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Circulating proteins as diagnostic breast cancer biomarkers

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ABSTRACT

In women, breast cancer (BC) is the most frequently tumor and is the main cause of cancer-related deaths. Breast cancer is a diverse tumors type with numerous genetic and morphological subgroups, making it challenging to diagnose the disorder and track patient outcomes over time. So, for each patient, biomarkers are required to aim pathologists choose and apply the best therapy. Several reports regarding biomarkers in liquid body fluids have increased. Blood proteins are an important tumor biomarkers source. These circulating components or secreted by cancers are attributed to several biological functions. These blood proteins (extracted from plasma or serum) can be used for minimally invasive, easy, simple and inexpensive determination of cancer risk, disease progression, prognostication and monitoring, treatment adjusting and early diagnosis. In this review, we discussed the main established reports on blood proteins in BC and evaluate the potential of blood proteins to be prognostic or/and predictive breast cancer biomarkers.

Key Words:

Breast cancer; Diagnosis; Prognosis; Blood biomarkers; Prediction.

1. INTRODUCTION

In women, BC is the most frequent, the second reported, tumor with great mortality causing annually millions of cancer-related deaths [1]. In 2020, BC was the most commonly detected female tumor around the world with incidence of > 2.3 million, accounting for 11.7% of total tumor subjects worldwide [2]. It is a heterogeneous disorder with 6 identified molecular subtypes [1].

Imaging of the breast is important in the BC diagnosis preoperative work and screening. Outside of routine mammography, owing to low likelihood of positive results and high cost, screening for recurrence is not recommended for subjects with early-stage BC [3]. In addition, on an ineffective treatment, BC may progress for a significant period before additional imaging is obtained [4]. From another view, clinical and biological BC behavior clearly differs from patient to patient, making disease predictions and patient outcomes evolution difficult [5]. Thus, serum markers are required to aim pathologists choose, for each patient, the best therapy. Tissue-based biomarkers have guided BC treatment for many years. These biomarkers include progesterone and estrogen receptors and human epidermal growth receptor 2 (HER2) [5]. Also, several reports on BC have suggested that almost all tumors produce their constituents into the blood [6, 7]. So, blood can be used to measure biomolecules releasing from tumors.

As a consequence, for discovering new biomarkers, liquid biopsies are more commonly obtained as less invasive alternative for tissue biopsies [5]. Several reports concerning with potential blood markers such as blood genetic material (exosomes, miRNA or circulating tumoral DNA), blood cells, circulating tumor cells [8, 9] or proteins [5].

Blood proteins are an important tumor biomarkers source. These circulating components or secreted by cancers are attributed to several biological functions [10]. Tumor cells gain many abilities for promoting metastasis and progression such as induction of invasion and angiogenesis, growth stimulation or immune response manipulation. These acquired abilities can be reflected or promoted by circulating proteins [5].

Nowadays, non-invasive techniques based on blood proteins quantification and detection is a straightforward way that can be performed frequently and routinely in clinical practice [11]. In addition, during the last decades, a variety of methods for evaluating proteins, including aptamer-based proteomics, antibody array, mass spectrometry (MS) or enzyme-linked immunosorbent assay (ELISA) has been developed [5]. Recently, these assays specificity and capacity have been significantly elevated by new technologies developments that permits the detection of thousands of proteins. So, targeted circulating proteomics is a promising method to identify new markers [5]. In this review, we discussed tumor-produced and the immune system-produced blood proteins that could be potential prognostic/predictive BC biomarkers.

2. BLOOD PROTEIN DETECTION METHODS

Antibody arrays serve as a method for simultaneous profiling of a set of interested proteins from blood or tissue samples using ELISA technique [12]. In this technology, antibodies coated a solid surface, and an immunofluorescent reaction is used to measure the antigen/antibody reaction [5]. Antibody microarray was first used by Miller et al. to assess serum markers of prostate cancer in 2003 [13]. Recently, antibody array, validated by ELISA, capacity to screen new blood biomarkers in BC has been reported [14].

