

## Diagnostic Utility of miRNAs in Cancer

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### Abstract

Cancer is the one of most prevalent and leading causes of death in the world. Current advancements in technology improve the understanding of the pathogenesis and pathology of cancers. But, due to enlarging mortality rates, poor prognosis, and lacunae in clinical early predictive biomarkers provide an important momentum to investigate novel early diagnostic/prognostic markers and specific targets for cancers therapeutics sufficiently sensitive to cancers. Recently, the emerging small noncoding microRNAs (miRNAs) are suggested as important and critical regulators in the oncogenesis pathways and serve as precise and useful early clinical biomarkers. This new class of biomarkers is emerging as a novel molecule for cancer diagnosis and prognosis and recent miRNA expression studies in tumors yield promising results. However, establishing miRNA expression in the blood circulation, cell-free as noninvasive marker, has advantages over determination of tumor in primary tissue. A better understanding of the involvement of this class of molecular markers in carcinogenesis could provide new insights into the mechanisms in the development of tumor and could be helpful to identify new specific novel early powerful markers for the early detection of cancer. The current review study aimed at summarizing the recent research studies supporting the utility of miRNAs as novel early diagnostic and prognostic tools, thus potentially illuminating future treatment strategies for cancers, which indicates the feasibility and clinical applications and the importance of miRNAs in cancer for researchers and clinical diagnostic centers.

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## INTRODUCTION

Till date, cancer remains an alarming clinical challenge due to its poor prognosis, restricted options of treatment, chemotherapy/radiotherapy resistance, and late diagnosis of the disease. Therefore, there is a need to develop early markers to detect cancer at the stage where it can be treated properly [1-8]. The implementation of assays enabling to detect circulating tumor cells (CTCs) sparked an additional and important boost of interest in blood-derived noninvasive biomarkers for patients with cancer. Various assays for CTC enumeration are described as the Cell Search™ Epithelial Cell test. Recently, the FDA-approval was acquired to use it as a prognostic

marker when measured in patients with metastatic breast [9, 10], colorectal [11], and prostate cancers [12]. Probably even more interesting than mere counting, CTCs in future can be isolated from the blood of patients with cancer for further analysis and improvement in cancer diagnosis [13].

CTCs isolation and their subsequent characterization can provide the opportunity to bypass the problems associated with obtaining metastatic tissue, and serve as a 'liquid biopsy'. CTCs is already characterized for the presence of gene amplification [14-16] and genetic aberrations [17, 18], for the expression of proteins [19] and several mRNAs [20-22]; and

recently, also for the expression of certain miRNAs. In recent years, miRNAs are known as key regulators of gene expression. It is not surprising that the miRNA expression in primary tumor tissue associates with the outcome in several recent research studies. However, it is required to determine miRNA expression in the peripheral circulation, either CTC-associated or as cell-free circulating molecules, since it has several advantages over determination in primary tumor tissue; thereby augments the important applications of miRNA profile determination in oncology.

### **Synthesis of miRNAs**

The miRNAs are small 20-22 nucleotide single-stranded RNA molecules noncoding for proteins and discovered in 1993 [23]. They are transcribed from miRNA genes by RNA polymerase-II and III to form primary miRNAs, or pri-miRNAs, cleaved by Drosha enzyme to create precursor miRNAs, or pre-miRNAs [24, 25]. This hair pin structure pre-miRNA is cleaved once transported into the cytoplasm to create a miRNA duplex by a protein called Dicer to give final mature miRNA, which dictates cellular events [26, 27]. The lesser stable strand of the miRNA duplex is typically added to another miRNA induced silencing protein complex; this formation is induced by Dicer and affects the target gene in terms of its protein expression. These effects are most often observed when one of the strands of the miRNA binds to the 3'-untranslated region (UTR) of the mRNA specific target sequence [28, 29].

