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Review

Therapeutic options for triple-negative breast cancers with defective homologous recombination

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ABSTRACT

Breast cancer is the most common malignancy among women in developed countries, affecting more than a million women per year worldwide. Over the last decades, our increasing understanding of breast cancer biology has led to the development of endocrine agents against hormone receptor-positive tumors and targeted therapeutics against HER2-expressing tumors. However, no targeted therapy is available for patients with triple-negative breast cancer, lacking expression of hormone receptors and HER2. Overlap between *BRCA1*-mutated breast cancers and triple-negative tumors suggests that an important part of the triple-negative tumors may respond to therapeutics targeting BRCA1-deficient cells. Here, we review the features shared between triple-negative, basal-like and *BRCA1*-related breast cancers. We also discuss the development of novel therapeutic strategies to target *BRCA1*-mutated tumors and triple-negative tumors with *BRCA1*-like features. Finally, we highlight the utility of mouse models for *BRCA1*-mutated breast cancer to optimize (combination) therapy and to understand drug resistance.

Contents

Abbreviations: ABC, ATP-binding cassette; APC, Adenomatous, polyposis coli; ATM, Ataxia telangiectasia mutated; ATR, ATM and Rad3-related; BER, base-excision repair; BRCA1, Breast cancer susceptibility gene 1; BRCA2, Breast cancer susceptibility gene 2; CGH, Comparative genomic hybridization; CK, Cytokeratin; CNA, Copy number alteration; CSC, Cancer stem cell; DSB, Double strand break; EGFR, Epidermal growth factor receptor; ER, Estrogen receptor; FA, Fanconi anemia; Fz, Frizzled; FFPE, Formalin-fixed paraffin-embedded; GEM, Genetically engineered mouse; GSI, γ-secretase inhibitor; HDR, Homology-directed repair; HER1, Heregulin 1; HER2, Heregulin 2; HH, Hedgehog; HR, Homologous recombination; ICL, Interstrand cross link; ID4, Inhibitor of differentiation 4; IR, Ionizing radiation; LOH, Loss of heterozygosity; MDR, Multidrug resistance; MRN, Mre11/RAD50/NBS1; MRP, Multidrug resistance-associated protein; NHEJ, Non-homologous end joining; ORF, Open reading frame; PALB2, Partner and localizer of BRCA2; PAR, Poly (ADP-ribose); PARP, Poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; PDGFRv, Platelet-derived growth factor receptor; P-gp, P-glycoprotein; PR, Progesterone receptor; RTV, Relative tumor volume; PTCH, Patched; SCF, Stem cell factor; SERM, Selective estrogen receptor modulator; siRNA, Small interfering RNA; SMO, Smoothened; SSB, Single strand break; TIC, Tumor-initiating cell; TMA, Tissue microarray; TNBC, Triple-negative breast cancer

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1. Triple-negative and basal-like breast cancer

Breast tumors are usually classified by immunohistochemical staining for the estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor (also known as HER2/neu or ERBB2). Expression of these receptors gives an indication about prognosis and treatment possibilities. The presence of hormone receptors is a good predictor of response to endocrine agents such as the estrogen receptor antagonist tamoxifen and aromatase inhibitors [1,2]. Amplification of HER2 is a strong predictor for response to HER2 targeting drugs such as trastuzumab (Herceptin, a monoclonal antibody against HER2) and lapatinib (a dual specificity EGFR/HER2 inhibitor) [3,4]. However, no specific treatment is available for the third group of so called triple-negative tumors, which are negative for ER, PR and HER2.

1.1. Triple-negative breast cancer

Triple-negative breast cancer (TNBC) has a high prevalence in premenopausal African-American women, compared to postmenopausal African-American and non-African-American women [5]. TNBCs have an aggressive phenotype and African-American women with late stage TNBC show the poorest survival of all US patient groups [6]. This may also explain the paradoxical finding that African-American women have a lower breast cancer incidence but higher mortality than Caucasian American women [7]. Compared to other breast cancer patient groups, women with TNBC have a lower recurrence-free and overall survival, regardless of disease stage at diagnosis [6,8,9]. On average, TNBCs are larger and show a higher rate of node positivity at the time of diagnosis than other breast cancers [8], although there is no correlation between these two parameters as seen in other tumors [10]. Despite their poor prognosis and survival, TNBC patients have significantly higher rates of pathological complete remission (pCR) than non-TNBC patients, following neoadjuvant chemotherapy [11,12]. Also, TNBC patients have increased frequency of distant metastasis formation, but not of local relapse [13], indicating that these tumors are generally sensitive to the (locoregional) adjuvant radiotherapy. Together, these observations suggest that TNBCs are very sensitive to chemotherapy or irradiation.

