Minireview: Basal-Like Breast Cancer: From Molecular Profiles to Targeted Therapies

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The classification of breast cancer into molecular subtypes with distinctive gene expression signatures that predict treatment response and prognosis has ushered in a new era of personalized medicine for this remarkably heterogeneous and deadly disease. Basal-like breast cancer (BLBC) is a particularly aggressive molecular subtype defined by a robust cluster of genes expressed by epithelial cells in the basal or outer layer of the adult mammary gland. BLBC is a major clinical challenge because these tumors are prevalent in young woman, often relapsing rapidly. Additionally, most (but not all) basal-like tumors lack expression of steroid hormone receptors (estrogen receptor and progesterone receptor) and human epidermal growth factor receptor 2, limiting targeted therapeutic options for these predominantly triple-negative breast cancers. This minireview will focus on new insights into the molecular etiology of these poor-prognosis tumors that underlie their intrinsic genomic instability, deregulated cell proliferation and apoptosis, and invasive tumor biology. We will also review ongoing efforts to translate these fundamental insights into improved therapies for women with BLBC. **(*Molecular Endocrinology* 25: 199–211, 2011)**

Breast cancer is the most common noncutaneous malignancy in women and second only to lung carcinoma in cancer mortality (1). In the United States, women have an estimated 12.0% lifetime risk of being diagnosed with breast cancer; the risk of breast cancer-related death is estimated at 2.82% (2). One of the genuine triumphs of personalized medicine in the last decade has been the molecular classification of breast cancer based on gene expression profiles. Transcriptome analyses of human breast tumors have revealed remarkably robust molecular subtypes with distinctive gene signatures (differential expression of an ~500 intrinsic gene subset) and clinical outcomes (3–6). These intrinsic subtypes include luminal A and B, defined by the expression of genes in the luminal epithelial layer of the mammary gland, such as the estrogen receptor (ER) and its targets; human epidermal growth factor receptor 2 (HER2/ErbB2), characterized by high expression of the HER2 oncogene and neighboring genes on its 17q12–21 amplicon; basal-like, defined by expression of genes characteristic of the outer or basally located epithelial layer of the mammary gland, such as cytokeratins 5 and 17 and the epidermal growth factor receptor (EGFR/HER1); and normal-like, which express adipose and other nonepithelial genes and have high basal-like and low luminal gene expression. Strikingly, these molecular subtypes are strongly associated with survival: luminal A tumors have the most favorable prognosis, normal-like tumors have an intermediate prognosis; luminal B, HER2-positive, and basal-like tumors are associated with the shortest relapse-free and overall survival (4–6). Molecular subtypes also predict treatment response, with HER2-positive and basal-like tumors paradoxically having higher rates of complete response to presurgery chemotherapy than luminal and normal-like

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Abbreviations: BLBC, Basal-like breast cancer; CGH, comparative genome hybridization; CNA, copy number aberration; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LOH, loss of heterozygosity; MEK, MAPK kinase; miRNA, microRNA; PARP, poly(ADP) ribose polymerase; PI3, phosphatidylinositol-3; PR, progesterone receptor; PTEN, phosphatase and tensin analog; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

tumors (7). Overall, gene profiling has radically altered our conceptualization of breast cancer and provided a myriad of translational opportunities to improve (*i.e.* personalize) prognostic and therapeutic approaches to this disease.

Of all the molecular subtypes, basal-like breast cancer (BLBC) remains the greatest challenge because of its clinically aggressive nature and poorly characterized molecular pathogenesis. Unlike ER-positive luminal tumors and HER2-positive tumors, the basal-like subtype typically lacks expression of the molecular targets that confer responsiveness to highly effective targeted therapies such as tamoxifen and aromatase inhibitors (ER) or trastuzumab (HER2 amplification) (8, 9). Indeed, identification of the relevant molecular targets in BLBC remains a formidable challenge. Although there are several excellent reviews on various aspects of BLBC (8–12), the present review will highlight recent discoveries that have led to fundamentally new insights into the molecular etiology of these tumors and emerging efforts to translate these discoveries into improved therapies.