Aptamers are short single-stranded oligonucleotides, which bind to different proteins with great specificity and affinity. In 2010, a new proteomic technology was developed that is based on aptamers [15]. Since this date, this technique has been used to detect circulating biomarkers in several disorders including cardiovascular diseases [16], lung cancer [17] and ovarian cancer [18].

Also, ELISA is well-established method for measuring circulating proteins. Briefly in the liquid sample using antibodies, ELISA assays use solid phase enzyme immunoassay to measure target proteins [19]. ELISA is the most frequently used technique to detect protein levels in plasma/serum of BC patients [10]. By using ELISA, several BC potential markers such as CA15-3 have been identified [20]. Nowadays for several proteins detection at the same time in the same sample, ELISA multiplex was used with significant improvements and great ability to quantify and assess different blood proteins [5].

In an accurate and rapid way, MS permits wide range targeted analysis, untargeted proteomic and body fluids or tissues molecular profiling [21]. MS is composed of a detector, a mass analyser and an ion source, and these methods separate proteins/peptides based on their mass-to-charge ratio [21]. Many reports concerning with protein profiling using MS to determine BC [22, 23], colorectal [24], prostate [25], gastric [26] and ovarian [27] cancers biomarkers.

3. BLOOD PROTEINS PRODUCED BY TUMOR TISSUE

3.1. Human epidermal growth factor receptor 2 (HER2)

HER2 extracellular domain (ECD) is the major example of a protein produced by tumor cells. In 15% of BCs, this transmembrane protein is overexpressed and a proteolytic process produce its ECD from the receptor and shed it from tumor cells into the blood [5, 28]. In BC, HER2 ECD is considered as prognostic biomarker that overexpresses HER2. In patients with HER2-enriched BC, elevated HER2 ECD concentrations positively associated with tumor characteristics such as angiogenesis or vascular invasion [29]. In BC patients, HER2 prognostic value has been studied [30]. By monitoring HER2 in HER2 + BCs, preoperative high HER2 level was reported to correlate with worse prognosis. In patients with disease recurrence, higher baseline HER2 concentrations were observed compared to patients who remained disease-free [31]. Before any treatment in HER2 + metastatic BC patients, elevated blood TIMP1 and HER2 levels predicted short progression free survival (PFS) [32]. Using ELISA, a report suggested that increased HER2 levels were related to poor outcomes including tumor size, histological grade and stage [33].

3.2. Hepatocyte growth factor (HGF)

HGF is attributed to several physiological processes like cellular growth, tissue and cell survival and morphogenesis. Also, it facilitates tumor metastasis and invasion by activating its receptor cMet [5]. Using ELISA, blood HGF in hormone receptor negative/positive BC patients was detected. Great levels were correlated with metastases and recurrent BC [34]. Other studies reported that serum HGF was associated with BC poor prognosis and metastatic BC [35, 36].

3.3. Transforming growth factor β1 (TGF-β1)

In tumoral progression promotion, TGF-β1 play a significant role at the tissue level [37]. Former studies reported that blood TGF-β1 in BC was correlated with treatment response and recurrence risk [38]. Also regardless of BC subtype, TGF-β1 plasma concentrations were markedly increased in BC late-stage (stage III-IV) compared to healthy controls [38, 39]. In triple negative BC (TNBC), TGF-β1 quantification after and before chemotherapy has shown a correlation between bad chemotherapy response, relapse and increased metastasis incidence and high TGF-β1serum levels. Moreover, decreased disease-free survival was notably associated with increased TGF-β1 blood concentrations [40]. In TNBC, serum proteomes analysis was quantitatively used to identify proteins predictive of metastases and progression. They reported that TGF-β-associated proteins high plasma levels were correlated to TNBC tumor poor outcomes and progression [41].

