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Mini Review

Drug Resistance in Triple-Negative Breast Cancer: Strategies to Overcome

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Abstract

Triple-negative breast cancer has fewer treatment options than other types of invasive breast cancers. This is because of the lack of estrogen, progesterone receptors and HER2 proteins, which limits the targeted therapy for TNBC. The main therapeutic options are chemotherapy and radiation therapy. However, these treatments are associated with drug resistance and ultimately poor prognosis and reduced survival. It is thus vital to overcome drug resistance and develop targeted therapy for TNBC for enhanced prognosis and prolonged survival. This mini review discusses drug resistance and targeted therapy for TNBC.

Keywords: Breast Cancer; Drug Resistance; Estrogen

Breast cancer is the leading cause of death word-wide specially in developed countries including the USA and Europe. In 2020, approximately 276,480 invasive breast cancers (BCs) were diagnosed among women in the United States. Breast cancer is a heterogeneous disease with several clinical and histological forms. Breast cancers vary in many ways, such as in their cell of origin, the molecular changes causing them and the vulnerability and defenses of the patient, which makes it difficult to give the most appropriate therapy.

For the treatment of breast cancer, it is crucial to know the subclasses of breast cancers (Table 1). Among the different classes of breast cancers, triple-negative breast cancer (TNBC), which lack three common markers, estrogen (ER), progesterone and HER2, is the most aggressive type with very low prognosis and survival. A total of six molecular sub-types of TNBC displaying unique characteristics has been reported including BL1, BL2, IM, M, MSL and LAR (Table 1) [1-5]. In addition to this classification by Lehman., *et al*. Burstein., *et al*. suggested four subtypes in TNBC: Basal-like immune suppressed (BLIS), basal-like immune activated (BLIA), mesenchymal and luminal androgen receptor [4,6].

TNBC is a very heterogeneous group, this heterogeneity is highlighted by high prevalence of rare histopathological subtypes, such

Breast cancer subtype	Cells	TNBC subtype	Cells
Normal Immortalized	76NF2V MCF-10A	Basal like 1 (BL1)	HCC2157
Luminal A	MCF-7, ZR751	Basal like 2(BL2)	HCC1806, SUM149PT,
Luminal B	MDA-MB-361 UACC812	Immunomodulatory (IM)	DU4475
HER2	SKBR3, AU565, HCC1954	Mesenchymal (M)	BT549
TNBC Claudin low	MDA-MB-468, HCC1937	Mesenchymal stem-like (MSL)	MDA-MB-231
TNBC Basal	MDA-MB-231, MDA-MB-436	Luminal androgen receptor (LAR)	MDA-MB-453

Table 1: Breast and TNBC subtypes and corresponding cell lines.

as metaplastic, medullary, adenoid cystic, apocrine carcinomas [2,3]. Some common markers including cytokeratin (CK) and EGFR has been identified for TNBC. Around 75% of TNBC are basal-like and remaining 25% comprising all other mRNA subtypes. The subtype includes mostly HER2+ breast cancer. Approximately 25% of TNBC lack ER, PR and HER2 but do not exhibit the basal-like features. TNBC involve genes associated with DNA damage, repair and phosphatidylinositol 3-kinase, PI3K. PI3K pathway occurs due to the loss of negative regulators such as PTEN or INPP4B or activating mutations PIK3CA along with the other genes in the PI3K/TOR signaling network. Alteration in DNA damage repair genes includes TP53, RB1, and BRCA1 function. BRCA1 mutations develop tumors with many similarities to basal-like sporadic breast tumors including ER, PR, and HER2 negative, and of having high frequency of TP53 mutations. Hallmark of BRCAness include basal-like phenotype, ER-negativity, EGFR expression, c-MYC amplification, TP53 mutations, loss of RAD51 focus formation, extreme genomic instability and sensitivity to DNA-crosslinking agents. Approximately 20% of TNBC are immunomodulatory, and are highly enriched in immune cell markers and signaling. More than 50% lymphocytic infiltrate are considered to have best prognosis in TNBC. The presence of TILs is correlated with improved survival, reduced metastatic progression and decreased distant recurrence [2,4,6].

BLI subtype are accompanied by elevated DNA damage response (ATR/BRCA) pathways. Observation of Ki67 mRNA expression and Ki67 staining supported the proliferative nature of BL1 subtype. The BL2 subtype involves growth factor signaling pathways including EGF, NGF, MET, Wnt/β-catenin and IGF1R as well as glycolysis and gluconeogenesis. This subtype is uniquely enriched with growth factor receptors such as EGFR, MET and EPHA2. Nearly all of the cell lines with known mutations with BRCA1 and BRCA2 have gene expression pattern correlated with the basal-like subtype. Generally, BRCA-mutant tumors display a basal-like subtype [2,4,6].

The IM subtype is enriched with the factors that involved in immune cell processes. BLIA exhibit an upregulation of immune-regulatory pathway. However, BLIS subtype display upregulation of genes controlling B cell, T cell and NK cell functions. BLIS subtype has the best prognosis, exhibit activation of the STAT transcription factor-mediated pathways and high expression of STAT genes [2-4,6].