Basal-Like or Triple-Negative: Capturing the Gene Signature in the Clinic

Although the intrinsic subtypes have robust prognostic and predictive value (4–7), standard microarray-based transcriptional profiling, which requires fresh frozen tissue, is not currently feasible in the clinic. One potential strategy to overcome this translational barrier is a 50-gene subtype predictor that utilizes quantitative RT-PCR analysis of clinically available breast tumor tissue to determine molecular subtype (13); however, this methodology is a research tool at present that needs to be validated in additional cohorts. A more practical strategy is the use of immunohistochemistry to identify protein expression surrogates for the basal-like gene signature. Basal-like tumors are generally ER- and progesterone receptor (PR)-negative and also lack high expression/amplification of HER2 (*i.e.* triple-negative tumors), but not uniformly so (4, 5, 14). In one series, 71% of triple-negative breast tumors had a basal-like gene profile, whereas 29% did not (14). To address these disparities between basal-like and triple-negative tumors, several biomarker surrogates have been proposed that incorporate basal-like markers in combination with hormone receptor negativity. A four-biomarker panel defined by positive staining for one basal maker [cytokeratin 5/6 and/or EGFR], and negative staining for both ER and HER2 has been shown to be 76% sensitive and 100% specific for BLBC identified by basal-like gene expression profile (15). The four-biomarker panel has also been expanded by adding PR or additional basal cytokeratins (cytokeratin 14 or -17) to identify BLBC (16–18). This distinction between BLBC and triple-negative breast cancer (TNBC) is not merely an academic subtlety: triple-negative tumors that express basal markers have distinct molecular lesions (*e.g.* p53 stabilization and higher mitotic indices) and are associated with worse survival than triple-negative tumors that lack basal-like markers (Table 1) (17, 18). In this review, BLBC refers to tumors defined by gene expression or biomarker surrogates, whereas TNBC refers to ER, PR, and HER2-negative tumors not otherwise characterized.

TABLE 1. Comparison of TNBCs: basal-like vs. nonbasal

	Triple negative: nonbasal	Triple negative: basal-like
Basal-like markers:		
CK 5/6 and/or EGFR-positive by IHC	No (47.4%)	Yes (52.6%) (17)
CK 5/6, CK14, CK17, and/or EGFR-positive by IHC	No (28.9%)	Yes (71.1%) (18)
Basal-like gene profile	No (28.5%)	Yes (71.5%) (14)
p53 positive by IHC	41.0%	62.0% (18)
Distant metastasis, 10-yr follow-up	26.0%	37.0% (18)
Breast cancer-specific survival, 10-yr follow-up	71.6% 75.5%	62.2% (17) 56.6% (18)

IHC, Immunohistochemistry; CK, cytokeratin.

Epidemiology and Clinical Presentation

The prevalence of BLBC ranges from 12.3–36.7% of breast cancer cases in different patient cohorts (3–6, 15, 16, 18–25). BLBC is more common in African and African-Americans and in young and premenopausal women (especially among African-Americans) (15, 23, 24). The incidence of BLBC is inversely related to duration of lactation. However, unlike luminal tumors, BLBC is more common in women with increased parity, early age of menarche, and first full-term pregnancy before age 26 (23, 24). Although body mass index has not been shown to be significantly associated with BLBC as it has for the other molecular subtypes, an increased waist-hip ratio is positively associated with BLBC in premenopausal women (23, 24).

Much more epidemiological data exists for TNBC. In addition to the above BLBC risk factors, TNBC is more common in Hispanic women (25–29), in women with lower social economic status (27), in women with the metabolic syndrome (30), and in some studies in women with more than 1 yr of oral contraceptive use or use before age 18 (31, 32). Of note, young African-American

women are especially adversely affected by TNBC: not only is their recurrence-free and overall survival rate reduced compared with postmenopausal and non-African-American women with TNBC, those women with stage III/IV disease at diagnosis have only a 14% 5-yr survival rate compared with 37% and 36% survival in Hispanic and Caucasian women, respectively (16, 26).

Despite often presenting as large, advanced stage tumors at diagnosis, TNBC/BLBC tumors may be more sensitive to presurgery chemotherapy as evidenced by higher rates (22–45%) of pathological complete response (*i.e.* no tumor found at surgery) (7, 33, 34). Meta-analyses by the Early Breast Cancer Trialists' Collaborative Group have examined the impact of combined chemotherapy on breast cancer recurrence and include early data from both treated and untreated controls. Among patients with ER-negative breast cancer (TNBC and HER2 subtypes) under the age of 50, the 5-yr recurrence rate in the untreated cohort is 38.8%, which is reduced to 25.5% by combined chemotherapy (35). Hence, chemotherapy is highly effective in patients with ER-negative breast cancer, including TNBCs (35, 36). The higher response rate to neoadjuvant chemotherapy may reflect the typically high tumor grade and mitotic index of BLBC (16, 24, 37). Importantly, patients who achieve pathological complete response have survival rates similar to non-TNBC/BLBC patients (33, 34). However, the majority of women with TNBC/BLBC do not have a complete response and are at high risk for early relapse within the first 2–5 yr after treatment, resulting in an overall lower 5-yr survival rate (26, 28, 34, 38). TNBC/BLBC has a distinctive pattern of organ-specific distant metastases, with the lungs, liver, and central nervous system as the preferred sites (39–41). A particularly devastating aspect of TNBC is the high frequency of parenchymal central nervous system metastases that are observed in up to 46% of women with metastatic TNBC (6.7%–9.6% of all TNBC cases) and are associated with a median survival of less than 5 months from the time of diagnosis (41–43). The reader is referred to the elegant work of Joan Massagué and colleagues (44–46) who have identified genes regulating organic-specific metastasis in breast cancer.