### **miRNAs and Tumorigenesis**

Short-interfering RNAs (siRNAs) (double-stranded) match perfectly with their mRNA target sequences, while miRN (single-stranded) are an imperfect match to their target sequences causing the bulge in the resulting structure [30]; this information implies that miRNAs inhibit translation whereas siRNAs only destabilize the molecule through cleavage. When gene expression profiles are used to compare cancerous and normal tissue, it is observed that miRNAs and also mRNAs are deregulated [31]; this information can be used to suppose that tumor genesis may occur due to the change within the collection of miRNAs in the genome (miRNome). In addition It is observed that certain miRNAs are deregulated more often than others, which suggests that they are playing a Major important role in tumorigenesis [32]. In the beginnings, it was believed that miRNAs had similar effects on gene expression (ie, negative regulation of

target mRNA), but recent studies show that miRNAs can either repress or activates, depending on the conditions of the cell as it is believed that microRNAs do not function by themselves, but in what are called effector complexes miRNPs (rib nucleoproteins). The miRNPs are able to gather enzymes and factors that can cleave mRNA.

And degrade the enzymes that further process mRNA. On the other hand, miRNAs can positively regulate gene expression. This up regulation is specific to the target RNA sequence and associated with the factors gathered by the miRNP [33-35]. The identification of new molecular miRNAs biomarkers yielded an exciting new array of easy accessible features, which may be employed in diagnosis, prognosis, and treatment of cancer.

### **miRNAs as Genetic Indicators of Cancer**

In the past, oncogenes and tumor-suppressor genes were thought of as the main genetic indicators of cancer, but according to the recent advanced research studies it is depicted that miRNAs are the main genetic indicators of cancer; the miRNAs involved in carcinogenesis are called oncomirs [36, 37]. It is reported that 50% of genes encoded by miRNAs are placed at certain sites called fragile sites where chromosomal rearrangements associated with cancer often occur [38]. In recent research studies it was found that in most cancers, miRNAs are apparently deregulated that may be caused by transcriptional deregulation, epigenetic alterations (DNA methylation, mutation, and DNA copy abnormalities), as well as problems in miRNA biogenesis pathways, these mechanisms can either work alone or together with each other in order to deregulate miRNAs [39]. Certain families of these miRNAs regulate cell-cycle and cell-cycle exit (senescence), in addition to cell differentiation and proliferation; and if mutated, can cause abnormalities in the cells. The mutation in any given miRNA of a somatic cell can lead to tumorigenesis and if present in germ line cells, it may be a precursor to cancer [39-42].

The miRNAs are a group of non-protein coding RNA molecules, which exert their function by base pairing between the seed region of miRNA and 3' un-translated regions (3'-UTR) of the target gene. Dysregulated miRNAs play either a tumor-suppressive or an oncogenic role in regulating cell growth, cell cycles, and cell migration, depending on their target genes in gastric cancer as in Figure 1 [43]. This group of miRNAs can be released from the

cancer cells to body fluids via secreting exosomes particles by which they are protected from RNase degradation in circulation.

**The miRNA Function**

It is predicted that these miRNAs regulate up to 30% of all protein coding genes [44]. They regulate post-transcriptional gene expression in a sequence-specific manner by recognizing the mRNA target with the 5'-end of the mature miRNA strand referred to as the 'seed-sequence for targeting' [23]. After the target mRNAs recognition, the regulation of gene expression may occur via two different mechanisms on the basis of complementarity of the miRNA sequence with its target mRNA. When perfect base-pairing homology exists between the miRNA and the mRNA due to which, the RNA-mediated interference pathway is induced, due to which cleavage of the mRNA occurs by Argonaute as already present in the RNA induced-silencing complex (RISC). When imperfect binding occurs to partially complementary sequences in the 3'-untranslated region of target mRNAs, at same time the target mRNA is regulated by repression of protein translation, which is more frequent than perfect binding. As a result, proteins are regulated by miRNAs without considerably disturbing the corresponding mRNA expression levels. Such a scientific knowledge underscores the

