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Review Article

Role of Small Breast Epithelial Mucin (SBEM) in Breast Cancer

Liang Liu*

Oncology Department, the Third Affiliated Hospital of Guiyang Medical University

**Corresponding author: Dr. Liang Liu, Oncology Department, The Third Affiliated Hospital of Guiyang Medical University, China, Email: jinshatanwo@163.com*

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Abstract

SBEM as a kind of secreted protein, which expressed only in mammary gland and salivary gland, can be used to be a tumor marker in breast cancer and specific target in treatment. SBEM detection in Peripheral blood (PB) and tissue of breast cancer patients maybe helpful for early diagnosis, choice of treatment, decision of the degree of malignancy and risk prediction of recurrence. The changing of expression level can predict the curative effect of neoadjuvant chemotherapy. SBEM-mRNA had sensitivity and accuracy in bone marrow micrometastases in breast cancer and had direct correlation with TNM stage. SBEM is an independent risk predictor and may offer utility as a prognostic marker in triple-negative breast cancer patients. The detection of SBEM will have better application prospect because of its clear advantage in detecting of micrometastasis in breast cancer and clinical supervision.

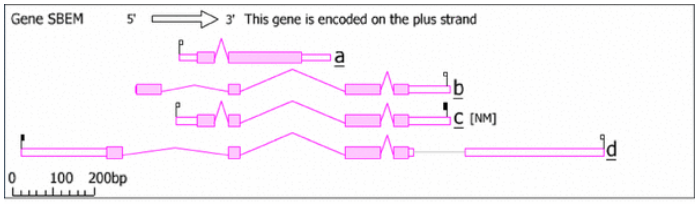
Keywords: SBEM; Breast cancer; Marker

Introduction

Breast cancer is the most common malignancy and is second only to lung cancer in mortality among women worldwide [1]. Breast cancer remains to be an important public health problem. The 5-year survival rate is approximately 75% for women with locally advanced breast cancer[2]. However, if the cancer has metastasized, the average survival time falls to <2 years [3,4]. It is clear that metastatic spreading occurs in about 50% of cases with localized breast cancer, and that up to 30% of patients with lymph nodes negative disease will develop distant metastases within 5 years [5-8]. Therefore, it is probably the establishment of micro-metastases that due to recurrence. Detection of breast cancer micrometastases based on specific genetic markers may provide useful information to guide early therapeutic methods [9]. Increased levels of these markers in a given fluid or tissue may result directly from their over-production by the tumor or from the body's response to the presence of this tumor [10]. Detecting and/or monitoring these changes might assist in the evaluation of cancer risk, diagnosis, or potential response to treatment. At present, immunohistochemistry (IHC), flow cytometry (FCM) and reverse transcription polymerase chain reaction (RT-PCR) have been widely used in the research of micrometastasis of breast cancer [11–13]. Although various biological markers, including cytokeratin 19, mucin-1, mammaglobin et al [14–16] have been proposed for the detection of breast cancer cells, they are often affected by tumor differentiation, lower specificity and detection rate. So, it is crucial to find specific markers to detect micrometastases and provide useful information to guide early therapeutic methods of breast cancer patients.

Structure

The Small Breast Epithelial Mucin (SBEM) gene, located on chromosome 12q13, spans a 3.9-kb region consisting of four exons and three introns (Figure 1). The transcript of 600–700 bp [17-18] encodes for a protein of 90 amino acids. The first 19 amino acids has all the characteristics of a signal peptide, indicating that SBEM protein is likely a secreted protein[17-19] .This assumption has been confirmed through the detection of the SBEM protein in cell culture medium [17] as well as through the recent identification of this molecule by the Secreted Protein DiscoveryInitiative [19].



SBEM-U-O	5′ CTT TGA AGC ATT TTT GTC TGT G 3′
SBEM-L-O	5′ AAG GTA AGT AGT TGG ATG AAA T 3′
SBEM-S-I	5′TGA TCT TCA GGT CAC CAC CA 3′
SBEM-A-I	5′TGG ATA CGT GTC AGC TGG AG 3′

Figure 1. Small breast epithelial mucin gene diagram and primers. The SBEM gene maps on chromosome 12, at 12q13. It contains five introns and four exons. Transcription produces four (a–d) alternatively spliced mRNAs.