Molecular Pathogenesis

BRCAness of BLBC: the BCRA1 connection

The study of hereditary breast cancer has revealed high-penetrance breast cancer susceptibility genes (*BRCA1* and *BRCA2*) that function as tumor suppressor gene products that preserve genome integrity (47, 48). Women with inactivating germline mutations in *BRCA1* or *BRCA2* have up to an 85% chance of developing breast cancer in their lifetime. Loss of heterozygosity (LOH) of the second *BRCA1/2* allele in breast epithelium results in disruption of double-strand DNA repair via the high-fidelity homologous recombination repair pathway. Instead, cells rely on nonhomologous end joining, which is error prone and may result in chromosomal translocations because the repair is not templated by the damaged DNA's sister chromatid sequence. Normally, the presence of double-stranded DNA damage leads to cell cycle arrest and cell death, but in the presence of p53 mutations, the checkpoint arrest is abrogated and widespread genomic instability and aneuploidy ensue (47).

One of the earliest insights into the pathogenesis of BLBC was the observation that sporadic BLBC phenocopies many aspects of hereditary breast cancer arising in *BRCA1* (but not *BRCA2*) carriers (49). Specifically, breast tumors in *BRCA1* carriers and nonhereditary BLBC share the following features: 1) they are largely triple negative and basal like by gene expression profile and biomarker surrogates (5, 50); 2) they are characterized by high tumor grade, high mitotic indices, p53 mutations, and chromosomal instability (51, 52); 3) they frequently have X chromosome abnormalities, including defects in X chromosome inactivation, a well-established function of BRCA1 (53, 54); and 4) they have similar clinical features, including young age at presentation, poor prognosis, early relapses, and favorable response to DNA-damaging chemotherapy (9, 49). However, mutational inactivation of *BRCA1* is uncommon in sporadic breast cancer (54, 55), suggesting that other mechanisms account for the BRCA1 dysfunction phenotype of these tumors. *BRCA1* inactivation by promoter CpG island methylation, often in combination with *BRCA1* LOH, has been observed in 11–13% of sporadic breast cancers, the majority of which are ER-negative tumors (56, 57). Additionally, the dominant-negative transcriptional regulator ID4 has been shown to regulate *BRCA1* expression and to be preferentially expressed in BLBC (58, 59). Nevertheless, many cases of BLBC have normal expression and nuclear localization of BRCA1 (54), suggesting that epigenetic and/or genetic abnormalities in other BRCA1-associated proteins [*e.g.* Fanconi anemia proteins, ataxia telangiectasia mutated gene product, Bloom syndrome protein, or Rad50 (60, 61)] might underlie the BRCA1 dysfunction phenotype of BLBC. Regardless of the underlying molecular mechanisms, the BRCAness of BLBC has emerged as a promising therapeutic target in these poor-prognosis tumors.

Apoptosis resistance

Defects in the apoptotic cell death machinery play a critical role in the pathogenesis of cancer, and BLBCs are

characterized by a distinctive pattern of apoptotic gene abnormalities. As noted, BLBC has a high frequency (44–82%) of *TP53* mutations, which impair DNA damage-induced checkpoint activation and apoptosis, thereby promoting genome instability (4, 16, 62). Indeed, loss of one *TP53* allele in mice with mammary-specific deletion of *BRCA1* dramatically accelerates mammary tumorigenesis (63), suggesting that p53 mutations may act synergistically with functional BRCA1 defects in sporadic BLBC to drive tumor initiation. The receptor tyrosine kinase EGFR is expressed in 39–54% of BLBC and confers resistance to apoptosis by ligand-dependent activation of the phosphatidylinositol-3 (PI3)-kinase/Akt/mTOR pathway (15, 64, 65). Another characteristic apoptotic abnormality in BLBC is expression of the molecular chaperone αB-crystallin, which suppresses apoptosis by inhibiting proteolytic activation of the proapoptotic protease caspase-3 (66, 67). αB-Crystallin is expressed in 45% of BLBC and only rarely (5%) in other molecular subtypes. Notably, αB-crystallin expression is associated with resistance to presurgery chemotherapy and poor survival in breast cancer patients, whereas ectopic expression of this molecular chaperone leads to an invasive tumor phenotype in preclinical models (67, 68). Additionally, loss of the phosphatase and tensin analog (*PTEN*) tumor suppressor gene, with resultant aberrant activation of the antiapoptotic PI3-kinase/Akt/mTOR pathway, is commonly observed in TNBC (69–71). Intriguingly, PTEN inactivation has also recently been linked to chromosome instability due to defects in Rad51-mediated DNA double-strand break repair, resulting in further genome instability in BLBC (72). Furthermore, mutational inactivation of Fbxw7, a component of an E3 ubiquitin ligase that degrades mTOR and Cyclin E (see next paragraph), has been reported in BLBC and likely results in enhanced levels of these key regulatory molecules (73–75).

