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# Exploring miRNA based approaches in cancer diagnostics and therapeutics

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ABSTRACT

MicroRNAs (miRNAs), a highly conserved class of tissue specific, small non-protein coding RNAs maintain cell homeostasis by negative gene regulation. Proper controlling of miRNA expression is required for a balanced physiological environment, as these small molecules influence almost every genetic pathway from cell cycle checkpoint, cell proliferation to apoptosis, with a wide range of target genes. Deregulation

*Abbreviation:* miRNA, microRNA; TRBP, Transactivating Response RNA-Binding Protein; RISC, RNA induced silencing complex; UTR, untranslated region; DDX, DEAD box protein; TS, tumor suppressor; OG, oncogene; TGF β, Transforming Growth Factor β; RT-PCR, Real Time-polymerase chain reaction; ER, Estrogen receptor; C13orf25, Chromosome 12 open reading frame 25; HSC, hematopoietic stem cell; VHL, Von-Hippel Lindau; HIF, Hypoxia Inducing Factors; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; PSA, prostate specific antigen; USPTO, United States Patent and Trademark Office; EMT, Epithelial-to-Mesenchymal Transition; HPV, Human Papilloma Virus; THBS1, thrombospondin-1; HER-2, Human Epidermal Growth Factor-2; TGFβR2, Transforming Growth Factor B Receptor 2; DAPK1, Death-Associated Protein Kinase 1; APC, Adenomatous Polyposis Coli; NR5A2, Nuclear Receptor Subfamily 5, group A, member 2.

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in miRNAs expression correlates with various cancers by acting as tumor suppressors and oncogenes. Although promising therapies exist to control tumor development and progression, there is a lack of efficient diagnostic and therapeutic approaches for delineating various types of cancer. The molecularly different tumors can be differentiated by specific miRNA profiling as their phenotypic signatures, which can hence be exploited to surmount the diagnostic and therapeutic challenges. Present review discusses the involvement of miRNAs in oncogenesis with the analysis of patented research available on miRNAs.


## 1. Introduction

Uncontrolled proliferation of damaged cells, as a result of deregulation of genes involved in the cell cycle machinery and apoptosis, leads to tumor formation (Vecchione and Croce, 2010). Accounting for approximately 3% of the human genome, miRNAs are 22 nucleotides long, single stranded RNAs found in both plants and animals (Setoyama et al., 2011). The biogenesis of miRNAs is well defined in literature. Briefly, a stem-loop structure of pri-miRNA (primary miRNA) of about 1 Kb in size, transcribed by RNA polymerase II undergoes a two step maturation phase. Initially, the RNase III enzyme Drosha and ds-RNA binding endonuclease Pasha (DGCR8) process it into a 70 nucleotides pre-miRNA by cleaving both the strands and generating a stem loop structure (Krishnan et al., 2011; Zhiguo et al., 2008). The pre-miRNA is then transported to the cytoplasm with the help of a RAN GTP-dependent transporter exportin 5 for further processing by RNA III enzyme Dicer and ds-RNA binding protein TRBP (Transactivating Response RNA-Binding Protein), hence generating a 22 nucleotides miRNA: miRNA* duplex. The duplex is incorporated to the RISC (RNA induced silencing complex) complex wherein the mature miRNA strand is retained and the miRNA* fragment is degraded, guiding the RISC to the target mRNA molecule for gene regulation, which is a sequence complementarity dependent process. Perfect complementarity of the "seed region" with target mRNA results into its RISC associated degradation while imperfect matching leads to translation repression as 5′ end of miRNA binds to the 3′ UTR (untranslated region) of the target gene (Zhang et al., 2007; Xiangyang et al., 2008; Stefanie et al., 2008) [Fig. 1].

Miss-expression or mutation of factors involved in miRNA biogenesis could result into alterations in miRNA processing, stability, and targeting, hence causing serious ailments including cancers. The potential role of miRNAs in cancer is suggested owing to their involvement in the regulation of cell proliferation and apoptosis by controlling the expression of tumor suppressor genes and oncogenes. Additionally supporting this, about 50% of miRNAs are found to be located at "fragile sites" in the genome, which are the sites mostly amplified or deleted in cancer. Microarray, bead-based flow cytometry, sequencing and RT-PCR (Real Time-polymerase chain reaction) are some of the techniques used for analyzing the differential expression of genes in normal and cancerous cells, to elucidate the exact role of miRNAs in carcinogenesis (Monya, 2010). It has been reported that miR-10b, miR-125b and miR-145 are down-regulated while miR-21 and miR-155 are up-regulated in cancer development, hence playing roles as tumor suppressors and oncogenes, respectively (Thalia et al., 2011). Moreover, rearrangements in the gene regions containing miRNAs have been identified indicating their altered expression levels in the neoplastic cells. Their differential expression profiling thus gives information both on the differentiation state and developmental lineage of tumor, thereby paving way for cancer diagnosis and therapy (Niamh et al., 2009).

## 2. Role of miRNAs in cancer development

Studies suggest that miRNAs are majorly involved in the onset and progression of cancer. In lung cancer, the expression of dicer is found to be down-regulated, further decreasing the post-operative survival rate as a result of truncated miRNA maturation process (Ruan et al., 2009). Knock down studies with DICER, DGCR8 and TRBP2 genes shows enhanced tumor formation while re-introduction of these genes cause reduction in tumor growth. Genes from other pathways such as LIN28A block processing of let-7 resulting into cancer, are also involved in disrupting miRNA processing. Moreover, helicases DDX5 (DEAD-box protein 5) and DDX17 (DEAD-box protein 17) induce the processing of several tumor suppressor miRNAs by interacting with TP53 gene, wherein a mutation drives the miRNAs to remain in their immature state, blocking their tumor suppressor function (Suzuki et al., 2009). Defects in miR-21 biogenesis resulting in its over-expression, due to mutation in SMADs (an effector of TGFβ superfamily which carries out RNASEN-mediated miRNA maturation through interaction with DDX5 helicase), cause brain and pancreatic cancers (Nikitina et al., 2012).

miRNAs have differential expression in cancers related to different tissues, as a result of hundreds of targets affecting multitude of transcripts in cancer-related signaling pathways. Down-regulated miRNAs lead to an increased expression of oncomers, while those up-regulated cause suppression of tumor suppressor genes, indicating that miRNAs may act as both tumor suppressors and oncogenes. Some of the majorly studied miRNAs regulating cancer associated genes are discussed further [Fig. 2].

### 2.1. Oncomirs as tumor suppressors

#### 2.1.1. miR-15 and miR-16

Homozygous loss in 13q14 region involving LEU1 and LEU2 genes is associated with the deletion of miR-15 and miR-16, which map within the introns of non-protein coding gene LEU2, is reported in more than half i.e. in about 68% of B-CLL (B-cell chronic lymphocytic leukemia) indicating their role as tumor suppressors associated with over 50% of mantle cell lymphoma, 16–40% of multiple myeloma and 60% of prostate cancers (Aqeilan et al., 2010). These miRNAs negatively regulate the anti-apoptotic gene BCL2, associated with various cancers. Therefore a loss in the activity of BCL2 regulatory miRNAs results into uninhibited proliferation of cells leading to cancer progression.

#### 2.1.2. miR-142

miR-142 gene, located at chromosome 17, is also responsible for aggressive B-cell leukemia due to the *t*(8;17) translocation of MYC gene to its upstream strong promoter resulting into the loss of a conserved region of 20 nucleotides present downstream of miR-142 precursor, which hence disrupts miRNA processing leading to the up-regulation of MYC gene (Kwanhian et al., 2012).

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