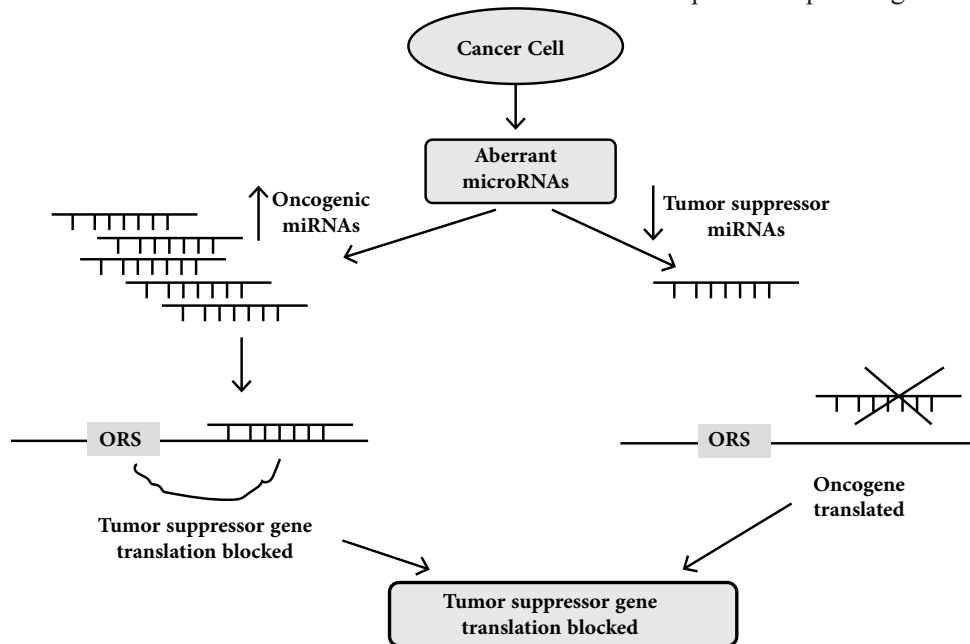
need to combine the mRNA and miRNA scientific data to generate or improve new precise and perfect predictive and prognostic models.

**Potential Applications of miRNA Sand Its Role in Primary Cancer**

In carcinogenesis, it is thought that miRN as play two different roles by functioning as 'oncomirs' and tumor suppressors. These facts are supported by the observation that miRNA expression in tumors can be up- or down-regulated when there is a comparison between cancerous and normal tissue [45]. As a result of the vital role of miRNAs in the tumor biology, there is a broad range of potential applications of miRNA measurement in oncology that can act as a diagnostic tool, and serve as prognostic and predictive factors. In other medical fields, it can play a measuring role; similar to miRNA signatures that can be potential drug targets and pharmacodynamics markers. All of these applications may be possible in primary tumors/ metastases, but the stability of miRNAs also enables their detection in the circulation. Therefore, in the field of cancer biology, circulating miRNAs can serve as biomarkers measured repeatedly and non-invasively in a wide array of cancer types [46, 47].

**The miRNA Expression Profiles to Classify Cancers**

The miRNA expression profiling is surprisingly



**Figure 1:** The miRNAs Can Act as Tumor Suppressors and Oncogenes.

Down regulation or loss of miRNAs with tumor suppressor function may increase translation of oncogenes and hence formation of excess oncogenic proteins, leading to tumor formation. On the other side, the up regulation of oncogenic miRNA scan block tumor suppressor genes and can lead to the tumor formation.

informative as it reflects the developmental lineage and differentiation state of the tumors. They show a general down regulation or up regulation of miRNAs in tumors compared with normal tissue, and are also able to successfully classify poorly differentiated tumors. On the other hand, messenger RNA profiles are highly inaccurate in classifying tumors when applied to the same samples [35, 45, 46]. Breast cancer is a notoriously heterogeneous disease while miRNAs can facilitate to classify the subtype origin of tumor cells, as in situ hybridization technique to disclose the spatial distribution of miRNA expression in archived formalin-fixed, paraffin-embedded breast tumors [46, 48, 49].