1.2. Basal-like breast cancer

Besides classification by histopathology, gene expression profiling has also been used for breast tumor classification. Perou et al. and Sørlie et al. have identified five subtypes of breast cancer [14–16]. Luminal subtypes A and B are characterized by ER expression and high expression of genes associated with luminal epithelial cells. Their luminal phenotype was confirmed by immunohistochemical staining for cytokeratin (CK) 8/18. These tumors usually do not express HER2 at high levels. Luminal B tumors show low to moderate expression of genes associated with luminal differentiation and are sometimes called the $ER^{+}HER2^{+}$ subgroup. The ER-negative tumors can be divided into three groups: the $HER2^{+}$ subtype, the normal breast-like subtype and the basal-like subtype. The $HER2^{+}$ tumors are characterized by high expression of a subset of genes associated with overexpression of the *HER2* oncogene. The gene expression profiles of normal breast-like tumors show many similarities with normal breast tissue. The basal-like subtype is characterized by high expression of basal *keratins 5* and *17*, *laminin* and *fatty acid binding protein 7*. The basal phenotype of these tumors was confirmed by immunohistochemical staining for the basal cytokeratins CK5/6 and CK17; however, not all basal-like tumors showed immunoreactivity for CK5/6 [17]. A large proportion of basal-like breast cancers lacks expression of ER, PR and HER2, and can therefore also be classified as TNBC [9,17,18]. Although the tumor dendrograms in individual studies are slightly different due to differences in the intrinsic gene sets used for hierarchical clustering, all studies show that immunohistochemically characterized TNBCs share distinctive features with the basal-like subtype [16]. In a set of 97 TNBCs, all tumors expressed the basal-like genotype [19]. However, when gene expression of ER, PR and HER2 in basal-like breast tumors is analyzed by microarray profiling, not all tumors are negative for all three markers [20–22]. This indicates that the TNBC phenotype alone is not sufficient to identify basal-like tumors.

Similar to TNBCs, basal-like breast cancers are more sensitive to preoperative or neoadjuvant chemotherapy than luminal tumors [21,23], whereas they show a worse relapse-free or overall patient survival than other molecular subtypes [9,18]. In a neoadjuvant chemotherapy study for basal-like breast cancer, Carey et al. [23] showed that patients who achieved a pathologic complete response had a good outcome whereas patients without a pathologic complete response had a poor outcome with a high chance of relapse. This indicates that there are at least two subgroups among basal-like breast cancer; one that is likely to give a complete response to standard therapy and a good outcome, and one that gives residual disease with a higher chance of relapse and death. Hence, it is of clinical importance to further characterize these subtypes of basal-like breast cancer.

2. *BRCA1*-related breast cancer

The breast cancer susceptibility genes 1 and 2 (*BRCA1/2*) were identified and cloned in 1994 and 1995, respectively [24,25]. Heterozygous *BRCA1* mutation carriers have a high lifetime risk of breast and ovarian cancer [26]. The breast and ovarian cancer risk among *BRCA2* mutation carriers is almost as high as for *BRCA1*, but with a later onset of the disease [27]. The likelihood of *BRCA1* or *BRCA2* mutations in families with breast and ovarian cancer correlates with the number of affected relatives, lower age at the time of diagnosis and ethnicity. The majority of pathogenic *BRCA1* and *BRCA2* founder mutations are small insertions, deletions or nonsense mutations that result in a premature stop codon and a shortened, non-functional BRCA protein [28]. *BRCA1* and *BRCA2* mutations are especially prevalent in Ashkenazi Jews, with *BRCA1-185delAG*, *BRCA1-5382insC* and *BRCA2-6174delT* as most common founder mutations [29,30].

2.1. BRCA1-related breast cancers are associated with a triple-negative and basal-like tumor phenotype

The majority of *BRCA1*-related breast tumors share many phenotypic features with TNBCs and basal-like tumors [31]. *BRCA1*-related