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Short communication

Proteomic markers in breast cancer diagnosis and treatment

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Introduction

Breast cancer (BC) is the most frequent malignancy among women, but also affecting men and is still a challenge for medical research and practice ("Breast cancer", 2021). Several approaches are currently implemented in its diagnosis, including mammography, ultrasound and magnetic resonance imaging, histopathological evaluation of bioptic/resected material, laboratory evaluation of soluble biochemical markers, molecular testing for Estrogen and Progesterone receptor (ER and PR) as well as HER2/neu protein abundance/gene copies, providing prognostic information for treatment effectiveness. Numerous analyses have been performed to evaluate the protein expression level in malignant cells, to determine the abundance of certain proteins and amino acids in samples of nipple aspirate fluid (NAF), saliva, serum as well as to isolate and characterize circulating tumor cells, circulating tumor DNA and RNA, but the search for sufficiently specific and sensitive markers continues.

Novel markers in diagnosis and treatment

Many studies showed that transmembrane protein (TMEM) expression can be down- or up-regulated in tumor tissues compared to adjacent healthy tissues. TMEM45A and TMEM205 have implications in tumor progression and invasion but also in chemoresistance. TMEM48 is a nucleoporin and is crucial for nuclear pore complexes and nuclear envelope assembly, TMEM45A is a potential biomarker of BC aggressiveness, TMEM97 overexpression is correlated with larger tumor size and tumor recurrences, while TMEM88 overexpression with tumor initiation and progression (Schmit and Michiels, 2018). An overexpression of another important TMEM protein TMEM16A is associated with a favorable prognosis in PR-positive or HER2-negative BC patients following Tamoxifen treatment (Hui et al., 2017). According to a recent study (Lovely, 2022), the activated leukocyte cell adhesion molecule (CD166-ALCAM Gene) is highly expressed in approximately 50% of patients with triple-negative BC (TNBC) and up to 80% of patients with HER2-negative and ER-positive BC. Praluzatamabravtansine is a monoclonal antibody prodrug (Probody® drug conjugate) that is conjugated with the cytotoxic agent Maytansinoid DM4 (with potential antineoplastic activity as a microtubule inhibitor) that binds to CD166 and induces cell death. The study by Ziegler et al. (2018) has identified a group of proteins including SUSD2, FASN, AHNAK, EEF1A1, EEF1A2, that could serve as diagnostic markers and therapeutic targets. In the study of Falchook et al. (2021), the FASN inhibitor, TVB-2640, in combination with paclitaxel, was tested for the first time in humans and demonstrated promising antitumor effects (Falchook et al., 2021), while in another study (Gruslova et al., 2021) TVB-3166 was evaluated as a potential therapy for endocrine-resistant BC. Some experimental models data indicated the involvement of fibroblast growth factor/fibroblast growth factor receptor (FGFR) axis in the tumor progression, paving the way for introducing FGFR inhibitors (including the FDA approved Erdafitinib and Pemigatinib) as a novel class of drug therapy promising effective treatment of breast as well as other types of cancers (Pérez Piñero et al., 2022). Apart from Carcinoembryonic Antigen and CA15-3, recent data also suggest prognostic and predictive importance of certain circulating biomarkers such as CA27-29, Serum HER2 Extracellular Domain and GP88 also known as progranulin-driver of Tumorigenesis (Seale and Tkaczuk, 2022). Shu et al. (2020) has identified 56 novel protein biomarkers significantly associated with BC via the integration of genomics and proteomics data. Moving forward, with the assistance of integrative transcriptome and proteome analyses, we can identify genes, predict

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candidate biomarkers and evaluate proteins that are related to the different stages of BC (Yao et al., 2021).

Components present in the saliva as a biological matrix obtained by non-invasive and cost-effective procedures are closely related to the blood, and biochemical salivary indicators have been identified to differentiate BC patients from healthy controls (Bel'skaya et al., 2022). Another promising source of biomarkers is NAF, originating from the location where BC arises and can be acquired repeatedly and easily for early diagnosis by non-invasive aspiration. This physiological fluid contains proteins specific to the tumor microenvironment but also DNA, RNA and microRNA which can be further investigated as potential laboratory biomarkers of the disease (Patuleia et al., 2022).

Discussion and Conclusion

Proteomics, being just one of the “omics” approaches gains larger involvement in discovering new diagnostic, prognostic and predictive markers of diseases as well as targets for personalized drug design. The currently available data summarized in this study, provide justification and directions for further research focused on the aberrant expression of proteins in various biological specimens obtained from breast cancer patients.

A continuously growing number of studies report the potential of proteomic markers in assessing the risk of developing, diagnosis and staging of BC, forecasting the outcome or predicting treatment effectiveness. Unfortunately, the expression pattern suggested biomarkers are expressed differently in various types of breast cancer, and also individual’s characteristics could affect the biomarker level in patients. Another disadvantage of the studies is the limited sample size if the required biomarker is not easily detectable. Many biomarkers ubiquitously exist in both healthy individuals and cancer patients and because of that many initially, promising biomarkers have not been validated yet, apart from the ones which haven’t demonstrated sufficient sensitivity, specificity, and applicability for clinical use. Hence, these findings warrant multiple independent validation studies for advancement in the clinical application of proteomic biomarkers in BC management.

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