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Mini-review

Roles of cancer/testis antigens (CTAs) in breast cancer

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ABSTRACT

Breast cancer is the most common cancer diagnosed and is the second leading cause of cancer death among women in the US. For breast cancer, early diagnosis and efficient therapy remains a significant clinical challenge. Therefore, it is necessary to identify novel tumor associated molecules to target for biomarker development and immunotherapy. In this regard, cancer testis antigens (CTAs) have emerged as a potential clinical biomarker targeting immunotherapy for various malignancies due to the nature of its characteristics. CTAs are a group of tumor associated antigens (TAAs) that display normal expression in immune-privileged organs, but display aberrant expression in several types of cancers, particularly in advanced cancers. Investigation of CTAs for the clinical management of breast malignancies indicates that these TAAs have potential roles as novel biomarkers, with increased specificity and sensitivity compared to those currently used in the clinic. Moreover, TAAs could be therapeutic targets for cancer immunotherapy. This review is an attempt to address the promising CTAs in breast cancer and their possible clinical implications as biomarkers and immunotherapeutic targets with particular focus on challenges and future interventions.

Introduction

30% percent of women in the United States are expected to develop breast cancer over their lifetime. Furthermore, breast cancer is responsible for the second most number of cancer deaths. Approximately 252710 newly diagnosed cases of invasive breast cancer and 40610 breast cancer-related deaths are expected to occur among American women in 2017. About 61,000 cases of female breast carcinoma in situ are expected to be diagnosed in US women in 2017 [1,2]. Breast cancer incidence is rising at an alarming rate with the modernization of lifestyle, altered fertility patterns, and improved socioeconomic status, imposing an enormous economic burden on health care system [3]. Hence, strategies for prevention and control of breast cancer are of the utmost importance in the field of medical research.

Clinical outcome in breast cancer (measured as Disease free survival, DFS and Overall survival, OS) has improved in the past decade [4]. The current focus of research is to identify specific molecular signatures with prognostic and predictive value in such a way that targeted therapies could be developed. Hormonal receptor (ER/PR) and human epidermal growth factor receptor-2 (HER2), the major biomarkers used to classify breast cancer into four subtypes, have been used to make clinical decisions [5]. The course of treatment is decided by the molecular classification as well as other clinical parameters such as menopausal status, performance status, and stage of the disease. However, this tailored treatment based on the molecular classification has some limitations with a significant subset of non-responders, contributing to an increase in mortality. Considering significant differences in the outcomes of similar patients, there must be factors that are different in subgroups. There is a continuous challenge to improve the protocols in human breast cancer management, underscoring the urgent need for new strategies to combat breast cancer. Therefore, understanding the variations in such individuals at the molecular level could shed a light in further classification of the different disease phenotypes. A number of studies have been done to identify novel biomarkers

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from cell cycle regulators, oncogenes, and tumor suppressor genes, all of which are involved in carcinogenesis to improve diagnosis and treatment for breast cancer [6,7].

Molecular signatures not only provide therapeutic targets but can also be explored to improve screening and early detection. Unfortunately, the biomarkers used to detect and treat malignancies present several limitations due to specificity, sensitivity, and cost-effectiveness. Cancer-testis antigens (CTAs) possess several features of ideal targets for cancer immunotherapy and early detection. More importantly, their highly immunogenic nature makes them excellent targets for immunotherapy, such as tumor vaccines [8]. CTAs that are normally biased towards expression in the testis are often induced in tumor cells which is a class of tumor-associated antigens. The future role of CTAs as tumor markers can tremendously aid screening, prognostic factors, disease progression, and treatment. Up-regulated CTAs expression has been associated with advanced disease and poorer prognosis, suggesting a key role of CTAs in tumorigenesis. With the update of CT gene and its recent research progress in breast cancer we will discuss and distinguish the roles of CTAs in breast cancer from different angles [9].