Proliferation

As noted, BLBC is characterized by high mitotic indices and rates of proliferation (76). EGFR is commonly expressed in these tumors and promotes cell proliferation via activation of the Ras/MAPK/MAPK kinase (MEK) pathway (64). BLBC is also characterized by low expression of the *RB* and *Cyclin D1* genes and high expression of *E2F3* and *Cyclin E* genes (77). Cell proliferation requires progression through the G_1 to S cell cycle transition that is negatively regulated by the *RB* tumor suppressor gene product (78). Cyclin D-CDK4/CDK6 complexes phosphorylate RB and promote S-phase entry by releasing E2F family transcription factors, which induce Cyclin E expression. Cyclin E-CDK2 complexes induce additional phosphorylation of RB and ensure S-phase entry. A 59-gene expression signature reflecting RB pathway dysregulation and a distinct RB LOH signature were more prevalent in TNBC than other subtypes (79, 80). *Cyclin E1* is present in higher copy number in BLBC than other molecular subtypes, and its expression correlates with poor survival in breast cancer (81–83). Taken together, these studies suggest a specific role of RB loss and/or Cyclin E overexpression in the highly proliferative phenotype of BLBC.

Epithelial-mesenchymal transition

A key step in the metastatic cascade of epithelial tumors is the epithelial-mesenchymal transition (EMT), a carefully orchestrated program whereby carcinoma cells lose epithelial characteristics, such as cell-cell adhesion and polarity, and acquire mesenchymal features, facilitating invasion of the extracellular matrix (84). Developmental EMT pathways may be co-opted by BLBC or stimulated by environmental pressures such as hypoxia (85, 86). EMT markers such as *N*-cadherin and vimentin are frequently highly expressed in BLBC, whereas epithelial markers such as E-cadherin are often lost (87, 88). Down-regulation of E-cadherin expression and promotion of EMT have shown to be achieved in BLBC through the activation of TGF-β, Wnt, and Notch pathways leading to expression of EMT-associated transcription factors such as FOXC2, Twist, Slug, Snail, and LBX1 (89–91). EGFR also promotes EMT by inducing expression of Twist and plays a key role in cell motility and invasion (92, 93). Moreover, the Src family tyrosine kinase LYN is an EMT mediator that is commonly expressed in BLBC and is associated with poor survival (94). Of note, the recently defined claudin-low gene expression signature is characterized by low expression of cell-cell adhesion genes (*e.g. Claudins* and *E-cadherin*) leading to an EMT phenotype (95). Most closely linked with the basal-like subtype, claudin-low tumors are generally ER and HER2 negative; however, claudin-low tumors have variable expression of basal-like markers and so constitute a distinct intrinsic gene expression subtype (95, 96). Overall, these findings point to multiple mechanisms promoting EMT and an invasive tumor phenotype in BLBC.

Angiogenesis

Vascular endothelial growth factor A (VEGFA/VEGF) is a potent mitogen for endothelial cells and regulates tumor angiogenesis and vascular permeability, thereby promoting primary tumor growth and metastasis (97). The actions of VEGF on endothelial cells are mediated by the receptor tyrosine kinases VEGF receptor (VEGFR)1/

Flt1 and VEGFR2/KDR/Flk1 as well as Neuropilin coreceptors. VEGF is expressed at approximately 3-fold higher levels in TNBC compared with non-TNBC as determined by ELISA (98). Moreover, the VEGF gene is located on a chromosomal region (6p21.2–6p12.3) characterized by frequent copy number gain in TNBC, and specific probes for VEGF have confirmed VEGF gene copy gain and increased mRNA expression in approximately one third of TNBCs (99). A 13-gene VEGF signature was recently reported to predict distant metastases in breast cancer (100), underscoring the link between VEGF and metastasis. Breast tumors with p53 mutations have higher VEGF levels, suggesting a mechanism by which p53 mutation may promote angiogenesis (101). Additionally, high VEGFR2 expression has been observed in a subset of TNBC and correlates with shorter survival (102). Interestingly, VEGF also promotes breast cancer growth independently of its proangiogenic actions by an autocrine loop involving VEGFR1 and the VEGF coreceptor Neuropilin-1; EGFR activation acts synergistically with this VEGF autocrine loop by inducing VEGF, VEGFR, and Neuropilin-1 via a MAPK-dependent mechanism (103). Collectively, these results implicate the VEGF pathway in the etiology of TNBC and provide a strong rationale for targeting this pathway therapeutically.

