REVIEW

Triple Negative Breast Cancer

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Abstract

Triple-negative breast cancers (TNBC), characterized by absence of the estrogen receptor (ER) and progesterone receptor (PR) and lack of overexpression of human epidermal growth factor receptor 2 (HER2), have a poor prognosis. To overcome therapy limitations of TNBC, various new approaches are needed. This mini-review focuses on discovery of new targets and drugs which might offer new hope for TNBC patients.

Keywords: Triple negative breast cancer - poor prognosis - targeted therapy

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Introduction

Breast cancer is one of the most common cancers in women in the developed countries of the world and it is the cause of death in approximately 20% of all females who. From cancer in these countries (Macdonald et al., 2004). Breast cancer is the most common type of cancer among women worldwide (Beiki et al., 2012). Breast cancer is increasingly regarded as a heterogeneous disease which can be classified into distinct molecular subtypes with prognostic significance (Lv et al., 2011). Breast cancer is a complex and heterogeneous disease with respect to histology, cellular origin, mutations, metastatic potential, disease progression, therapeutic response, and clinical outcome (Ossovskaya et al., 2011). Among the causes of breast cancer, hormonal risk factors such as estrogen and progesterone exposure and genetic risk factors such as inheritance of BRCA1 and BRCA2 genes play an important role (Martin and Weber, 2000; Colditz et al., 2004). Long-term exposure of breast tissue to estrogen plays a major role in breast tumor formation. Consequently, reproductive factors such as total numbers of pregnancies, age at first pregnancy, breastfeeding, age at first menstruation, age at menopause and hormone replacement therapy, which affect a woman's lifetime exposure to estrogen, have been shown to be strongly associated with breast cancer risk (Hebert, 2009).

The histological features may now be extended with molecular biological techniques, which reveal at least five clinically important subtypes based on gene expression profiles (Choi et al., 2012). These include 'luminal A' [ER positive and/or progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative], 'luminal B' (ER positive and/or PR positive, HER2 positive), 'HER2 overexpressing' (ER negative, PR negative, HER2 positive), 'basal-like' (ER negative, PR negative, HER2 negative, cytokeratin 5/6 positive and/or epidermal growth factor receptor positive) and 'normal breast-like' tumours (Boyle, 2012). In addition to gene expression patterns, distinctive clinical features may characterize these subtypes (Choi et al., 2012). More recently, a new subtype classified as "claudin-low" has also been identified (Malhotra et al., 2010).

Categorizing breast tumors based on the ER, PR and HER/Neu 2 receptor status is necessary in order to predict outcome and assist in management of breast cancer (Zubeda et al., 2013). Triple-negative breast cancers (TNBC), characterized by lack oestrogen receptor(ER), progesterone receptor (PR), nor over-express human epidermal growth factor receptor 2 (HER2), are typically associated with poor prognosis, due to aggressive tumor phenotype(s), only partial response to chemotherapy and present lack of clinically established targeted therapies (Podo et al., 2010; Brady-West and McGrowder, 2011).

Epidemiological studies have shown that TNBC tends to occur in pre-menopausal women, particularly in young African-American women (Carey et al., 2006). TNBC accounts for 39% of breast cancer cases in African-American women under 50 years old, but only 16% in Caucasian women with a breast cancer in the same age group. In post-menopausal African-American women with breast cancers, the rate of TNBC is 14% (Furberg et al., 2001; Ghafoor et al., 2003; Trivers et al., 2009).

Although triple-negative breast cancer possesses many basal-like characteristics, equating triple-negative breast cancer with basal- like breast cancer is not fully supported by many studies (Rakha et al., 2007; Yang et al., 2007; Cheang et al., 2008; Tan et al., 2008; Rakha et al., 2009). In an investigation of the association between triple-negative phenotype and basal cytokeratin markers, Tan et al. reported that 6 out of 31 (19.4%) triple-negative breast tumors were negative for basal makers (CK 5/6, CK 14, CK 17, and EGFR), while 15 out of 207 (6.3%) non-triple-negative tumors expressed basal makers (Tan

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et al., 2008). Based on gene expression profiles in breast cancer patients, TNBC may be stratified into basal-like (39-54%), claudin-low (25-39%), HER-2 enriched/ molecular apocrine (7-14%), luminal B (4-7%), luminal A (4-5%), and normal breast-like (1%) subtypes. TNBC is most sensitive to chemotherapy with 19% achieving clinical-complete-response (cCR) followed by HER2 enriched [2/22 (9%) cCR], luminal B [1/6 (7%) cCR] and luminal A [0/10 (0%) cCR] (Khokher et al., 2013). Thus, TNBC represents a heterogeneous group of tumors that may differ in clinicopathologic features and, accordingly, in therapeutic requirements (Choi et al., 2012).