**The Role of miRNAs as Diagnostic and Prognostic Biomarker in Cancer**

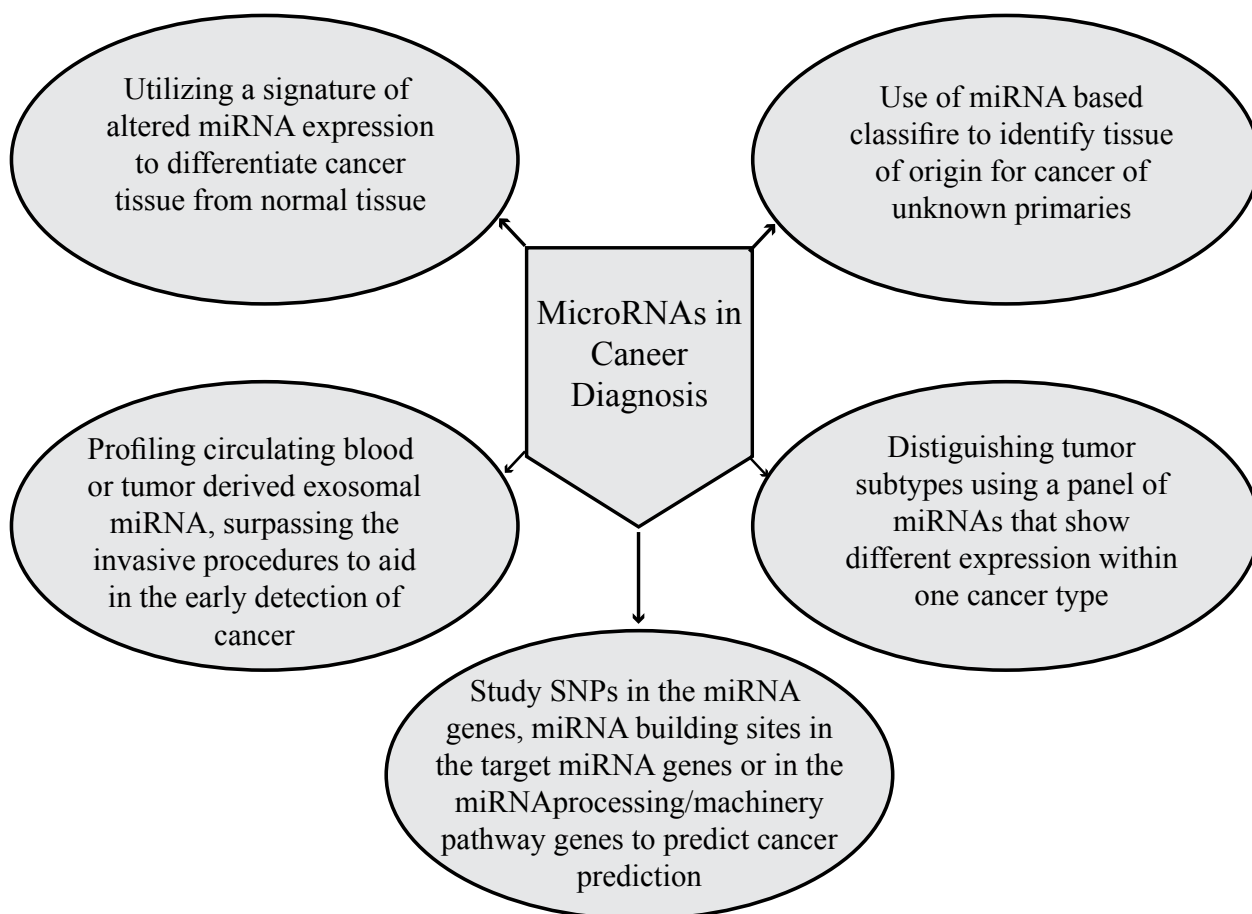
There are various aspects of miRNAs that provide novel ways of utilizing miRNAs in disease diagnosis and prognosis, as shown in Figure 2.

