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BIOMARKERS (S DAWOOD, SECTION EDITOR)

Biomarkers and Therapeutic Targets in Inflammatory Breast Cancer (IBC)

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Abstract Inflammatory breast cancer (IBC) is the most aggressive type of breast cancer with survival rates far lower than other types of breast cancer. Patterns of development, invasion, and presentation are unique to IBC compared with other breast cancers. However, therapies targeted specifically to the treatment of IBC are lacking. Specific therapies, which address the unique features of IBC, are needed to improve prognosis for this type of breast cancer. The first step in developing improved treatments is to identify biomarkers and genes, which are preferentially expressed in IBC and to develop therapies targeted to these markers. In this paper, we discuss advances made in the studies of biomarkers and gene expression in IBC over the last 5 years. Some of the markers have proven to be prognostic or predictive of response to therapy. In some cases, therapies targeted for biomarkers are already used in the treatment of cancer and could be evaluated in IBC patients.

Keywords Inflammatory breast cancer · Biomarkers · Gene expression · Targeted therapy

Introduction

Inflammatory breast cancer (IBC) is the most aggressive type of locally advanced breast cancer. IBC is characterized by poor prognosis, early metastatic development, and rapid proliferation of tumor [1]. The 5-year overall survival rate among IBC patients without metastatic disease at time of diagnosis is approximately 40 % [2]. Because IBC is relatively rare among breast cancer patients (approximately 1 %–5 % of new breast cancer cases) [3, 4], there are no treatments specific to this patient population. This is a sorely needed area in breast cancer research and treatment, given the more aggressive nature and higher mortality rate of this disease. In working toward the goal of specialized treatment for patients with IBC, multiple studies have been conducted to elucidate biomarkers and potential targets for treatment in this population. In this review, we will summarize recent data regarding biomarkers and possible targets that may prove to be useful in the treatment of IBC patients. Table 1

One of the difficulties in studying IBC is that there are few models available. Most studies have been performed on SUM149, a triple negative cell line, and SUM190, an estrogen receptor (ER) and progesterone-negative(PR), and Her-2 overexpressed cell line [1]. Fernandez and colleagues report the characterization of another triple negative IBC model, FC-IBC02. These tumor cells were grown from the pleural effusion of a patient with IBC. The FC-IBC02 cells successfully grew in SCID mice and metastasized in the lung and nodes quickly developed. Furthermore, tumor emboli, a characteristic pathologic and biological feature of IBC, formed in the lymphatics of the mice. The FCB-IBC-02 cells, breast xenograft and lesions in the mice expressed both E-cadherin and β-catenin. The cells also showed expression of the membrane tetraspanin 24 (TSPAN24/CD151). The expression of these markers suggest that adhesion molecules that maintain cells-cell adhesions may provide a survival advantage for IBC cells in transit through circulation. Interestingly, IBC cells in this line did not show all of the characteristic patterns of epithelial-mesenchymal transition (EMT), which is thought to contribute to metastatic progression. Rather, IBC cells expressed more markers of epithelial cells. Several genomic changes

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Table 1 Biomarkers in IBC

Biomarker/process	Type of studies conducted	Associations
EZH2 (cancer stem cells)	In vitro, In vivo, patient samples	Inhibition slows growth in vitro, in vivo, expression correlates with poor prognosis, higher grade, ER- and triple negative cancer, decreased OS in patient specimens.
VEGF A (angiogenesis)	Patient samples	Expression correlates with decreased BCSS and OS.
P53 (tumor suppressor)	Patient samples	Expression correlates with decreased OS in patients with visceral metastases.
ALDH1 (cancer stem cells)	In vitro, In vivo, patient samples	Mediation of tumor invasion in vitro, in vivo. No correlation with prognostic factors in patient specimens.
EGFR (growth-factor receptor)	In vitro, In vivo, patient samples	Inhibition slows growth in vitro, in vivo. Expression correlates with decreased OS, increased risk of recurrence in patient specimens.
Amphiregulin (EGFR ligand)	In vitro, In vivo	Inhibition slows growth in vitro, in vivo.
CXCR4, CCR7 (chemokines)	Patient specimens	Expression correlates with decreased OS.
Androgen Receptor (nuclear receptor)	Patient specimens	Decreased OS, DSS in patients with ER-/AR- tumors. Trend toward improved survival in ER-/AR+tumors.
Histone deacetylase (chromatin modeling)	In vitro, In vivo	Inhibition decreases tumor size, destroys tumor emboli and vascular architecture.