The M phenotype is responsible for invasiveness and chemoresistance of TNBC cells. The M subtype is enriched in components and pathways involved in cell motility, extracellular receptor interaction, and cell differentiation pathways. The MSL subtype shares the enrichment of the genes for similar biological processes with M subtype. However, MSL genes represent components and processes that are linked to growth factor signaling pathways including inositol phosphate metabolism, EGFR, PDGF, calcium signaling, G-protein coupled receptor, and ERK1/2 signaling as well as ABC transporter and adipocytokine signaling. This subtype expresses genes normally exclusive to osteocytes (OGN) and adipocytes (ADIPOQ, PLIN1), and growth factors (IGF-1) are also expressed in this subtype [2,4,6].

The LAR subtype tumors exhibit AR, ER, prolactin, and ErbB4 signaling but Erα-negative staining. Gene expression profiling demonstrated expression of ESR1 and other estrogen-regulated genes including PGR, FOXA, XBP1 and GATA3. AR mRNA is expressed around 9-fold greater than all other subtype [2,4,6].

Basal-like subtype are usually treated using genomic instability as therapeutic target. Rucaparib effectively treats BRCA-muted TNBC. Around 40% of the TNBC patient with BRCA-mutation experienced a 12-weeks progression free survival (PFS) under rucaparib monotherapy. This TNBC drug received FDA approval in 2015 for the treatment of TNBC [7]. The figure 1 indicates different breast cancer subtype and **c**omparison of the current subtyping schemes between breast cancer cell lines and tumors, and corresponding aggressiveness **[3].**

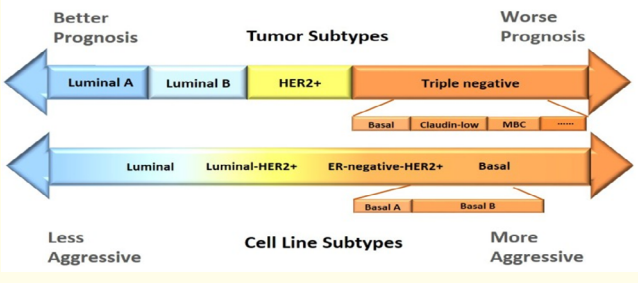

Figure 1: Different breast cancer subtype and comparison of the current subtyping schemes between breast cancer cell lines and tumors, and corresponding aggressiveness. (Adapted from ref.3, J. Cancer, 2017; 8(16): 3131-3141.).

All LAR TNBC cell lines harbor an activating mutation in the kinase domain of PIK3CA and exhibit sensitivity to PIK3CA inhibi-

tors. The anti-androgen enzalutamide was effective in woman with advanced TNBC whose tumor express AR [8].

Immune checkpoint inhibitors have been used for the treatment of IM subtype of TNBC. Pembrolizumab monoclonal anti PD-1 antibody in metastatic PD-L1 showed a preliminary ORR of 18% in TNBC [9]. Atezolizumab has also shown promising activity in TNBC. Combination treatment of atezolizumab and nab-paclitaxel in metastatic TNBC as first line therapy has been approved by FDA and EC. The monoclonal antibody tremelimumab for inhibiting CTLA-4 has been evaluated in hormone positive breast cancer and found appreciable activities [10,11]. There have been several approaches to develop effective therapy for TNBC targeting, TGIF protein and sensitizing cisplatin, TRPC6 channels, XBP1 mRNA, oncogenic MYC, and urokinase plasminogen activator (uPA or uPAR) etc. [12-16].

Due the heterogeneity in breast cancer cell lines, sometimes there are difficulties with inconsistent nomenclatures, classifications and even contradictory molecular characterization, and subtyping. On the other hand, number of cell lines used for breast cancer research is extremely limited with the cell lines such as MCF7, T47D and MDA-MB-231 account for more than two-thirds of the cell lines used for the breast cancer study [3]. This raises the question, how representative these few cell lines for the vast diverse spectrum of the breast tumors for their clinical translation.

TNBC lacks targeted therapies and has worse prognosis and survival compared to other subtypes. IRE1α is an endoplasmic reticulum stress sensor. Constitutive IRE1 RNase activity contributes to the basal production of protumor-genic factors including IL-6, IL-8, CXCL1, GM-CSF and TGFβ2 in TNBC, making treatment more difficult. Further, some chemotherapeutic drugs enhance IRE1 RNase activity enhancing tumor-infiltrating cells in TNBC tumors. For example, paclitaxel, doxorubicin enhance IRE1 RNase activity and consequently triggering the chemoresistance and cancer recurrence. Inclusion of IRE1 RNase inhibitor, MKC8866 with paclitaxel can sensitize paclitaxel against TNBC and inhibit disease recurrence successfully in preclinical settings [17].

Combination therapy strategies are promising for TNBC therapy. A nanobioconjugate with a combination of anti-TfR and 2C5 mAbs antibodies along with polymalic acid, are promising targeting tools for drug delivery into TNBC cells. In vivo studies used an attached antisense oligos/siRNA to nanoplatform, PLMA, to block molecular markers such as HER-2, EGFR and laminin 411 and suppressed the TNBC growth [18].

ADC drugs such as Trastuzumab emtanstine has been approved by FDA, sacituzumab govitecan and trastuzumab deruxtecan are in late phases of clinical trial for patients with TNBC. Very recently, the FDA has approved sacituzumab govitecan-hziy for adult patients with unresectable locally advanced or metastatic TNBC.

Conclusion

Finally, the development of state-of-the-art technologies for the classification of TNBC subtypes, identification of suitable molecular markers, inhibition of drug resistance and recurrence, and ef-

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