In this review we discussed about limitations in triple-negative breast cancer and targets including poly (ADP-ribose) polymerase, epidermal growth factor receptor, vascular endothelial growth factor and cancer stem cells to overcome these limitations.

Limitations in TNBC

Hormone receptor-positive tumors have been considered to have favorable outcome because of their response to endocrine manipulations such as tamoxifen, aromatase inhibitors, or ovarian ablation (Sethi et al., 2011). The armory of "targeted therapy" for the treatment of metastatic TNBC has been inadequate due to the lack of identification of pathway specific targets (Conlin and Seidman, 2008; Elias, 2010; Carey, 2011) and the absence of a validated targeted therapy (Marchio, 2008; Corkery et al., 2009). Patients with triple-negative breast cancer do benefit from chemotherapy, but better treatment options are needed that are less toxic, reduce the risk of disease progression, and are more targeted to this patient population.

A lot of further investigations are needed to identify biomarkers that can be used to monitor the therapeutic efficacy as well as to develop novel targeted and personalized treatments of TNBC (Li et al., 2013).

The development of newer biologic and targeted therapies, such as PARP inhibitors, EGFR inhibitors and therapies that target cancer stem cells continues to be a promising area of research (Perou, 2010; Brady-West and McGrowder, 2011).

Novel Therapeutic Options in TNBC

Targeting Poly (ADP-ribose) polymerase

DNA is unstable and exposure to environmental agents, as a result of by-products of normal cellular metabolism and by spontaneous disruption of chemical bonds in DNA cause alterations in DNA structure (Hoeijmakers, 2001). It causes a variety of lesions including base modifications, SSBs, DSBs, and intrastrand or interstrand cross-links. Repair of SSBs involves BER, NER, and MMR while repair of DSBs involves HR and NHEJ (Underhill et al., 2010).

Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes that are involved in many cellular processes guided by an ability to modify various target proteins through the conversion of nicotinamide adenine dinucleotide (NAD+) into long poly(ADP-ribose) (PAR) chains coupled to the proteins. PARP1 is the best known member of an eighteen PARP domain protein family. PARP1 is a chromatin-associated enzyme that is involved in a number of distinct nuclear functions, such as DNA repair, regulation of chromatin structure and transcription, cell survival and cell death, maintenance of genome stability and pro-inflammatory signal transduction. PARP2, sharing homology with PARP1, also regulates different cellular processes, including DNA damage response (Wang and Weaver, 2011).

DNA-binding antitumor drugs directly damage DNA, inducing DNA breaks and subsequent PARP activation. Inhibition of PARP in cells exposed to DNA-damaging drugs would decrease DNA repair and would induce apoptotic cell death, decreasing necrotic cell death and preventing the pathological side effects of necrosis. It is interesting to note that PARP inhibitors might be more effective against tumor cells than against normal cells (Shiobara et al., 2001).

This therapeutic approach is currently under investigation in several clinical development programs. Inhibition of PARP has potential for use in cancer treatment through at least two mechanisms, i.e., by increasing tumor sensitivity to chemotherapeutic agents that damage DNA, and also by inducing "synthetic lethality" in cells that are highly dependent on PARP, due to deficiency in HR, such as BRCA1 mutants (Morales et al., 2013). BRCA has a function of repairing DNA double strand breaks (Ashworth, 2008). BRCA mutation can occur by genetic inheriting or sporadicly in basal-like breast cancer, or another reason for dysfunctional BRCA is lower BRCA protein expression in basal-like breast cancer. (Husain et al., 1998; Shen et al., 1998; Byrski et al., 2009).

A number of PARP inhibitors are under clinical development: rucaparib (CO-338; AG014699, PF-0367338; oral/IV), iniparib (BSI-201), olaparib (AZD-2281; oral), veliparib (ABT-888; oral), MK-4827, BMN-673, CEP-9722 (oral) and E7016 (GPI 21016, oral). The loss of BER capacity produced by PARP inhibition has prompted the evaluation of these drugs as potential enhancers of DNA damaging cytotoxic chemotherapeutic agents such as alkylating agents (for example, platinum, cyclophosphamide) and topoisomerase 1 inhibitors (for example, camptothecin analogs) (Zhang et al., 2011). However, recent studies strongly suggest that, unlike the other drugs, the mechanism of action of iniparib is unclear and is probably not related to PARP inhibition per se (Ji et al., 2011).

Targeting EGFR

Epidermal growth factor receptor (EGFR) is membrane receptor and has been shown to play an important role in the growth and survival of many solid tumors. Pathways involved in EGFR signal transduction have been proposed as possible anticancer targets, and agents to specifically target the EGFR have been developed (Baselga, 2000; Raymond et al., 2000; Goel et al., 2002).