AR androgen receptor, *BCSS* breast cancer specific survival, *DSS* disease specific survival, *ER*, estrogen receptor, *IBC* inflammatory breast cancer, *OS* overall survival

were noted, including amplification of NOTCH3, MYC, ATAD2, metadherin (MTDH), and FAK1 [1]. This cell line represents a novel cell line, which will be useful in further characterizing biomarker expression and behavior of IBC cells in vitro and in vivo.

Biomarker Expression in IBC

A study conducted on SUM149 and FC-IBC-02 investigated the expression of EZH2, enhancer of zeste homolog, which is a catalytic subunit of polycomb repressive complex 2 (PRC2). EZH2 is upregulated in cancer and is associated with proliferation, apoptosis, invasion, and self-renewal [5]. An in vitro study of FC-IBC-02 cells demonstrated that EZH2 knockdown suppressed the formation of tumor spheroids. In vivo, tumor growth was suppressed. Expression of EZH2 in IBC was evaluated in 88 tumor specimens from patients with IBC and residual disease after neoadjuvant chemotherapy. EZH2 expression was associated with poor prognosis, higher tumor grade, ER negative status, and triple negative status and worse clinical outcome, including decreased overall survival [6].

Because IBC is an angiogenic disease, a retrospective study of tumor samples from IBC patients was conducted to determine the value of levels of VEGF-A and its receptors in tumor specimens by immunohistochemistry [7]. One hundred-seventeen IBC samples were used, 103 ductal IBC, and 25 normal specimens. VEGF-A expression was found to be a prognostic marker for disease free survival (DFS) and breast cancer specific survival (BCSS) in IBC patients. Survival analysis found that high stromal VEGA-A expression was prognostic for poor BCSS in ER +, Her-2+ patients. VEGA-A expression was also correlated with poor BCSS and DFS in node positive patients. VEGF-A expression in ER-positive breast cancer was predictive of poor BCSS in patients receiving tamoxifen [7].

Accumulation of p53 protein in the primary tumor was found to be a prognostic factor for overall survival in IBC patients with metastatic disease. In this study, tumor samples from 45 patients with metastatic IBC were examined for expression of p53 and ER, PR, c-erbB-2, and Ki-67. In a univariate analysis, p53 accumulation and presence of visceral metastases was predictive of poor survival. The median OS for patients with p53 positive disease was 17 months compared with 43 months for those without organ involvement. Accumulation of p53 was found in 51 % of the patients [8].

The role of cancer stem cells (CSC) in IBC metastases was examined in in vitro cell lines and mouse xenografts. Cells were isolated from human IBC samples grown as xenografts in NOD/SCID mice. Aldehyde dehydrogenase 1 (ALDH1), a stem cell marker was measured by immunostain in paraffin-embedded sections. The SUM149 cell line from a patient with primary IBC and the Mary-X xenograft from a patient with IBC were used in the study. ALDEFLUOUR-positive cells were able to mediate tumor invasion in vitro and in vivo as metastases in mouse xenografts. Expression of ALDH1 was associated with early metastasis and poor prognosis in IBC patients [9]. A study of the expression of ALDH1 is IBC tumor samples after surgical resection showed that 32 % of 74 samples expressed ALDH1, but the expression was not significantly associated with tumor grade, ER/PR status, node status, or Her-2 expression. There was no significant

association between ALDH1 expression and overall survival rate in this series [10].

Notch pathways play a role in self-renewal of breast cancer stem cells. Notch signaling was inhibited by a gamma secretase inhibitor, R04929097, in an in vitro model of SUM 149 and SUM 190 cell lines. T-cell synthesis of cytokines TNF-α, which mediated IL-6 and IL-8 production were inhibited. Expression on NOTCH receptors in IBC stem cell population was evaluated and a 2-fold higher expression of Notch1, Notch2, and Notch3 receptors was found in ALDH+ subpopulation vs the ALDH- subpopulation. Growth inhibition when treated with R0429097 was inhibited 20 % for SUM149 and 10 % for SUM190, relative to controls. Colony formation was also inhibited [11].