3.4. LRP6 ectodomain (LRP6N)

LRP6N serves as co-receptor for inducing Wnt signals and is important in β-catenin-dependent canonical Wnt signalling pathway stimulating. It is reported to promote tumor development and progression [5]. In metastatic BC patients, LRP6N serum levels were analysed in in vivo and in vitro and they suggested that LRP6N may be BC diagnostic biomarker for early disease diagnosis. In the metastasis groups, blood LRP6N was downregulated [42].

3.5. Tissue inhibitor of metalloproteinase 1 (TIMP-1)

TIMP-1 may affect tumor invasion and growth through limiting matrix metalloproteinases (MMPs). Compared to normal tissues, TIMP-1 concentrations are greater in cancers tissues and these proteins promotes angiogenesis, tumorigenesis and cell growth [43]. Tissue as well as serum TIMP-1 levels negative prognostic impact was reported in BC and other tumors. In metastatic BC, Increased TIMP-1 levels serve as prognostic biomarkers [44]. In metastatic BC (HR +, HER2 +, and TNBC) using ELISA, it was reported that median PFS was 11.4 and 7.2 months with low and increased TIMP-1 concentrations, respectively [44]. Another study conducted on BC patients, they found that elevated blood concentrations of both TIMP-1 and MMP-9 were attributed to over survival and lower progression-free survival rates [45]. In metastatic HER2 + BC patients treated with trastuzumab or lapatinib, TIMP-1 concentrations were serving as shorter PFS prognostic factors [32].

3.6. Matrix metalloproteinase (MMP) 9

MMPs are intracellular endopeptidases that require zinc (Zn2+) ions [46]. MMPs are attributed to ECM proteins degradation like fibronectin or collagen and help in ECM remodelling in pathological and physiological processes [47]. In several tumors MMP levels are elevated and are correlated to poor clinical outcomes and elevated metastases [48].

In BC tissues MMP9 expression is high [49]. Over the past few years, MMP9 potential for BC metastasis prediction has been explored and they suggested an association between BC metastasis and high serum MMP9 levels [50-52]. MMP-9 serum levels in BC patients using ELISA were reported to be markedly higher than benign tumor group, regardless of BC subtype [51]. In HER2 + BC patients, other studies demonstrated that elevated MMP9 and HER2 serum levels were related to brain metastases [53]. One of clear TNBC features is the high tissue MMP9 level which is correlated with poor prognosis [54].

3.7. Vascular endothelial (VE)-cadherin

In endothelial adherens junction maintenance and assembly, VE-cadherin plays important role. It controls vessels permeability and integrity [55]. VE-cadherin was reported to has the ability to promote TGF-β pathway, which is implicated in cell proliferation and tumor growth [56]. In TNBC, HER2 + and luminal BCs, VE-cadherin concentrations assessment is appropriate to differentiate between non-recurrent and recurrent tumors [57]. In contrast to patients with no recurrence, VE-cadherin concentrations were increased in metastatic BC. Interestingly in hormone-resistant metastatic BC, VE-cadherin serves as survival prognostic factor [58].

3.8. Vascular endothelial growth factor (VEGF)

Angiogenesis affects cancer spread and development. It is generally recognized that VEGF is crucial for tumor metastases, blood vessel permeability and angiogenesis [59]. Close association between BC disease prognosis and serum VEGF concentration was reported using ELISA [60]. Compared to before surgery, VEGF level declined significantly after breast surgery. In patients with elevated VEGF concentrations, advanced BC stages were found [60]. Several reports suggested that elevated VEGF blood concentrations are related to BC poor outcome [61-63]. In about 30-60% of TNBC patients, VEGF is highly expressed and represented a prognostic biomarker [OS was 10.2 and 4.2 months in high and low VEGF concentrations, respectively] [60]. Later, a high VEGF expression in TNBC was correlated with poorer OS, metastasis and a worse response to chemotherapy [40, 64].

