Blood Biomarkers for Breast Cancer

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The expression of two oncogenic miRNAs, miR526b and miR655, in poorly metastatic breast cancer cells enhances aggressive breast cancer phenotypes. miR526b and miR655 expression in breast tumors is associated with poor patient survival. Both miRNAs are major regulators of the tumor microenvironment and can be detected in cell-free tumor cell secretions. Precursors of both miRNAs, pri-miR526b and pri-miR655, are sensitive and robust blood biomarkers to distinguish cancer from benign plasmas.

Keywords: pri-miRNA ; miRNA ; biomarker ; breast cancer ; early detection ; plasma

1. Introduction

Breast cancer (BC) is the most common solid organ-specific cancer, affecting about 30–40% of women under the age of 40 years in North America [1]. While BC accounts for about 15% of all cancer-related deaths in women, early detection and treatment strategies have contributed significantly to reducing disease-related mortality [2][3]. Mammographic screening is a painful breast examination procedure, currently used as the gold standard for tumor detection. However, this screening excludes women below the age of 50 years in Canada [4] and is limited by a high percentage of false positive results, which requires further investigation for molecular signatures using invasive biopsy techniques [5]. A blood test can be a less invasive procedure for BC screening, and there are a few routine cancer markers in the blood, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)15-3, which have been used as biomarkers. Their low sensitivity and specificity to detect disease make them poorly reliable screening tools [6]. Hence, breast cancer screening requires a sensitive blood biomarker. Recently, the identification of microRNAs (miRNAs) in body fluids and specifically in the blood make them strong candidates as cancer biomarkers [7].

MiRNAs are endogenous noncoding small RNA (22 nt) molecules that regulate gene expression at the post-transcriptional level. Primary microRNAs or “pri-miRNAs”, which can be more than 1000 nt in length, contain an RNA hairpin in which one of the two strands includes the mature miRNA. The hairpin, which typically comprises 60–120 nt, is cleaved from the pri-miRNA in the nucleus by the double-strand-specific ribonuclease, Drosha. The resulting precursor miRNA, or “pre-miRNA”, is transported from the nucleus to the cytoplasm, where it matures to become miRNA [8].

MiRNAs, and to a lesser extent pri-miRNAs and pre-miRNAs, are secreted by both tumor and healthy cells into the interstitial fluid contributing to the fluid part of the tumor microenvironment (TME) [9]. Circulating miRNAs are exported by exosomes into body fluids, such as blood plasma, and they have recently emerged as candidate biomarkers for detecting and monitoring disease progression in cancer patients [10]. Only a few mature miRNAs in the blood plasma of BC patients have shown promise for the detection of malignancy [11][12]. On the other hand, the diagnostic usefulness of circulating double-stranded RNA-like pre-miRNA or pri-miRNA is a very new field. The first report on plasma pri-miRNA as a cancer biomarker was published for lung cancer [13]. However, very few reports are available for pri-miRNAs as a biomarker of cancer, likely because of their low abundance in the plasma.

Overexpression of cyclo-oxygenase (COX)-2 promotes breast cancer progression and metastasis via multiple mechanisms [14][15], including induction of two oncogenic miRNAs miR526b [16] and miR655 [17]. Overexpression of these two miRNAs in poorly metastatic cell lines promoted cancer cell migration, invasiveness, and stem-like cell phenotypes; moreover, upon orthotopic transplantation in immune-compromised mice, they enhanced tumor growth and metastasis. Furthermore, miR526b and miR655 overexpression in human breast cancer was correlated with reduced patient survival and disease progression [16][17]. However, the biomarker potentials of these two miRNAs or pri-miRNAs for the early diagnosis of breast cancer remain unexplored.

