

## Tissue microRNAs as Cancer Tissue Biomarkers

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### Abstract

microRNA (miRNA) is non-coding RNA sequences that modify DNA, typically through cleavages. They can have an effect on cell cycle progression, namely through inhibiting regulators for tumorigenesis control. Because of this, specific miRNA sequences can be monitored for cancer detection purposes. This detection is conducted through a variety of methods, such as in tissue, blood plasma, serum, ductal lavage fluid and nipple aspirate fluid. Recent research has been done to compare miRNA detection accuracy between these methods, especially with tissue analyses since this tends to be more invasive. Imaging methods have been utilized for cancer detection, but they are less effective in staging cancers, which is necessary for clinicians to provide individualized treatments. In several cases, detection accuracy has been compared to the accuracy from biopsy methods, which is a common practice but also invasive. In the future, non-invasive techniques of detection and personalized treatments will be the emphasis of research in cancer detection.

**Keywords:** microRNA; Chemotherapy; Tumor; Tissue

### Introduction

In the United States, cancer leads to the second-most number of deaths, with an occurrence of 42% in men and 38% in women [1]. For tissue tumors, early diagnosis is crucial because it can result in tumor removal before the onset of metastasis. These forms of surgeries have a cure rate of approximately 45%, which is well-improved over the 5% success rate in therapies involving chemotherapy and radiation. This type of success has corresponded to an emphasis on researching early detection strategies, in addition to innovations in treatments [2].

Traditionally, various imaging modalities have been used in the past for cancer detection in biological tissue *in vivo*. Magnetic resonance imaging (MRI) can detect cancer based on proton positions in tissue [3]. Despite positives in sensitivity, MRI lacks in specificity, making it difficult for clinicians to stage cancers. This difficulty adds unnecessary obstacles in the treatment process [4]. Other popular methods such as X-ray computed tomography (CT) have similar problems in staging due to low resolution, even with the use of contrast agents [5,6]. Having low contrast and sensitivity can be dangerous, however, because it can lead to false negative diagnoses [7].

MicroRNAs (miRNAs) are small non-coding RNA sequences that are able to control cell cycle progression by modifying DNA expression. These single-stranded sequences typically down regulate expression of mRNAs for tumorigenesis control, so they can potentially be utilized as cancer biomarkers and indicate the presence of an invasive tumor [8,9]. Detection can be applied to a clinical setting for minimal invasiveness because microRNAs can be observed in body fluids and they can maintain stability against changes in pH, RNase activity and temperature changes. As a result, microRNAs have been useful in diagnoses of bladder, kidney, prostate and testicular cancers [8,10]. There are still challenges for microRNAs in its applications, as it can be difficult to assay for miRNA and miRNAs may affect multiple genes that are not of interest [11].

### microRNA Biomarkers

miRNAs interact with cell growth and development, cell cycle and apoptosis pathways. Depending on the form of cancer, proteins in the tyrosine phosphorylation pathway can affect cell growth, adhesion and cell death. For example, Purkinje cell protein 2 (PCP2) is a protein tyrosine phosphatase that down regulates the growth of colon cancer cells. So

miRNAs associated with the cleavage of mRNA coding for this protein could be a biomarker for colon cancer.  $\beta$ -catenin, which is involved in cell adhesion, triggers the Wnt and E-cadherin pathways, so miRNAs can similarly lead to cancers by leading to less expression of  $\beta$ -catenin [12,13].

miRNA biomarkers can be observed in a variety of cases. Lung cancer, which is the most common cause of death for cancers, is typically in the form of non-small cell lung cancer (NSCLC). miR-574-5p presence has been shown to correspond to an increase in small-cell lung cancer as this miRNA affects  $\beta$ -catenin signaling. While miRNAs resist degradation by RNases to a certain extent, miR-574-5p can be detected in the plasma, which contains substantial RNase activity, in stages I and II NSCLC [13]. This protection from RNase activity can be attributed to the incorporation of circulating miRNAs into exosomes and vesicles [14].

