Calin et al., 2004b). Accumulation of DNA damage caused by mutations or errors in DNA replication (Loeb and Loeb., 2000) and defects in expression of proteins or factors involved in DNA repair cause cancer. Defects in miRNAs itself or miRNAs involved in these processes (Hu and Gatti., 2011) alters the base level of gene regulation causing the abnormalities. Alterations in genes encoding protein machineries associated with miRNA genesis and processing causes disruption in regular process of regulation of gene expression that is associated with abnormal cellular processes causing cancer. For example any alteration in synthesis, structure and regulations of genes encoding [RNA polymerase II](https://en.wikipedia.org/wiki/RNA_polymerase_II) (Pol II), Poly(A)-binding protein, Ribonuclease III, [Paip2b](https://en.wikipedia.org/wiki/Paip2b), [DGCR8](https://en.wikipedia.org/wiki/DGCR8) , [Drosha](https://en.wikipedia.org/wiki/Drosha), ADARs, TARBP2, Exportin-5 (XPO5), [Ran](https://en.wikipedia.org/wiki/Ran_%28biology%29) protein, AGO2, andDicer can interrupt in formation of RISCs and miRNP complex and thus inhibiting miRNA formation (Esteller et al., 2011; Huang et al., 2014). This inhibition has been found to be associated with gene alterations in different types of cancer. Thus, the miRNA can serve dual role as oncoactivator or oncosuppressors depending upon the activation or suppression of the genes concerned (Welch et al., 2007; Yu et al., 2010). The versatile Ras oncogene was found to be regulated by let-7 group of mi-RNAS (Esquela-Kerscher and Slack, 2006). Similarly, the expression of oncogenes PTEN and SPRY2 are also regulated by the miR-21(Meng et al., 2007; Sayed et al., 2008). Any deviation in expression and regulation of these genes was found to be associate with altered cellular processes causing cancer (Hatley et al., 2010). The miR-21 have been found to be associated with liver, lung, gastric, pancreas, colorectal, skin, thyroid, cervical and mammary gland (Volinia et al., 2006). Similarly, miR-34a, is also associated with cancer as it alters the normal process of cell cycle, development, differentiation and apoptosis targeting the molecules associated with these processes (Misso et al., 2014). Whereas miR-96 and miR-34a act as an oncosupressor downregulating the target protein associated with the process of cell invasion and migration (Yu et al., 2010) as indicated in case of glioblastoma (Liu et al., 2011; Yan et al., 2014). The miRNA that acts as oncosuppressor in one type of cancer may act as oncoactivator in cancer associated with other organs. Like miR-29a suppresses cancer in lung, liver and blood (Fabbri et al., 2007; Xiong et al., 2010; Pekarsky and Croce, 2010) but has been reported to activate colorectal and ovarian cancer (Resnick et al., 2009; Huang et al., 2010). A range of altered mi-RNA profiles has been studied and reported in cancer of blood, breasts, ovarian, prostate, pancreas and liver. (Calin et al., 2004; Iorio et al., 2005; Iorio et al., 2007; Porkka et al., 2007; Wang and Sen, 2011; Qi et al., 2013). The microRNA miR-155, that represses MLH1 expression causes colon cancer as indicated in MLH1-deficient rats. The epigenetic methylation of the MGMT gene and nonmethylation of its promoter increases microRNA miR-181d level with decreased synthesis DNA repair enzyme MGMT is associated with glioblastomas in humans (Spiegl-Kreineckeret al., 2010; Zhang et al., 2012). Expression of oncogene HMGA for HMGA1a, proteins are also regulated by miRNAs causing thyroid, prostatic, cervical, colorectal, pancreatic and ovarian cancer (Borrmann et al., 2003; Sgarra et al., 2004; Xuet al., 2004). Whereas expression of DNA repair gene of ERCC1 is inhibited by HMGA2 in case of colon cancers (Facista A, et al., 2012).

The comparative level of oncoactivating and oncosupressing miRNAs in cells, tissues, serum, blood, urine and other biological fluids reflects the balance and imbalances of different cellular processes and its relation with development of cancer. Detection of normal and abnormal level of these miRNAs in the biological samples can indicate about the particular type and stage of cancer (Heneghan et al., 2010; Xing et al., 2010; Ben-Dov et al., 2014; Wang et al., 2014b; Wang et al., 2015). Further single-nucleotide polymorphisms associated with the genes and the associated miRNAs can indicate the possibility of development of cancer in the concerned group. SNPS in miR-196a2 C > T (rs11614913) and miR-499 C > T confer risks in development of hepatocellular carcinoma and lung cancer (Chen et al., 2013; Qi et al., 2014). Thus, functional miRNA-single-nucleotide polymorphisms in miRNAs may act as biomarkers of disease risk and can predict the clinical outcome in cancer. Single Nucleotide polymorphisms (SNPs) can alter the binding of miRNAs on 3'UTRs for example the case of hsa-mir181a and hsa-mir181b on the CDON tumor suppressor gene.