2. Potential Blood Biomarkers for Breast Cancer

In Canada and other countries around the globe, breast cancer incidence in younger women continues to rise. Mammographic screening starts at the age of 50, and this procedure contributes to 9% of all false-positive results [18]. However, if cancer is detected early, a patient's survival is enhanced up to 98% [19]. This highlights the necessity of identifying a blood-based biomarker that would detect BC at an early stage with a minimally invasive blood test. Recently, circulating markers in the blood such as miRNAs and pri-miRNAs have emerged as highly sensitive biomolecules, which can be used as diagnostic and prognostic biomarkers [7][13].

We have established that mature miRNAs, miR526b and miR655, are oncogenic and tumor-promoting in breast cancer, and miRNA functions are regulated by the COX-2/EP4/PI3K/Akt signaling pathways [16][17][20][21][22]. These two miRNAs can be found in the cell-free conditioned media of miRNA-overexpressing cell lines [20] and these miRNAs can change the TME and enhance tumor-associated angiogenesis [21], hypoxia [22], and oxidative stress [20] in breast cancer. Extracellular vesicles carry miRNAs and release them into the interstitial fluid, while cell-free miRNAs have also been found in blood plasma and are being tested as blood-based biomarkers [7][23][24][25]. However, specific miRNA detection in the blood plasma has some limitations, including the necessity of a large volume of specimens for miRNA-specific cDNA synthesis and detection. This also limits the capacity to screen a panel of miRNAs per sample.

We found that expressions of both pri-miR526b and pri-miR655 in the plasma of cancer patients were significantly high relative to the control. There are no pri-miRNA expression data available in The Cancer Genome Atlas (TCGA), and we were unable to find any report on pri-miRNA as a blood biomarker for breast cancer. We could only find one report of circulating mature miRNA in the plasma as an early detection biomarker in breast cancer [11].

We also observed that both pri-miR526b and pri-miR655 expression in the plasma can distinguish benign lesions from tumor stage I. This is a very significant finding; this indicates the potential of pri-miRNA to serve as an early diagnostic biomarker. As reported by another group, the systemic plasma miRNA expression was heightened in breast cancer patients at various tumor stages [26]. Hence, to examine the varying expressions of pri-RNAs in plasma as an indicator of tumor progression, we compared pri-miRNA expression across tumor stages. However, we did not find a significant difference between stage I and Higher-stage tumors. This could have been due to few samples of higher-stage tumors (stage III and IV) in our dataset.

In stratified samples, we conducted a *Z*-score analysis to determine if there was any significant difference in the proportional distribution of high pri-miRNA expression. We found the distribution of pri-miR526b and pri-miR655 in plasma of ER-positive cancer patients to be significantly higher compared to that in the ER-negative cancer patients. We also observed a significantly higher proportion of high pri-miRNA expression in HER2-negative compared to the HER2-positive tumor plasma. This is very crucial since ER-positive and HER2-negative breast cancers are the predominant subtypes of breast cancer detected worldwide [2][3]. Therefore, these two pri-miRNAs can be used as biomarkers to distinguish ER-positive from ER-negative tumors and can be used to manage endocrine therapy. This is supported by another study showing similar effects to miRNA expression in distinguishing hormone receptor-positive vs. -negative tumors [27].

Mature miR526b and miR655 expressions are regulated by COX2 and EP4, and inhibition of COX2 and EP4 with a specific COX-2 inhibitor and EP4-antagonist (EP4A) significantly inhibited miRNA-induced functions in breast cancer [15] [21][22] Moreover, EP4A has already been approved by the FDA for arthritis treatment [28]. Therefore, the establishment of a link between these pri-miRNA expressions with COX-2 and EP4 expressions in blood plasma would be interesting. Hence, in the future, these two pri-miRNAs could be used as screening tools for monitoring EP4A treatments.

3. Conclusions

Circulating pri-miR526b and pri-miR655 in the blood can improve noninvasive BC detection and can serve as liquid biopsy alongside traditional BC screening procedures. Pri-miR526b can serve as an early diagnostic biomarker for BC. In ER-positive breast cancer, these pri-miRNAs might play a role in the management of endocrine therapy. Precursors of miRNA could be considered as a novel breast cancer blood biomarker.

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