**The miRNAs and Gastric Cancer**

Due to the poor prognosis, treatment limited options,

resistance to chemotherapy/ radiotherapy, and its late diagnosis detection markers GC is currently an alarming and major clinical challenge. Thus, a longstanding goal of GC research is to discover new methods for the early diagnosis, prognosis, and management of cancer. There are some miRNAs that show positive links with the gastric cancer and can act as early diagnostic and prognostic biomarkers for gastric cancer in future:

- The miR-372 with the oncogenic role in controlling cell growth, cell cycle, and apoptosis via down-regulation of LATS2 tumor suppressor gene [48];
- GC proliferation and growth of cancer cells show positive relationship with the over expression of miR-650 at least partially through directly targeting ING4gene [50];
- The down regulation of mir-663 in tumor cells may lead to the development of GC, in association with the hyperplasia of aberrant cells [51];
- Overexpression of miR-126 in association with the down regulation of SOX2 might contribute to gastric carcinogenesis [52];



**Figure 2:** The miRNAs as Potential Diagnostic Biomarkers.

Various aspects of miRNAs provide novel ways of utilizing the min disease diagnosis. Blood-based miRNA profiling as a diagnostic test provides a non-invasive and fast alternative to traditional methods.



- NF-kappaB1 may be targeted by miR-9, miR-16, and miR-21 and regulate the growth of GC cells, which suggests an impressive tumor suppressive activity in gastric pathogenesis [53];
- There is a lot of evidence that CCKBR was targeted by miR-148b and significantly suppressed the growth of GC cells [54];
- The inhibitory effect on cell proliferation of miR-451 and miR-141 could be involved in the development of GC [55-57];
- Family of miR-29 and ectopic expression profiling of miR-101 could obviously inhibit the cell proliferation, migration, and invasion of GC cells by targeting the Cdc42 and EZH2, Cox-2, and Mcl-1 Fos genes, respectively [58, 59];
- In different previous studies it was observed that miR10b, miR-223, miR-21, miR-338, miR-30a-5p, and miR 126 were closely and significantly associated with relapse-free and overall survival in patients with GC [60-63].

Over the past years, the scientists investigated the viability of utilizing miRNAs as biomarkers, since many of them were involved in GC tumorigenesis, proliferation, invasion, and metastasis [64-66]. Several circulating miRNAs are detected in serum, plasma, urine, tears, amniotic fluid, and gastric juice and their different expression patterns in these body fluids might originate from different cell types under certain physiological status. Therefore, miRNA might be a useful noninvasive biomarker to diagnose recurrent GC.

In addition, genome-wide [66-69] studies showed that miRNA genes were frequently located within regions of the loss of heterozygosity, amplification, fragile sites, and other cancer-associated genomic regions, suggesting the vital role of miRNAs in tumor genesis [70]. Further investigations showed that up regulated and downregulated miRNAs expression profiling could be important in tumorigenesis as new broad-spectrum oncogenes and tumor suppressor genes in GC, respectively [71].

### **The miRNAs and Ovarian Cancer**

In ovarian cancer, miR-214 is identified as a miRNA involved in resistance to cisplatin, through targeting PTEN [72, 73]. In a recent scientific study, four of the most differentially expressed miRNAs among a total of 515 miRNAs were tested in 10 ovarian tumor samples and further validated within 10 normal cell line pools. One of the most frequent miRNAs was miR-214 up regulated in 30 primary ovarian

tumor samples and its role in cisplatin resistance was elucidated by the knocking down of miR-214 causing the increased PTEN protein expression and decreased Protein Kinase B (PKB) also known as AKT phosphorylation (AKT is its activated form). Recent scientific studies revealed that dysregulation of miRNAs was involved in a variety of human diseases as well as ovarian cancer [72, 74, 75]. The recent scientific Cancer Genome Atlas (TCGA) project suggested that ovarian cancers could be separated into three miRNA subtypes while analyzing mRNA expression, miRNA expression, promoter methylation, and DNA copy number in a total of 489 HGSOCS [76]. In a recent scientific study it was observed that 17 miRNAs were dysregulated in HGSOCS in comparison with normal ovary samples. Among them eight miRNAs (miR-183-3p, miR-15b-3p, miR-15b, miR-590-5p, miR-18a, miR-16, miR-96, and miR-18b) were upregulated and nine downregulated (miR-140-3p, miR-145-3p, miR-143-5p, miR-34b-5p, miR-145, miR-139-5p, miR-34c-3p, miR-133a, and miR-34c-5p) [77-81]. Emerging evidence regarding miRNAs revealed that microRNAs can play a role in ovarian cancer as oncogenes or tumor suppressor genes. The recent miRNAs studies on ovarian cancer showed that miR-199a-3p was downregulated in serous ovarian high-grade carcinomas and the loss of miR-199a-3p was involved in ovarian carcinogenesis and there was peritoneal dissemination by causing the up regulation of receptor c-Met against the hepatocyte growth factor [82, 83].