miRNAs can possibly be used in diagnosis of hepatocellular carcinoma (HCC), which is the most common form of liver cancer. Imaging poses an issue, especially for liver cirrhosis, making the use of invasive biopsy more likely, unless miRNA biomarkers can be used. Distinguishing HCC are high circulating levels of miR-520b. In an *in vivo* study, high levels of miR-595 and miR-765 in plasma resulted in accurate diagnoses [15]. Also, a wide screen of miRNAs in blood plasma was done to measure accuracy of diagnoses for colorectal cancer. miR-532-3p, miR-331, miR-195, miR-17, miR-142-3p, miR-15b, miR-532 and miR-652 could accurately distinguish polyps from control groups. To detect stage IV colorectal cancer, miR-431, miR-15b and miR-139-3p were effective [16]. So miRNAs can be predictive for stage of cancer, which results in accurate diagnoses.

### MicroRNA in the Cancer Treatment Process

Bodily fluids can typically be analyzed for miRNA biomarkers, as

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is done with blood plasma or serum. As introduced earlier, NSCLC is a common form of lung cancer and can be detected with miRNAs, which can indicate survival chances and treatment strategies based on the stage of cancer. miR-221, let-7a, miR-137, miR-372 and miR-182 are associated with progression-free survival in early stage NSCLC, which corresponds to success in surgical removal of the tumor. miR-1, miR-30d, miR-221 and miR-486 correlate to advanced (stage IV) NSCLC. The typical treatment in these cases is 4-6 cycles of chemotherapy and then maintenance therapy for a group of patients with progression-free cancer. miRNA can also be tracked for post-therapy checkups to determine how well the patient responds to the treatment. In these ways, miRNA applications result in a more personalized treatment strategy [17].

A common form of cervical cancer is squamous cell carcinoma (SCC), which widely affects women. Patients with lymph node metastases (LNM) have significantly lower survival rates (about 50-60%), as compared to those without LNM who have a survival rate of 80-95%. When comparing tissue and serum miRNA expression levels, a unique benefit was demonstrated in predictive qualities of serum miRNA. This is because serum miRNA has a smaller, narrower range of miRNAs. Recently, a link was exhibited between miR-1246 and cervical carcinoma. This occurs as the tumor suppressor p53 targets miR-1246, which in turn affects the dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A). These serum miRNA levels can also indicate the success of treatment if monitored over time [18].

For breast cancers, some non-invasive methods of miRNA collection are done through the use of ductal lavage and nipple aspirate fluid. For example, in DL fluids, miR-126, miR-363, miR-638 and miR-663 expression can be monitored by clinicians to determine how well the patient responded to treatment. However, serum and plasma can also be monitored as significant differences were found in miRNA levels between breast cancer patients and controls. Only as recently as 2016 has DL fluid been studied for potential use in miRNA detection for cancers [19].

### microRNA Pitfalls

There are some problems associated with some advancement in miRNA cancer research. In several cases in which research is in development, additional studies are required to observe the link between miRNA levels and patient outcomes. Also, a substantial amount of the studies have shown accurate detections for early-stage cancers but need an improved representation for middle and late-stage cancers [18]. Tissue studies for miRNA expression may also be flawed, which explains why serum levels seem to be better indicators. In many cases, the normal control tissue chosen can be adjacent to the cancerous tissue. This normal tissue may be too nearby to the cancerous tissue that it experiences molecular modifications that make it similar in nature. This means miRNA expression would not be markedly different in cancerous tissue for these cases [8].

### Conclusion

Having an effect on the cell cycle progression, miRNAs can be important to utilize for detection of specific cancers, as illustrated in this review. Detection mediums, such as through tissue, blood plasma, DL fluid and nipple aspirate fluid have been compared in the literature. The monitoring of biomarkers is crucial for determining the subgroup of cancer the patient falls within, staging the cancer and observing how well the patient responds to treatment over time. This allows for personalized treatment strategies and affects the clinician's decision-

making. More research needs to be done in the future in strengthening the link between miRNA expression and patient outcomes.

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