The expression of CTA in breast cancer

The CTAs are proteins that are normally expressed in germinal cells of testis and Placenta yet exhibit aberrant expression in multiple malignancies. The first identified cancer-testis antigen was melanoma associated antigen-1 (MAGE-1) which was discovered in 1991 by Van der Bruggen and his colleagues, using autologous cytotoxic T-cell clones and autologous tumor mRNA [10]. Subsequently, the other members of the family, MAGE (MAGE-A2, MAGE-A3), BAGE and GAGE-1 were identified by using the same strategy as described in the former [10], and shown to be expressed in several other malignancies as well. Later, due to development of serological analysis of cDNA expression libraries (SEREX), increasing numbers of CTAs were discovered, including synovial sarcoma/X breakpoint 2 (SSX-2) and New York oesophageal squamous cell carcinoma 1 (NY-ESO-1). Following this, Sperm associated antigen 9 (SPAG9) and A-kinase anchor protein 4 (AKAP4) were discovered by comparing total mRNA of normal tissues to testis. Up until now, more than 200 members of CT antigens have been identified and divided into two groups: the cancer/testis (CT)-X antigens located on the X chromosome and non-X CT antigens located on various autosomes. A database (http://www.cta.lncc.br/) was established to compile the growing list of CT antigens. Expression of those CTAs was found in a number of cancers including breast cancer [11,12], lung cancer [13], gastric cancer [14], liver cancer [15], kidney cancer [16], prostate cancer [17], colon cancer [18], etc. In breast cancer most of the CTAs are activated. WBP2NL, also known as post-acrosomal sheath WW domain-binding protein (PAWP), a testis-specific protein with no expression in other tissues, is localized in the post-acrosomal sheath (PAS) of spermatozoa. Seyedmehdi et al. found that the WBP2NL gene was expressed in 45 out of 50 (90%) breast cancer tissues and overexpressed in the MDA-MB-231 cell line. Previous studies have shown that WWP2 N-terminal like (WBP2NL) is associated with cell proliferation by induced meiotic resumption and oocyte activation events [19,20]. Golnesa et al. by means of quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) evaluated the expression of 4 CTAs, acrosin binding protein (ACRBP), outer dense fiber 4 (ODF4), Rhox homeobox family member 2 (RHOXF2) and spermatogenesis associated 19 (SPATA19) in two breast cancer lines (MCF-7 and MDA-MB-231), In 40 invasive ductal carcinoma samples and their adjacent normal tissues samples, it was discovered that all four genes were expressed in both cell lines and overexpressed in cancerous tissues compared with their normal adjacent tissues [21]. A research team used immunohistochemical to study 1234 patients with breast cancer and found that NY-ESO-1 expression correlated with a higher level of tumor-infiltrating lymphocytes, and the survival analysis revealed the NY-ESO-1 expression was significantly associated with poor disease-free survival, which suggests that NY-ESO-1 has the potential to act as a prognosis marker and treatment target of breast cancer [11].

However, in different types of breast cancer the expression of CTAs is different. G. Curigliano et al. used immunohistochemical to confirm that MAGE-A and NY-ESO-1 had significantly higher expression in triple negative breast cancers (TNBC) compared to ER-positive tumors [22]. In another study to investigate the protein expression of eight CT genes, MAGEA, CT7, NY-ESO-1, CT10, CT45,GAGE, SAGE1 and NXF2, in 454 invasive ductal carcinomas, including 225 ER/PR/HER2-negative breast cancers (TNBC), immunohistochemical found that all eight CT antigens in ER-negative cancers display significantly more frequent expression. However, HER2 status had no consistent effect on CTAs expression. In this study MAGEA and NY-ESO-1 were also highly expressed in triple-negative carcinomas, showing similar frequencies with other research data, indicating that CT antigens expression is closely related to the ER status [23]. Analogous to those studies, many of CTA express in breast cancer were confirmed, like ATAD2, RHOXF2, ODF4 and SEPT9 [21,24,25]. While major functions of CTAs in breast cancer remain elusive, a few key roles in cellular processes have been uncovered. The exact role of CTAs in breast cancer development and progression is currently being explored; contemporary theory hypothesizes that their function could be related to cell cycle deregulation and invasive properties of cancer. Many studies have contributed to the identification of CTAs in breast cancer. We have summarized these in Table 1.

Prognosis and tumor progression

Although CTAs are undoubtedly the sure-shot targets for various clinical interventions for breast cancer based on their unique expression patterns, there is a marked variation in the expression frequencies observed by different studies, which means CTAs could be potent prognostic biomarkers in breast cancer. A prominent example, the family of MAGEs that comprises of over 65 genes encoded from X chromosome [95], which has been proven to have a critical effect on most biological process of cancers, would be a potential new target in tumor diagnosis and treatment. The majority of studies showed that MAGEs was heightened in breast cancer tissues and correlated with TMN stage, lymphatic metastasis, size of tumor as well as overall survival, manifesting its involvement in breast cancer progression. MAGEs could be a potential target for diagnosis and also as an independent predictor for overall survival. Meanwhile, elevated MAGEs was markedly associated with tumor recurrence and short overall survival, suggesting MAGEs could be a potent prognostic biomarker in breast cancer. For instance, Lian et al. discovered the expression rates of MAGE-A10 and MAGE-A11 were 73.3 and 52.0% respectively in breast cancer specimens. Survival analysis revealed that overall survival of patients with negative MAGE-A11 expression was significantly longer than those patients with positive MAGE-A11 expression, but no difference of overall survival was found between patients with negative and positive MAGE-A10 expression [65]. Another work by Maha Ayyoub et al. discovered that the expression of MAGE-A3/6 was significantly correlated with estrogen receptor (ER) and progesterone receptor (PR) negative status, and that the expression was significantly associated with high histologic grade. In MAGE-A3/6-expressing breast cancer, patients bearing MAGE-A3/6