3.9. Insulin growth factor 1 (IGF I) and platelet-derived growth factor (PDGF)

IGF I is clearly implicated in BC and it is an critical for growth regulation, invasion, migration and survival [5]. High IGF I serum levels were related to recurrence and metastasis in TNBC [14]. Another growth factor known to work in concert with IGF-I is PDGF [5]. By analyzing postmenopausal BC patients' sera, the impact of blood PDGF and IGF I concentrations on recurrence risk was reported [65].

Compared to low PDGF level, BC recurrence hazard ratio (HR) for high PDGF level was 2.8. For high IGF-I, HR of recurrence was 3.7. Interestingly in the presence of increased blood PDGF concentrations, they reported that IGF-I may elevate recurrence risk [65].

3.10. Haptoglobin (HP)

A serum glycoprotein called HP binds unbound haemoglobin and inhibits oxidative activity and prevents the iron loss [66]. Blood HP overexpression has been found in several tumors, including leukemia, lung, bladder, oesophageal and gastric cancers [67]. Also in some trials, elevated serum HP levels were also found in BC patients and have been related to poor outcomes [68]. In TNBC patients, it was reported that serum HP expression could be a potential biomarker [69]. BC patients with elevated HP concentrations had the lowest survival rate and the worst prognosis [69]. Blood proteomes analysis were detected using MS in non-TNBC and TNBC patients, they found significant elevated serum HP expression in TNBC [70]. Also, in a TNBC xenograft human model, up-regulation of serum HP was found after disease metastasis, indicating HP potential as a metastasis marker [71].

3.11. TIE-1/2 and angiopoietin 2 (Ang-2)

Angiopoietins family is constituted of released proteins that all linked to an endothelial receptor (Tie2) and are promoted by both Tie-1 and -2. In presence of VEGF, Ang-2 is markedly implicated in angiogenesis. And Tie2 controls metastatic production and tumor development (growth and angiogenesis) by Ang/Tie axis [72]. Correlation between the outcome and/or progression of patients with various tumors and Ang-2 levels has been studied. Varied studies suggested that aberrant Ang-2 expression stimulates tumor progression and tumorigenesis [73, 74]. In BC patients and regardless of BC subtypes, serum Ang-2 was greater than in healthy controls and was related to metastasis and worse OS [75]. Compared to benign breast disease, other studies found that serum Ang-2 was clearly overexpressed in BC, yet there was no proof of a relation between BC clinical-pathologic parameters and serum Ang-2 levels [76].

3.12. Programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1)

PD-1 is an immune checkpoint receptor that promotes immune surveillance and T-cell activation [77]. The primary PD-1 ligand, co-inhibitory receptor that could be activated in normal epithelial, lymphoid, myeloid and tumor cells is PD-L1. PD-L1/PD-1 binding under physiological conditions is important in immune tolerance, as it stops extra immune cell activity that can resulted in autoimmunity and tissue destruction [77]. By numerous tumors, expression of PD-L1 is immune elusion mechanism that is suggested as immunotherapies response predictive biomarker [5]. PD-1/PD-L1 inhibitory treatments are becoming interested new antitumor treatments in varied tumor types like melanoma, lung tumor, and many others [77]. In BC, expression of PD-L1 in tumor cells is related to OS and chemotherapy response [74]. Moreover, blood mononuclear cells expression of PD-L1 mRNA may be related to BC development and progression [78]. In TNBC, PD-1 and PD-L1 high serum concentrations were observed compared to healthy controls. Also, TNBC patients with partial or complete treatment response had significantly lower PD-1 and PD-L1 levels after compared to before treatments [79]. In HER2-positive metastatic BC treated with lapatinib or trastuzumab, increased blood PD-L1 concentration before treatment was significantly related to longer OS in the lapatinib group [80]. Before treatment, another study found that elevated PD-L1 concentration was related to poor prognosis and short PFS of metastatic BC [81].