### **The miRNAs and Non-Small Cell Lung Cancer**

The validation in the patient samples were performed in a study on the predictive value of miR-128b expression on response to gefitinib, an EGFR inhibitor, in non-small cell lung cancer (NSCLC) [72, 84]. In recent multivariate miRNAs analysis it was found that only histology, line of treatment, and loss of miR-128b were predictive of response, but there was no such response regarding the EGFR expression or mutation [72, 84]. It is well known that the onset of cancer impacts the immune system leading to changes in the gene expression of blood cells [85]. It was observed that in some recent research reports that the expression of let-7a was low in lung cancerous tissue, and it was also observed in the blood of patients with lung cancer compared with healthy individuals [85, 86]. As already mentioned in many of the research studies, miRNAs are also present in other body fluids and also stably

present in sputum, which can differentiate the patients with lung adenocarcinoma from healthy individuals by the help of four sputum miRNAs panel of namely miR-486, miR-21, miR-200b, and miR-375, with high sensitivity (80.6%) and specificity [87].

### **The miRNAs and Hepatocellular Carcinoma**

In three independent cohort studies, a total of 455 patients with HCC were taken and it was identified that miR-26 had lower expression in the tumors than in paired noncancerous tissue [72, 88]. Additionally, of the patients that were not treated by the interferon, the control arm of the cohorts, the ones with lower expression of miR-26 in their tumor had shorter overall survival. The patients in the treatment arm of the cohorts that did not receive interferon, the ones with lower miR-26 expression, improved their survival compared with patients with higher miR-26 expression. In another multivariate analysis, a significant relationship was observed between miR-26 expression and the response towards the interferon therapy [88]. Murakami et al., for the first time reported that the hepatic malignancy exhibited an abnormal miRNAs expression pattern as dysregulation of its expression was identified as a common characteristic of liver cancer and after that a number of studies confirmed that the miRNAs had important regulatory roles in hepatocarcinogenesis and malignant transformation [89, 90].

### **The miRNAs and Breast Cancer**

Different studies on breast cancer cell lines showed that five candidate predictive miRNAs from 249 miRNAs in a small discovery set of breast cancer specimens were analyzed by the expression profile in an independent series of 246 ER-positive primary breast tumors [91, 92]. In multivariate analysis, higher expression of miR-30c was associated with benefit from first line tamoxifen monotherapy and longer progression-free survival [93, 94]. Mostert et al., stated that cancer-initiating cells or CSCs were responsible for tumor development and progression. These cells share a number of different biological properties with the normal somatic stem cells including the capacity for asymmetric cell division and the ability to efflux the small compounds [72, 93]; however, the CSCs vary from normal stem cells in their tumor seeding and abilities of metastasis. In addition, the phenotypic plasticity of the CSCs, which is their capacity to distinguish into non-CSCs, is thought to be an important factor to prevent tumor malignancy [95]. Therefore, CSC theory for cancer