Functions of SBEM

SBEM would show much more advantages than other protein–based biomarkers and would be used as prognostic indicator. Meanwhile, SBEM expression in Peripheral blood (PB) of breast cancer patients was markedly higher than that of healthy donors and other cancer patients [20]. Determination of SBEM protein in tissue and mRNA expression in PB of TNBC patients maybe helpful for early diagnosis, choice of treatment, decision of the degree of malignancy and risk prediction of recurrence [21] .

Detection marker

SBEM might represent a suitable marker for molecular detection of isolated tumour cells (ITC) in bone marrow (BM) in breast cancer patients. SBEM mRNA in BM aspirates were significantly associated with presence of clinically active disease, including locally advanced and metastatic patients (47%,P=0.021) and tumours with positive hormonal receptors (36.7%,P=0.035) [22].

To investigate the potential role of SBEM as a marker for detecting hematogenous micrometastasis in breast cancer and explore its clinical significance in neoadjuvant chemotherapy, Liu ZZ, et al [20] detected SBEM protein expression in 82 tissue specimens of primary breast cancer and in PB samples of 109 primary breast cancer patients. SBEM mRNA expression was monitored before and after 3 cycles' neoadjuvant chemotherapy. SBEM expression correlated with tumor node metastasis (TNM) staging and lymph node metastasis at both mRNA and protein levels. SBEM expression in PB of breast cancer patients was markedly higher than that of healthy donors and other cancer patients. SBEM was found expressed in PB of 50 cases among 94 cases at stage I–III and expressed in PB of 11 cases among 15 cases at stage IV.

After 3 cycles' neoadjuvant chemotherapy, SBEM expression levels were significantly down-regulated in up to 58% breast cancer patients. SBEM has the potential to be a specific marker for predicting hematogenous micrometastasis and response to neoadjuvant chemotherapy in breast cancer. SBEM is tissue-specific protein and only expressed in mammary and salivary glands [18]. SBEM can serve as a useful marker for breast nodal metastasis, and for detection of micrometastatic cells within lymph nodes. Also, it is used for the differential diagnosis of the primary origin of an unknown metastasis, especially in high grade and ER/PR negative tumors [23].Valladares-Ayerbes M et al [22] defected that Bioinformatics approach based on Serial Analysis of

- Gene Expression (SAGE) and expressed sequence tag
- EST data confirms the selective and high expression of
- SBEM both in normal and breast cancer tissues.

Moreover, SBEM was over expressed in breast cancer comparing normal mammary gland based on SAGE counts ($p< 0.005$). In addition moderate to high expression was found in 41% of breast cancer libraries comparing with 37% for mammaglobin [22]. Skliris GP et al. [23] found that SBEM expression was observed in 22% of Era- and 13% of ERa+ breast cancers. A definite trend toward significance between SBEM protein levels and disease outcome of patients was observed in ER+ breast cancers, suggesting that SBEM may be associated with worse survival and shorter time to progression in this specific subgroup. In ER- cancers, SBEM protein expression was highly associated with some markers of poor prognosis.

Prognostic marker

SBEM is an independent risk predictor and may offer utility as a prognostic marker in triple-negative breast cancer (TNBC) patients. Liu, L et al. [21] analyzed the correlations between the SBEM protein different expression levels and disease-free survival (DFS) and overall survival (OS) in 87 available formalin-fixed paraffin-embedded (FFPE) tissues specimens from TNBC patients by means of immunohistochemistry, respectively. SBEM 3+ score significantly correlated with DFS ($p = 0.000$) and OS ($p = 0.001$) of TNBC patients. There was a marked associations ($p <0.05$) between SBEM 3+ score and tumor size, grade, node status, TNM stage and Ki67. Multivariate

analysis results showed that HR for SBEM which was adjusted for Ki67, node status, tumor grade and disease stage remained unaffected and significant (HR= 3.370 with p= 0.008 for DFS and HR= 4.185 with p= 0.004 for OS). SBEM may perhaps be best viewed as an independent prognostic factor of DFS and OS. SBEM could be a promising prognostic biomarker in TNBC patients for cancer diagnostics, as well as be a possible future target for the treatment of TNBC [21].

Overall, SBEM holds much promise to become a clinically relevant molecule for breast cancer detection and follow up [24]. Its tissue-specific expression makes it perhaps be best viewed as an independent prognostic factor of DFS and OS. But, because no one of markers including SBEM efficiently detect all breast cancers, a combination of two or more markers could achieve higher sensitivity in detecting hematogenous metastasis of breast cancer [20]. A large scale of validation of SBEM are being currently undertaken to explore its role.

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