3.13. Carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA15-3)

For decades, serum CEA and CA15-3 are studied as predictive/prognostic BC biomarkers [5]. CEA identified as a tumor-specific antigen and it is a cell-surface glycoprotein. In some adenocarcinomas, it is a useful biomarker. It is the most frequently approved blood BC biomarker. CA15-3 is a mucin-1 family member that is overexpressed in tumors [5, 82]. Prior

to chemotherapy, serum CEA and CA15-3 levels and other factors of TNBC were tested. Compared to low concentrations, increased CA15-3 (HR: 2.627) and CEA (HR: 2.293) concentrations were related to shorter OS [83]. Other studies also reported that increased serum levels of the 2 proteins were related to high death risk in TNBC [84].

3.14. Proteins ratios

Some studies reported the value of the ratio between blood proteins. Attallah et al., for example, evaluated the value of epithelial membrane antigen (EMA)/ cytokeratin-1 (CK1) ratio in BC diagnosis. They found that this ratio improved the efficacy of BC diagnosis (sensitivity of 82% and specificity of 76%) than any single biomarker could achieve alone. The EMA/CK1 ratio was correlated significantly with BC stage, grade and size [85].

4. THE IMMUNE SYSTEM SECRETED PROTEINS

4.1 Interleukin-6 (IL-6)

IL-6 is a cytokine released specifically by normal haematopoietic and endothelial cells. It is involved in acute phase response proteins upregulation that involved in several processes including inflammation or cell proliferation [5]. Clearly, IL-6 represent as tumor progression and promotion factor. For example, it stimulates P53 gene and thus promotes growth. Also, IL-6 promotes tumor metastasis and invasion and several other tumor processes [86]. IL-6 may be involved in VEGF construction and in its upregulation. The IL-6 and VEGF prognostic values were tested in hormone-resistant metastatic BC and suggested IL6 as survival prognostic biomarker. Increased IL-6 concentrations were related to poor survival (13 versus 4 months in low and high serum IL-6 concentrations, respectively) [62]. Other studies in ductal BC patients highlighted the correlation between lymph node metastasis, advanced clinical BC stages and elevated blood IL-8 and IL-6 concentrations [87].

4.2 Lipocalin 2 (LCN2)

In innate immunity, LCN2 glycoprotein is serve as a factor inhibiting bacterial growth. In neutrophils, it was initially found in a compound with MMP-9 and found to be highly expressed [5]. In acute organ injury, it was know that LCN2 involved and is in particular used as acute kidney injury biomarker [88]. It is also has significant role in several biological processes like cancer growth, lipophilic molecules transport and inflammatory response [5]. Some trial reported its role in tumors establishment especially BC. Compared to healthy women, higher LCN2 serum levels were found in BC patients [89]. In invasive ductal BC, great levels, as detected by ELISA, were associated with increased severity score. In addition, LCN2 and MMP9 blood levels were correlated [90].

4.3 Cytokines

Cancer and inflammation are intrinsically related. Alters in cytokine concentrations affect tumor development and progression [5]. In BC subjects treated with bevacizumab and paclitaxel with/without capecitabine, association between hypoxia- and blood angiogenesis-associated proteins and patient outcome was reported [91]. Serum cytokine profiles were analysed in BC patients through ELISA [14]. Macrophage Inflammatory Proteins-1 α and β were markedly increased in BC subjects. In $HER2^+$ patients, an association between increased distant recurrence risk and IL-6 was demonstrated [92]. In premenopausal ER^+ BC patients, based on IFN-γ blood levels, some authors classified subjects into 2 groups. In contrast to the IFN-γ low subgroup (33%), they found a decline (4%) in incidence of distant recurrence in the IFN-γ high group [93].

5. CONCLUSION

This review discussed serum or plasma proteins represented potential BC prognostic and predictive biomarkers. For example, high MMP-9 serum levels have been suggested to predict metastasis and treatment response whereas high TIMP1 serum levels are promising poor OS indicators of BC patients. Moreover, increased serum TGF-β1, VEGF and Ang-2 levels remain important short OS biomarkers.

Interestingly across studies, we can see similar findings on clinical relevance and the role of each protein presented in our review that confirms the importance of further investigations.

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