Insights from microRNA (miRNA) expression analysis

miRNAs are noncoding RNAs that regulate gene expression predominately at the level of translation. After sequential processing, mature approximately 22-base miRNAs become part of silencing complexes that associate with the 3′-untranslated regions of target genes and inhibit translation and/or promote target RNA degradation (104). miRNA cancer signatures have been reported, as have miRNA signatures characteristic of different histological and molecular subtypes of breast cancer (105–107). The expression of the let-7 family of miRNAs, including let-7a, is commonly reduced in BLBC/TNBCs (105, 108). Let-7 miRNAs are also down-regulated in rare breast cancer cells with stem-like properties (breast cancer stem cells) and have been implicated in the self-renewal, tumor-initiating, and metastatic properties of breast cancer stem cells via their actions on several targets including *H-Ras*, *HMGA2*, and *IL-6* (109, 110). These findings suggest a link between reduced expression of let-7 miRNAs and an aggressive cancer stem cell phenotype in BLBC. Moreover, miR-126, a suppressor of primary/metastatic tumor growth and cell proliferation, is down-regulated in a subset of BLBCs (105, 111), suggesting that reduced expression of miR-126 may promote tumor progression and metastasis in these breast carcinomas.

Integrating genomic and transcriptome analyses

Comparative genome hybridization (CGH) studies using bacterial artificial chromosome and higher resolution single nucleotide polymorphism and oligo arrays have revealed distinctive chromosomal aberrations in each molecular subtype of breast cancer. Copy number aberrations (CNAs) are distributed throughout the genome in BLBC resulting in a sawtooth pattern, which is similar to that seen in *BRCA1*-associated hereditary breast cancer (112). In contrast to luminal and HER2 tumors, regions of high-level amplification are rare in BLBC (112–114). Low-level copy number aberrations in BLBC often include gains at 1q, 6p, 8p, and 10p, with losses at 4p, 5q, 14q, and 15q (112–115). Cluster analyses of CGH data have identified three molecular classes of breast cancer based on CNAs (99); 64% of TNBCs fall into class I, characterized by frequent gains on chromosome 6p21-p23 and frequent losses on chromosome 15q14-q22. 6p21-p23 contains many cancer-relevant genes; specific probes for *VEGFA* and *E2F3* were gained in approximately one third of TNBCs but only 10% or less of non-TNBCs. Furthermore, *EGFR* gain and *PTEN* loss were observed with similar frequencies in TNBC. These specific CNAs were accompanied by corresponding mRNA expression levels, *i.e.* high expression of *VEGFA*, *E2F3,* and *EGFR* and low expression of *PTEN* in TNBC. Another study integrating CGH and transcriptional profiles of TNBCs identified 40 genes that were both amplified and overexpressed, including *FGFR2, BUB3, RAB20, NOTCH3,* and *PKN1* (116). *FGFR2* is amplified in 4% of TNBC and encodes a receptor tyrosine kinase that confers resistance to apoptosis by activating the PI3-kinase/Akt/mTOR pathway (116, 117). TNBC cells with *FGFR2* amplification are selectively sensitive to apoptosis induction by silencing *FGFR2* or a pan-FGFR tyrosine kinase inhibitor, highlighting the functional relevance of this pathway in *FGFR2*-amplified TNBC cells (116). Taken together, these studies underscore the translational potential of integrating CGH and transcriptome platforms to illuminate molecular pathways deregulated in BLBC.

Translating Molecular Profiles into Targeted Therapies

Chemotherapy: a platinum lining?

Given the absence of validated molecular targets in TNBC, conventional chemotherapy (typically including a DNA-damaging anthracycline such as doxorubicin and a