progress is usually accepted in the fields of basic and translational cancer research. The first CSCs in solid tumors were recognized and isolated from breast cancers. Al-Hajj et al., reported in their study that the CD44+/CD24-/low lineage-cells from human breast samples showed a remarkably high tumor-seeding capacity, and in 2007 it was Yu et al., reported that the let-7 was the main regulator of the CSC properties, as self-renewal action and tumor-seeding ability [96, 97]. By the application of mammosphere culture conditions and treatment with the anti-cancer reagents, Yu et al., confirmed that the CSCs showed a CD44+/CD24-/low antigen phenotype and had significant down-regulation of let-7 expression; furthermore, they also demonstrated that let-7 inhibited self-renewal and de-differentiation of the breast cancer cells through direct targeting of the genes encoding the RAS and high mobility group AT-hook 2 (HMGA2), respectively. Mani et al., reported that CD44+/CD24-/low cell populations from the cancerous breast tissue specimens showed the features of epithelial to mesenchymal transition (EMT) and high tumorigenicity [98]. Since EMT is always observed during the tumor invasion and metastasis, the genetic controls and molecular mechanisms underlying the acquisition of invasiveness and the subsequent systemic spread of the metastatic cells are the areas of intensive research. The EMT phenotype is characterized by the loss of the epithelial markers such as E-cadherin, the up-regulation of the mesenchymal markers such as N-cadherin and vimentin, the loss of cell-cell adhesion and cell polarity, and the acquisition of cell invasive capabilities. A molecular link between the EMT and miRNAs was reported by Gregory et al., they found that miR-205 and other five members of the family among miR-200, namely, miR-200c, miR-200a, miR-200b, miR-429, and miR-141 are downregulated in the Madin Darby canine kidney cells undergoing EMT [99]. The family of miR-200 is classified into two clusters, namely miR-200b, miR-200a, and miR-429 on human chromosome 1, and miR-141 and miR-200c on human chromosome 12 [100]. The expression among miR-200 family, which inhibits the EMT phenotype, induced by transforming growth factor- $\beta$  by direct targeting the genes encoding the E-cadherin transcriptional repressors of zinc finger E-box-binding home box 1 (ZEB1), ZEB2, and on the other hand the ZEB1 suppress the transcription of miR-200c and miR-141; since both of the are strong inducers of epithelial differentiation, therefore EMT phenotype is closely regulated by a reciprocal

interaction among the ZEB1 and miR-200 family [99, 100]. Martello et al., demonstrated that miR-103/107 attenuated miRNA biosynthesis via targeting the gene encoding the Dicer and leading to the global down regulation of miRNAs, including miR-200 family, and the succeeding progress of EMT and a metastatic phenotype of the epithelial cancerous cells [101, 102]. Song et al., provided the first confirmation that the chromatin-remodeling systems with opposing effects on cell fate (self-renewal versus differentiation) and EMT induction were regulated by balance of opposing sets of the miRNAs.

### Evidence of Promise in the Future of Cancer Prevention

However, with a lot of the recent information on miRNAs, the future of cancer prevention and prognoses seems promising. There is still much of the work to be done in this field, but progress is being made daily to understand how miRNAs work and how this can be applied to prevent cancer. The miRNAs are budding new markers that can serve as diagnostic and prognostic markers and they are also considered as biomarkers to predict the response to therapy and other treatments in several malignancies. Due to the miRNA expression specificity towards the tissue and disease stage; they can identify the presence or absence of tumors and also determine the affected primary organ or tissue. In addition, they can also identify the clinical and pathological stage of the disease. Furthermore the miRNAs can expect risk of progression, relapse, and metastasis, and help to evaluate possible clinical scenarios in relation to the therapy response. The clinical strength of these candidate miRNAs signatures should be determined by large independent cohorts in multi-centric studies. In addition, by other robust platforms, additional appropriate bio-computational and advanced statistical analysis should be used to recognize candidate miRNA signatures. Past and current literature suggest that to diagnose cancer early, the focus should be on the type of circulating miRNAs in body fluids; therefore, there will be a panel of miRNAs in future that can act as early diagnostic marker for cancer detection at curable stage.

### CONCLUSIONS

Micro-RNAs which are specific to cancer may act as ultimate noninvasive early diagnostic and prognostic biomarkers for cancer, due to their involvement in the progression of cancer. However cancer molecular

biology has been well characterized, but works on miRNAs in cancer is still in its evolving stage. So there is need of quantification and normalization strategies and should be standardized before any noval miRNAs can act as a noninvasive marker for early diagnosis of cancer.

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### CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

### ETHICS APPROVAL

Ethically approval by institution of Govt. Medical College Srinagar

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