1. **miRNA as biomarker in cardiovascular diseases:**

Development of heart and associated vascular system in human and animals is a complicated process that involves genesis, differentiation, programming and reprogramming of progenitor stem cells. The expression and repression of different genes translating into proteins and other factors involved in cardiogenesis are modulated by a group of miRNAs (Zampetaki and Mayr, 2012; Philippen et al., 2015). Alterations in the level of these miRNAs are reported to be associated with pathological conditions like heart failure, atrial fibrillation, fibrosis, hypertrophy, myocardial infarction, atherosclerosis, etc (Corsten et al., 2010; Fichtlscherer et al., 2010; da Silva and Silbiger, 2014;). Mutation and deletion of myocardial dicer gene in certain population is linked to myocardial infarction (Albinsson et al., 2010). The miRNAs are reported to be more sensitive in detection of end-stage heart failure in humans (Matkovich et al., 2009). Further profiling of miRNA has been found to be useful in differential diagnosis of heart ailments and cardiomyopathies at different stages of development (van Rooij et al., 2006b; Thum et al., 2007). The MiR-205 in humans and miRNA-712 in murine has predictive value in atherosclerosis as indicated in murine experimental model. The miRNA-712 is involved in regulating expression of pro-atherogenic genes including matrix metalloproteinases (MMPs) mediating pro-inflammatory and pro-angiogenic signals. Anti-miR-712 has been found to inhibit vascular hyperpermeability, thus reducing development of atherosclerosis and immune cell mediated inflammation (Son DJ et al., 2003; Yang B et al., 2007; Basu R, et al., 2012; Keller T et al., 2017).

1. **miRNA as biomarker in renal diseases:**

Renal FoxD1-Dicer knockout mouse model indicates upregulated pro-apoptotic [Bcl2L11](https://en.wikipedia.org/wiki/BCL2-like_1_%28gene%29)  (Bim) gene and dysregulated [p53](https://en.wikipedia.org/wiki/P53) gene pathway including altered [Bax](https://en.wikipedia.org/wiki/Bcl-2-associated_X_protein), [Trp53inp1](https://en.wikipedia.org/wiki/TP53INP1), Jun, [Cdkn1a](https://en.wikipedia.org/wiki/P21), [Mmp2](https://en.wikipedia.org/wiki/MMP2), and [Arid3a](https://en.wikipedia.org/wiki/ARID3A) gene activity. The vast range of miRNAs like miRs‐10a, 18a, 19b, 24, 30c, 92a, 106a, 130a, 152, 181a, 214, 222, 302a, 370, and 381 regulate renal Bcl2L11 (Bim) expression. Whereas, the miRs‐15b, 18a, 21, 30c, 92a, 106a, 125b‐5p, 145, 214, 222, 296‐5p and 302a regulate p53-effector gene expression. The alteration in transcription of these genes was found to be associated with defective renal functioning due to lower number of  [renin](https://en.wikipedia.org/wiki/Renin) cells, smoothening of  [arterioles](https://en.wikipedia.org/wiki/Arteriole), [mesangial](https://en.wikipedia.org/wiki/Mesangium) loss and glomerular aneurysms (Phua YL, et al., 2015).

1. **miRNA as Biomarker in Neural diseases:**

The miRNAs- 132 / 134/ 124 are reported to be involved in the process of dendritogenesis whereas [miR-134](https://en.wikipedia.org/wiki/MiR-134) and [138](https://en.wikipedia.org/wiki/MiR-138) are associated with  synapse maturation. Abnormal functioning of these miRNAs along with silencing of [dicer](https://en.wikipedia.org/wiki/Dicer) causes [neurodegeneration](https://en.wikipedia.org/wiki/Neurodegeneration) as reflected in  [alzheimer](https://en.wikipedia.org/wiki/Alzheimer%27s_disease%22%20%5Co%20%22Alzheimer%27s%20disease), [schizophrenia](https://en.wikipedia.org/wiki/Schizophrenia)  and [anxiety disorders](https://en.wikipedia.org/wiki/Anxiety_disorder) ( Maes OC et al., 2009; Hébert SS et al., 2010; Hommers LG et al., 2015: Hosseinian S et al., 2020). Further loss of motoneuron-specific microRNA-218 causes systemic neuromuscular failure (Amin ND et al.,2015).

1. **miRNA as Biomarker in Stroke:**

I[schemic strokes](https://en.wikipedia.org/wiki/Ischemic_stroke) is a pathophysiological condition resulted from decreased blood supply to brain due to arterial blockage depriving the brain getting essential nutrients, glucose, oxygen etc. Different miRNAS are found to be actively involved posttranslational gene silencing in the process of inflammation, angiogenesis, and apoptosis resulting in cerebral ischemia (Rink and Khanna S, 2011; Ouyang et al.,2013)