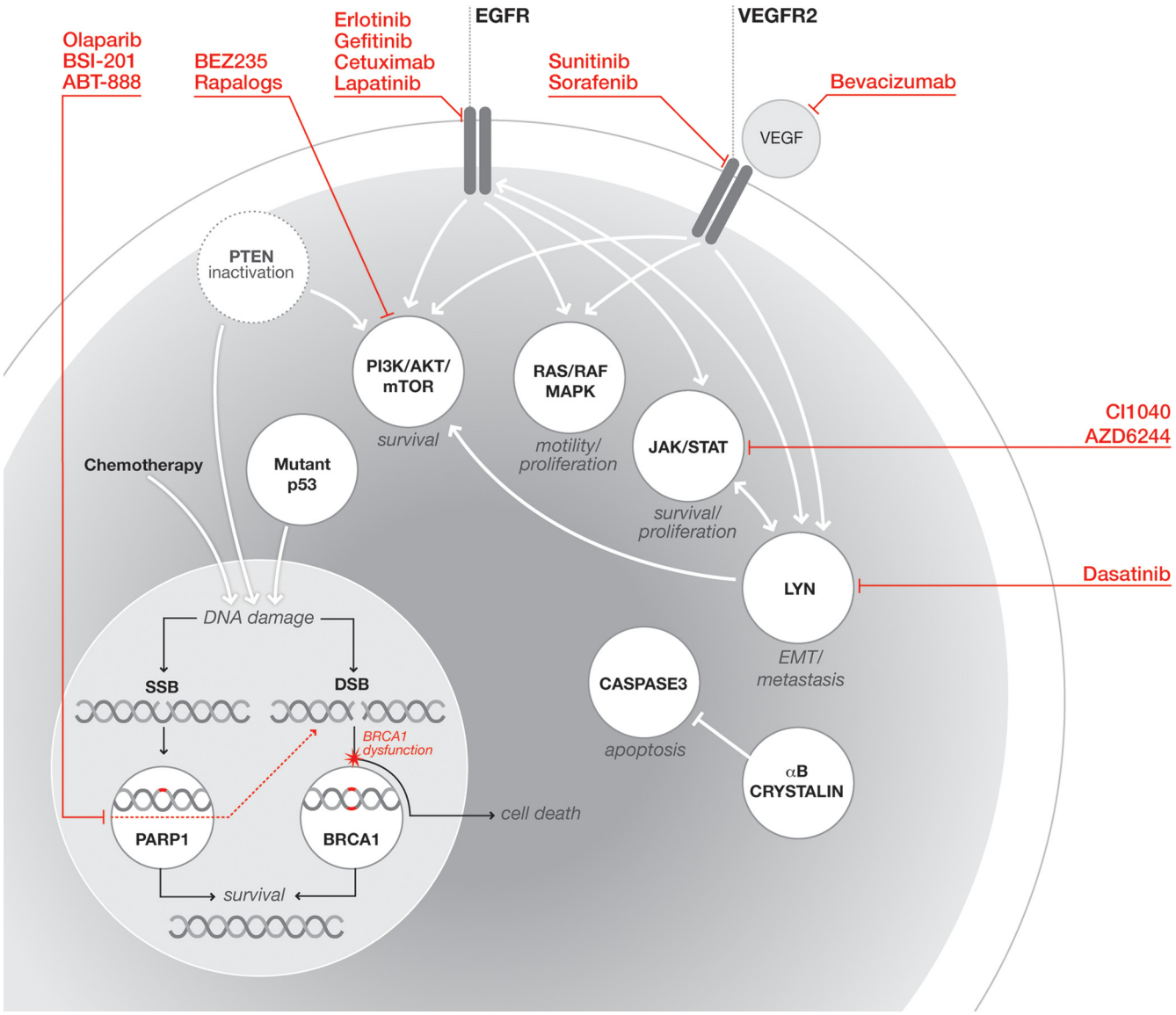

FIG. 1. Schematic representation of key signal transduction pathways implicated in the pathogenesis of BLBC and targeted therapies. Commonly dysregulated pathways and their biological outcomes are depicted. Representative drug inhibitors are indicated in *red*. DSB, double-strand break; JAK, Janus family of tyrosine kinases; SSB, single-strand break; PI3K, phosphatidylinositol-3-kinase; STAT, signal transducer and activator of transcription.

microtubule-stabilizing taxane) has been the only therapeutic option for women with these poor-prognosis tumors. Although the rates of pathological complete response (22–45%) for presurgery chemotherapy are higher for TNBC than luminal and normal-like tumors, the majority of women with TNBC have residual disease and are at high risk for relapse and death within the first 2–5 yr of diagnosis (7, 33, 34). Moreover, the nonspecific cytotoxicity of these agents results in significant dose-limiting side effects. Hence, the development of targeted therapies with improved therapeutic indices is of paramount importance (Fig. 1 and Table 2).

Based on the BRCA1 dysfunction phenotype of BLBC, one approach has been the exploration of platinum chemotherapy agents (carboplatin, cisplatin, and others) in these patients. Platinum agents produce DNA cross-links, which lead to DNA double-strand breaks, normally repaired by BRCA1/2-mediated high-fidelity homologous recombination repair mechanisms (47, 118). Consequently, BRCA1/2-deficient cells are highly sensitive to apoptosis induced by these agents (119). Cisplatin also promotes apoptosis in TNBC by disrupting a complex between the p53 family members ΔNp63 and TAp73 that is present selectively in TNBC with mutant *TP53* (120). Specifically, cisplatin induces c-Abl-mediated phosphorylation of TAp73, which releases pro-apoptotic TAp73 from the inhibitory complex and triggers apoptosis. A recent small clinical study of 28 women with TNBC (including two *BRCA1* mutation carriers) who were treated with presurgery cisplatin resulted in a 22% pathological

TABLE 2. A subset of basal-like markers associated with poor survival: candidate BLBC molecular targets