Biomarkers in IBC with Therapeutic Implications

Epidermal growth factor receptor (EGFR) has been found to be overexpressed in as much as 30 % of IBCs in 1 case series [12, 13] and is correlated with poor prognosis with worse OS and increased recurrence risk [13]. In a study of 44 tumor specimens from IBC patients, 30 % expressed EGFR, and chemokines, CXCR4 and CCR7, were expressed in 40 % and 22 %, respectively. Expression of EGFR or chemokine receptors correlated with worse OS. In vitro studies of EGFR inhibitors have shown that this class of agents may be useful in the treatment of IBC [13]. Amphiregulin is an EGFR ligand that regulates the EGF-independent growth of SUM-149 cells in vitro [14] and activation of a self-sustaining amphiregulin/EGFR loop results in increase in steady state levels of EGFR, decreased phosphorylation of EGFR, and less ubiquitination of the receptor compared with EGFR activated by epidermal growth factor [14]. Knockdown of amphiregulin in vitro in SUM 149 cells slowed the rate of growth of the cell line and a decrease in the invasiveness of the cells [15]. An in vitro study of AZD8931, a small molecule inhibitor of EGFR, Her-2, and Her-3 demonstrated suppression of growth and apoptosis in SUM149 and FC-IBC-02 lines. In vivo growth studies were also performed in immunodeficient mice. AZD8931 was given as a single agent and in combination with paclitaxel twice weekly. Paclitaxel twice weekly was also administered as a single agent. AZD8931 alone and in combination with paclitaxel showed activity in EGFR-overexpressed IBC. The combination was more effective in demonstrating signal inhibition and antitumor activity than either single agent [12].

Alterations in expression of the anaplastic lymphoma kinase (ALK) gene have been implicated in a variety of cancers, including anaplastic large-cell lymphoma, neuroblastoma, and non-small cell lung cancer (NSCLC) [16]. Fusion of ALK gene and EML4 (echinoderm microtubule-associated protein-like 4) is a therapeutic target in NSCLC patients. Treatment with crizotinib (Xalkori), an ALK inhibitor, increased progression-free survival in a population of previously treated, metastatic ALK+NSCLC patients compared with standard second-line chemotherapy and were approved by the FDA for use in this patient population. There have been few studies of ALK in breast cancer in IBC. Reverse phase microarray pathway mapping studies demonstrated amplification of ALK in 13/15 patient tumor specimens and 66 % of IBC cell lines. In this study, ALK amplification was not found in SUM149, SUM190, or KPL-04 cells. Tumor cells isolated from the pleural effusion of an IBC patient showed sensitivity to treatment with crizotinib and resistance to paclitaxel. An analysis of 25 IBC patient tumors for ALK genetic abnormalities showed that 80 % of the samples demonstrated an abnormality in the expression of ALK. These finding included alterations in ALK copy numbers, gene amplification and translocation of EML4-ALK. Cells lines from FC-IBC01, FC-IBC02, and Mary-X cells expressed the highest levels of ALK gene expression. In vivo studies of FC-IBC01 and SUM149 cells demonstrated that the crizotinib was cytotoxic [17]. A study of core biopsy samples from 30 IBC patients showed no ALK gene rearrangement, but increased copy levels of the ALK gene as a consequence of chromosome 2 aneusomy [16]. The role of ALK inhibitors in IBC is a promising avenue that merits further study, particularly due to the availability of crizotinib, an agent targeted to this genetic alteration.

The role of androgen receptor signaling in breast cancer is an emerging area of research. Androgen receptor (AR) is a member of the steroid hormone family and can be targeted by anti-androgen agents, which are currently approved for the treatment of patients with advanced prostate cancer [18]. A study of 88 patients with primary IBC was conducted to evaluate the expression of androgen receptor. AR expression was found in 39 % of IBC tumors. Expression of AR was associated with lymphovascular invasion. Patients with AR negative/ER negative tumors had significantly worse OS and disease specific survival (DSS) compared with other patients, but there was a trend toward improved survival among patients with ER-negative/AR positive tumors [18]. This was the first study of AR expression in IBC and represents a promising treatment option for patients IBC and thus, should be validated in additional studies.