1. **miRNA as** B**iomarker in Alcoholism:**

Around 35 miRNAS are discovered to be involved in the process of [addiction](https://en.wikipedia.org/wiki/Addiction) associated alterations in downstream gene expression related to functioning of brain, synaptic transmission and neural adaptations. The medial [prefrontal cortex](https://en.wikipedia.org/wiki/Prefrontal_cortex) miRNAs dysregulate translation of the genes associated with [cell cycle](https://en.wikipedia.org/wiki/Cell_cycle), [apoptosis](https://en.wikipedia.org/wiki/Apoptosis), [cell adhesion](https://en.wikipedia.org/wiki/Cell_adhesion), [neuronal development](https://en.wikipedia.org/wiki/Neural_development), synaptic transmission and [cell signaling](https://en.wikipedia.org/wiki/Cell_signaling) (Lewohl JM et al., 2011; Tapocik JD et al., 2013; Gorini G et al., 2013). In mice, it has been observed that chronic alcoholism induces upregulation of the microRNA-155 that causes TLR4 mediated neuroinflammation (Lippai et al., 2013) responsible for abnormal behaviour. Similarly, the overexpression of miRNA-206 and down expression miRNA-382 in rat medial prefrontal cortex was reported to downregulate BDNF and DRD1expression causing synaptic plasticity (Li J et al., 2013; Tapocik JD et al., 2014).

1. **miRNA as Biomarker in Obesity:**

The miR-155, miR-221, and miR-222 (Romao JM et al., 2011are reported to be negatively expressed during the process of adipogenesis in both immortalized and primary hMSCs causing repression of PPARγ and CCAAT/enhancer-binding protein alpha (CEBPA) associated with differentiation (Zuo Y et al., 2006). The overexpression of let-7 classes of miRNAs ( Frost RJ,and Olson EN, 2011; Zhu H et al., 2011; Jun-Hao ET et al., 2016) in course of aging is found to be the reason for development of insulin resistance, obesity and diabetes. Let-7 accumulates in human tissues during the course of aging causing dysregulation of gene expression associated with obesity and associated risks.

1. **miRNA as Biomarker in Hemostasis:**

miRNAs also play crucial roles in the regulation of complex enzymatic cascades including the hemostatic blood coagulation system (Teruel-Montoya R et al., 2015). Large scale studies of functional miRNA targeting have recently uncovered rationale therapeutic targets in the hemostatic system (Nourse Jet al., 2018; Nourse J and Danckwardt S. 2021) They have been directly linked to Calcium homeostasis in the endoplasmic reticulum, which is critical in cell differentiation in early

1. **miRNA as Biomarker in Pregnancy and Associated Conditions:**

miRNAs are also reported control the important physiological processes like pregnancy and associated reproduction disorders. miRNAs play vital role in different stages of pregnacy like fertilization, endometrial receptivity, vasculature development, uterine immunomodulation, immunosuppression, implantation, labor and also in conditions like abortions and foetal loss. The uteral hormones most likely estrogen and progesterone regulates the action of miRNAs in the process of transcription, processing, RNA editing, function and intracellular localization etc. Estrogen upregulates the expression of miR-451/429/99b/155 and 7a while downregulates miR-24 and -181b expression in the endometrium during pregnancy (Qian K et al., 2009: Nothnick WB et al, 2010; Xia HF et al., 2010a,b: Zhu XM et al., 2010: Williams KC et al., 2012; Liu Fet al, 2012; Morandi F and Pistoia V. 2013). Further miR-152/ 148a has been reported to be associated with maternal recognition of foetus. The role of miR-451 and miR-210 in immunomodulation of uterine microenvironment has also specific role in maternal recognition and implantation of foetus.

The miRNA clusters C19MC including miR517a-3P, miR519a-3P, miR-520c-3P, miR-371-3 (Bortolin-Cavaille et al., 2009: Luo L et al., 2012; Donker RB et al., 2012; Kurashina R et al., 2014) expressed in trophoblast and placenta-derived stromal cells have been evaluated as a biomarker for pregnancy disorders like pre-term labor and pre-eclampsia.

**III. PREDICTION AND DETECTION OF miRNAS**

Several online software’s (MicroTar, miTarget, mirror, PicTar, Rna 22 etc) are available to detect miRNA, its interaction with target RNAs, its predictive performance etc.
Further, miRNAs are reported in intracellularly and extracellularly also. Extracellular miRNA in serum, blood,urine sweat, lymph and other biological fluids can be detected by PCR and the expression status can be studied by RT-PCR. Circulating miRNAs have already been assessed as biomarkers for prediction and confirmation of myocardial infarction and cardiovascular diseases (Ai et al., 2010; Wang et al., 2010). Exosomal miRNAs has also been functionally evaluated as biomarker for assessment of disease conditions. Techniques like microarray, northern blot analysis, real-time PCR, in situ hybridization, NGS etc have been employed for detection, estimation and analysis of miRNAs associated with a particular clinical condition (Sempere et al., 2004; Thomson et al., 2004; Valoczi et al., 2004; Chen et al., 2005; Kloosterman et al., 2006; Wang et al., 2009; Wang et al., 2014a; Wang et al., 2015). Accurately determination of expression level of miRNAs in a specific cell, tissue, organ, body fluids associated with specific clinical condition is the prerequisite for assessment of miRNA as diagnostics.

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