Gene	Function	Expression pattern	Impact
αB-crystallin	Antiapoptotic small heat shock protein	High expression in 45% of BLBC	Hazard ratio 2.23 for reduced survival (67)
Cyclin E	G_1-S phase cell cycle regulation	Preferentially expressed by BLBC	High expression associated with reduced survival (82, 83)
EGFR	Receptor tyrosine kinase	High expression in 39–54% of TNBC	Hazard ratio 1.98 for reduced survival (66)
LYN	Src family tyrosine kinase, EMT mediator	High expression in ~50% of TNBC	Hazard ratio 2.29 for reduced survival (94)
PTEN	Inhibits PI3K/mTOR/ AKT; loss leads to chromosome instability	Expression lost in ~1/3 of TNBC (99)	Hazard ratio 4.63 for reduced survival (not specific to BLBC) (144)
RB1	Tumor suppressor	RB dysregulation and LOH common in BLBC	RB LOH gene signature predictive of pathological complete response and poor survival (79, 80)
VEGFA	Angiogenesis	High expression in 34% of TNBC (99)	VEGF 13-gene signature hazard ratio 1.54 for relapse-free survival (not specific to BLBC) (100)
VEGFR2	Angiogenesis	Preferentially expressed by 22% of TNBC	Hazard ratio 2.6 for reduced survival (102)

complete response rate, similar to that observed with nonplatinum agents (121). Both women with *BRCA1* mutations had a complete response, and breast tumors with low *BRCA1* mRNA expression or *TP53* mutations were associated with a favorable cisplatin response, suggesting that BCRA1 dysfunction may be linked to cisplatin response. Whether platinum agents will indeed improve survival in TNBC will have to await the outcome of several current clinical studies.

Synthetic lethality: a paradigm shift in cancer therapy

One of the most exciting recent developments in translational cancer research is the concept of synthetic lethality (122). Two oncogenic pathways are in a synthetic lethal relationship if mutation of either oncogene is well tolerated, but mutation of both results in robust cell death. Synthetic lethal screens have been used to identify drugs or genes that induce cell death only in the presence of specific oncogenic alterations. For example, drug inhibitors of poly(ADP) ribose polymerase (PARP), an enzyme involved in DNA base-excision repair, prevent the repair of DNA single-strand breaks, which are converted to double-strand breaks at stalled DNA replication forks. These DNA double-strand breaks are normally repaired by BRCA1/2-mediated homologous recombination repair, and there are no untoward consequences for the cell. However, in the presence of *BRCA1* or *BRCA2* mutations, this repair mechanism is defective: cells accumulate DNA double-strand breaks and ultimately undergo apoptosis. Hence, PARP and BRCA1/2 are in a synthetic lethal relationship: PARP inhibitors potently induce cell death only in cancer cells with mutations in *BRCA1* or *BRCA2* (123, 124). Indeed, mutations in *BRCA1* or *BRCA2* confer 57- and 133-fold increase sensitivity to PARP inhibitors compared with cells with wild-type *BRCA1* or *BRCA2* (124). Preclinical studies of several PARP inhibitors have demonstrated impressive single-agent antitumor activity in multiple BRCA1/2-deficient tumor models and have shown robust synergy between PARP inhibitors and DNA-damaging agents, including platinum agents (123–125). In a small phase I clinical study, the oral PARP inhibitor olaparib (AZD2281) was well tolerated and induced partial and complete responses in some patients with *BRCA1*- or *BRCA2*-associated-cancer (12 of 19 patients had a clinical benefit), but the drug had no activity in nonmutation carriers (126). Preliminary analysis of a randomized phase II study in 86 patients with metastatic TNBC demonstrated that adding a PARP inhibitor (BSI-201) to chemotherapy (gemcitabine plus carboplatin) significantly improved progression-free (>2-fold increase) and overall survival compared with chemotherapy alone (127). There are currently 13 clinical trials listed in ClinicalTrials.gov to evaluate PARP inhibitors alone and in combination with platinum agents, which should provide invaluable information. As with all cancer therapies, *de novo* and/or acquired resistance to PARP inhibitors are likely to be encountered. Indeed, intragenic mutations in *BRCA1/2,* which restore expression of the wild-type protein, have been described as mechanisms of resistance to platinum agents and PARP inhibitors (128, 129). Nevertheless, PARP inhibitors have the potential to transform our therapeutic approach to hereditary and sporadic TNBC, and the pace of clinical translation in this area is likely to be unprecedentedly rapid given the dearth of existing options.

Antiangiogenics

Given the accumulating evidence of aberrant VEGF pathway activation in BLBC (and other neoplasms), antiangiogenic therapies targeting VEGF and its receptors have emerged as promising therapies for BLBC. Many small-molecule multikinase inhibitors, including sunitinib and sorafenib, have been developed as potential antiangiogenic agents (130). Sunitinib inhibits several receptor tyrosine kinases including VEGFR, platelet-derived growth factor receptor, c-KIT, RET, CSF-1R, and FMS-like tyrosine kinase 3. A phase II study of 64 women with metastatic breast cancer previously treated with an anthracycline and taxane found an 11% response rate to sunitinib as a single agent; three of 20 TNBCs had demonstrable response to treatment (131). In a later study of 22 patients with newly diagnosed locally advanced or metastatic breast cancer, the addition of sunitinib to paclitaxel was shown to produce an objective response in about one third of patients, including three of nine TNBCs (132). Other VEGFR multikinase inhibitors have not shown as much promise. A phase II trial of sorafenib, which has kinase specificity similar to sunitinib, failed to demonstrate any response in 23 metastatic breast cancer patients, 52% of whom were ER negative (133).