In vitro and in vivo studies of HDAC inhibitors, which target histone deacetylase have provided evidence that this class of drug may be efficacious in the treatment of inflammatory breast cancer [19]. In vitro data derived from treatment of 2 IBC cell lines with HDAC inhibitors, CG-1521 and Trichostatin A (TSA) suggest activity of the 2 drugs [20]. Preclinical models of spheroids of IBC developed from pleural effusion aspirates were treated with a pan-HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA). The spheroids showed inhibited self-renewal, a decrease in aggregation of cells, and decrease of invasion of the cells. There was also a loss of the 3D structure of the spheroids, associated with a

change in location of expression of the E-cadherin [19]. Preclinical studies have also been performed with the class I HDAC inhibitor, romidepsin (Istodax), in IBC [21]. Treatment of a preclinical model of IBC with romidepsin showed destruction of IBC tumor emboli and vascular architecture. In addition, treatment with romidepsin alone and with paclitaxel in mouse models with an IBC cell line, SUM149, demonstrated that both single agent romidepsin and the combination eliminated primary and metastatic tumors [21]. The clinical utility of romidepsin in combination with a taxane is a promising therapeutic option for the treatment of IBC. A phase I/II trial is currently being conducted with the combination of romidepsin and nab-paclitaxel in patients with metastatic inflammatory breast cancer to determine the tolerability of the combination and the activity in IBC patients (NCT01938833).

Genetic Expression in IBC

Gene expression profiling has also been investigated to identify specific signatures and pathways for prognostic stratification and therapeutic targeting. Woodward and colleagues performed a comparison of microdissected IBC and non-IBC tumor cells in gene expression. In this study, 20 IBC samples from core biopsies were used. Twenty non-IBC and 5 normal breast tissues were used for comparison. While differences in gene expression were found between IBC and non-IBC samples, a specific IBC signature was not found. Fifteen genes were found to be correlated between mRNA upregulation and increased gene expression, clustered at 6p21 [22].

Van Leare et al conducted an expression profiling analysis of 137 patients with IBC that were compared with 252 samples from patient with non-IBC. Affymetrix profiles were determined for 3 datasets from 3 different sites. Each sample was classified according to molecular subtype by PAM50. Seventy-five percent of the IBC samples were more aggressive subtypes, basal-like, Her-2 –enriched, claudin-low, or luminal B, compared with 54 % of non-IBC tumors. Some IBC-specific molecular changes were identified. MARCKS, a gene involved in cell motility was differentially expressed between IBC and non-IBC. Other genes overexpressed genes in IBC included RAC1, RHOF, and FNBP1. Reduced signaling of TGF-B was found in the IBC patients compared with non-IBC. This finding suggests that the epithelial-mesenchymal transition (EMT), which is induced by TGF-B may not be the primary means of cell migration in IBC [23].

Bertucci et al examined 137 IBC samples and 252 non-IBC samples for prognostic and predictive signatures for response to neoadjuvant chemotherapy. Among patients who had achieved a pathologically complete response in treatment with neoadjuvant chemotherapy, 2 immune pathways (IFN-α and INF-γ) were found to be hyperactive, and 3 pathways were hypoactive (EGFR, P53, and TGBβ). In a list of 107 genes with different expression between responders and nonresponders, T-cell dependent immunology was overrepresented among the genes [24].

Expression of tazarotene-induced gene 1 (TIG1) was studied in IBC in vitro and in vivo. Increased expression of this gene was first reported in triple negative breast cancer [25]. Operative tissues from 88 patients with IBC and 3 IBC cell lines (SUM149, KPL-4, and SUM190) were studied for TIG1 expression [25]. Seventy-three percent of IBC tissues were TIG1 positive, and this expression correlated with worse clinical outcomes. In vitro data showed expression in 2 of 3 cell lines. The in vitro models demonstrated reduction of proliferation of IBC cells with inhibitions of TIG1 and reduced migration and invasion of IBC cells. Likewise, inhibition resulted in decreased tumor growth in a xenograft model. The in vitro model also provided evidence for interaction between TiG1 and the Axl gene, which codes for a receptor tyrosine kinase [25].