The anti-VEGF antibody bevacizumab has been shown to prolong disease-free survival of breast cancer patients, including TNBC patients also treated with paclitaxel by 4 months on average *vs.* treatment with paclitaxel alone; however, overall survival was not affected (134). When combined with the small-molecule reversible EGFR kinase inhibitor erlotinib, bevicizumab showed limited activity in metastatic breast cancer. In this study of 38 patients, 50% of the tumors were TNBC, and 10 of 19 demonstrated EGFR expression; however, response rates of the distinct tumor subtypes were not reported (135). Currently, 32 active trials are listed at ClinicalTrials.gov involving breast cancer and VEGF-based antiangiogenic agents. To date, the response to antiangiogenic agents has been disappointing in unselected TNBC patients. It remains to be seen whether the discovery of biomarkers to stratify patients who are likely to respond to these agents and/or identification of synergistic combination therapies will improve treatment response. An additional cautionary note is the recent observation in preclinical studies that antiangiogenic agents may paradoxically increase distant metastases (136).

Targeting EGFR and downstream kinases

Based on the frequent expression of EGFR in BLBC, small-molecule and antibody-based EGFR inhibitors are being explored as targeted therapies. In a small study of 41 previously untreated breast cancer patients, presurgery erolotinib reduced phospho-EGFR levels in most patients, but erolotinib inhibited cell proliferation, phospho-MAPK, and phospho-Akt levels only in ER-positive breast cancer (not in TNBC or HER2-positive tumors) (137). Phase I and II studies of another EGFR small-molecule inhibitor (gefitinib), a humanized anti-EGFR monoclonal antibody (cetuximab), and a dual EGFR/HER2 dual kinase small-molecule inhibitor (lapatinib), which is Food and Drug Administration (FDA) approved for relapsed HER2-positive breast cancer, have also failed to show efficacy of these agents as single agents or combined with chemotherapy in patients with largely pretreated metastatic TNBC (138–140). One potential explanation for the limited impact of EGFR-targeted therapies in TNBC to date is the lack of a biomarker (*e.g.* gene mutation or amplification) to identify potential responders; predictive biomarkers have been a cornerstone for the successful translation of targeted therapies (141). Moreover, constitutive activation of signaling pathways downstream of EGFR in TNBC, such as MEK/MAPK, PI3-kinase/Akt/mTOR, and Src family kinases (*e.g.* Lyn), may confer resistance to EGFR inhibitors. Indeed, preclinical studies suggest that TNBC cells may be particularly sensitive to MEK inhibitors by virtue of high expression of MAPK pathway genes (142). Intriguingly, MEK inhibition in TNBC cells led to activation of the PI3-kinase/Akt/mTOR pathway, whereas combined inhibition of the MEK and PI3-kinase/Akt/mTOR pathway resulted in synergistic cytotoxity or growth arrest. Similarly, BLBC cells highly express LYN, a Src family kinase, and are exquisitely sensitive to dasatinib, an inhibitor of Src and Abl kinases (94, 143). Collectively, these studies strongly suggest that identification of predictive biomarkers and targeting of multiple kinase pathways (*e.g.* MEK/MAPK and PI3-kinase/Akt/mTOR) is likely to be required for optimal therapeutic benefit in BLBC. Given the explosion of small-molecule inhibitors of these pathways, it seems likely that clinical data will be forthcoming shortly.

Concluding Comments

A decade has elapsed since the initial recognition of BLBC as a distinctive molecular subtype with a basal epithelial gene signature and an aggressive clinical course characterized by early relapses and poor survival. Major pathogenic insights include the apparent BRCA1 dysfunction phenotype of these sporadic tumors, resulting in widespread genomic instability and potentially profound vulnerability to PARP inhibitors due to synthetic lethality. Preclinical and clinical studies have also identified other signature molecular abnormalities in BLBC, including deregulated activation of αB-crystallin, EGFR and down-

stream kinases, and VEGF, resulting in an invasive apoptosis-resistant tumor phenotype. Clinical translation of these molecular insights is currently ongoing and will likely require careful patient selection based on the specific molecular targets of therapeutic agents and rationally designed combinatorial regimens to counteract treatment resistance. Although these obstacles are potentially daunting, early clinical success with some agents, particularly PARP inhibitors, suggests that targeted therapies for BLBC are within our grasp in the near future.

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