MicroRNAs (miRNAs) are a class of naturally occurring small noncoding RNAs. Mature miRNAs are 19- to 25-nucleotide-long molecules that are cleaved from 70- to 100-nucleotide hairpin pre-miRNA precursors [26]. miRNAs regulate the expression of genes and play a vital role in almost every biological process, including cell differentiation, turning signaling pathways on/off, apoptosis, and cell proliferation [27]. It has been revealed that miR-21 overexpression was correlated with advanced tumor stage, lymph node metastasis, and poor survival of the on-TNBC patients, indicating that miR-21 may serve as a molecular prognostic marker for BC and disease progression [28]. As the most significantly upregulated miRNA in breast tumor biopsies [29], miR-21 was significantly higher in ERα positive than ERα negative breast cancers.

Anfossi and colleagues conducted a prospective study of 113 IBC patients for a study of serum micro RNAs (MiRNAs), a class of noncoding RNA molecules. The serum of the IBC patients was compared with that of healthy donors. MiR-21, miR-10b, and miR-19a are overexpressed in breast cancer. These markers regulate invasion, metastases, and angiogenesis. Levels of these markers were quantified in the serum of the IBC patients and healthy controls. There was an association found between patients with metastatic IBC and higher serum levels of miR-19a compared with nonmetastatic IBC patients. Higher levels of MiR-19a were associated with favorable clinical outcome in patients with metastatic IBC. Higher levels of miR-21 were found in serum of patients with nonmetastatic Her-2 overexpressed IBC, and higher levels of miR-10b were found in the serum of patients with metastatic IBC compared with stage-matched patients with Her-2 negative breast cancer [30].

Another study using miRNAs analysis was conducted in 203 breast cancer patients, 77 of these were IBC patients [31]. Eight normal breast tissues, 31 non-IBC and 12 IBC samples

were used as a screening set to identify miRNAs expressed between IBC and non-IBCs. The selected miRNAs were then validated in 95 non-IBC and 65 IBC tumor samples. After examining 804 miRNA in IBC and non-IBC patients, 13 were confirmed to be deregulated in IBC compared with non-IBC and 7 of them were deregulated in IBC compared with normal controls and IBC compared with non-IBC. Hierarchal clustering analysis of the original 13 miRNAs identified a group of 5 that most accurately discriminated between IBC and non-IBC tumors. The signature was composed of miR-720, miR-503, miR-486, miR-421, and miR-1303. This signature correctly clustered 60 of 65 IBC tumors and 82 of 95 non-IBC tumors. This signature was also able to distinguish between tumors with aggressive behavior, higher recurrence, and poorer prognosis. The tumors that had a signature, which was "IBC-like" were most likely to be more aggressive. However, the signature could not predict aggressiveness among an all IBC tumor sample. MiR-503 was the most overexpressed in IBC compared with non-IBC samples [31].

Conclusions

As more research is conducted into biomarker and gene expression associated with IBC, rational approaches to clinical treatment of IBC can be translated into the clinical arena. This is vitally important to advance the treatment and prognosis of patients in this select patient population. Preclinical studies demonstrate that IBC is a disease with aggressive clinical features, including early local and distant recurrence and resistance to standard systemic and local therapies. The resistance can be due to the presence of high proportion of tumor cells with phenotypic characteristics of cancer stem cells. Therefore, therapeutic interventions that affect the various processes of self-renewal of these cells can contribute to improved sensitivity to standard therapy and improved survival. Among the therapeutic agents that target properties of cancer stem cells are EZH2-inhibitors, NOTCH-inhibitors, and HDACs-inhibitors, which are currently undergoing clinical testing in IBC.

The use of the next genomic sequencing (NGS) is expanding our understanding of genomic abnormalities in IBC while contributing to the identification of actionable molecular targets with the chance of better therapeutic options and reducing empiricism. Such approaches have been able to identify mutations in ESR1, EGFR, and Her-2 translating in effective therapeutic options using available drugs [32, 33].

In summary, the prognosis of IBC remains dismal in consideration of the aggressive nature of the disease and the resistance to standard therapies. Using advanced diagnostics and novel preclinical models is contributing to improve understanding of the molecular features of the disease translating in innovative clinical trials and more standard therapeutic options for this deadly disease.

Compliance with Ethics Guidelines

Conflict of Interest Tiffany Avery and Massimo Cristofanilli declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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