Inhibiting of EGFR causes cell cycle arrest, potentiation of apoptosis, inhibition of angiogenesis, inhibition of tumor cell invasion and metastasis and augmentation

of the anti-tumor effects of chemotherapy and radiation therapy (Mendelsohn and Baselga, 2006). MAbs and small molecule inhibitors of the EGFR tyrosine kinase enzymatic activity are the therapeutic approaches that have been shown most promising and are currently being used to inhibit the EGFR in clinical studies (Ciardiello and Tortora, 2001).

More recently, it has been shown that the 'triple negative' breast cancer subtype expresses the EGFR at higher frequency as compared with other subtypes (Reis-Filho and Tutt, 2008). The study by Liu et al. Showed that TNBC to be a heterogeneous disease that consists of at least two phenotypes based on the expression of basal markers (CK5/6 and/or EGFR) (Liu et al., 2012). EGFR status correlates negatively with survival in patients with triple-negative breast cancers, and thus focus has turned on this receptor as a potential clinical target. Two classes of EGFR inhibitors are currently in clinical use: the monoclonal antibodies and the small molecule tyrosine kinase inhibitors (Burness et al., 2010). EGFR inhibitors currently in clinical use include the small molecule tyrosine kinase inhibitors gefitinib and erlotinib and the mAb cetuximab, which are approved for treatment of a number of solid tumours (Goldstein et al., 1995; Baselga and Averbuch, 2000).

Targeting VEGF

Angiogenesis is the production by a tumor of a new blood vessel system for the purpose of providing nutrients to the tumor. Therapies for inhibiting angiogenesis are being investigated (Pardee and Stein, 2009). One of the most important proangiogenic factors is vascular endothelial growth factor (VEGF) (Hoeben et al., 2004). Intratumoural expression of VEGF is significantly higher in TNBC than in non-TNBC (Linderholm et al., 2009). The vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis and has been shown to be a valid target for monoclonal antibody therapy in several solid tumors (O'Shaughnessy et al., 2009). According to a study with angiogenesis, majority of the breast cancer patients had advanced stage disease with poorer prognostic factors as compared to other local and western studies. Breast cancer in younger patients might be more proangiogenic (Ch'ng et al., 2012).

VEGF became a target for pharmacological inhibition of tumor angiogenesis (Linderholm et al., 1998; 2000; Foekens et al., 2001). Potential approaches for blocking VEGF action include inhibiting secretion of endogenous tumor VEGF, neutralizing VEGF in the microcirculation, and preventing VEGF binding and subsequent signal transduction (McMahon, 2000).

Antiangiogenic agents include antibodies such as bevacizumab that binds to VEGF and ramucirumab that binds to the VEGF receptor, receptor mimetics such as aflibercept, and small molecule oral tyrosine kinase inhibitors (TKIs) that inhibit a wide variety of targets, including VEGFR, platelet derived growth factor receptor, and many others (Rugo, 2012).

Targeting cancer stem cells

Many solid tumor types, including breast cancer, exhibit a functional hierarchy of cancer cells of which only a small subpopulation of replenishing stem-like cells can give rise to the differentiated cells that comprise the bulk tumor. In human breast cancers, these tumorigenic breast cancer stem cells are enriched in cells with a CD44+/CD24-/low/ESA+phenotype (Fillmore and Kuperwasser, 2008). These cancer stem cells represent only 1% of the tumor (Gold and Dean, 2009). Triple-negative basal-like breast cancer cells resemble many features of breast CSCs, including expression of CD44 high, CD24 low and ALDH-1. The triple negative basal like subtype of breast cancer is characterized by a high content of breast CSCs, aggressive proliferation, high metastatic capability and poor overall survival of patients (Naujokat, 2012).

Unlike rapidly dividing cancer cells within the tumor mass, CSCs have a slower cycle under the effect of various factors such as microenvironment in which they reside and therefore following conventional cancer therapies that kill rapidly dividing cells, CSCs can survive (Cetin and Topcul, 2012). This tiny subset of cells, referred to as cancer stem cells (CSCs), is also considered to be more chemoresistant than the bulk of tumor cells and is thus more difficult to target and eradicate. Thus, CSCs need to be specifically targeted and eliminated to achieve tumor ablation, a concept that has begun to revolutionize approaches to cancer therapy and drug design (Bapat, 2009).

CSC-specific pharmaceutical interventions are being developed that may eliminate both primary and acquired CSC chemo-resistance. This may dramatically improve the treatment of cancer by abrogating the potential for CSC-induced tumor regrowth and systemic disease spread after initial treatment (Hu and Fu, 2012).

Using CSC gene expression profile in the generation of therapeutics mAbs. Creation of modified mAbs with more human characteristics has allowed the efficient binding of these with the receptors expressed on immune effector cells. The identification, using gene expression profiles of new functional targets and epitopes on cancer stem cells from CSC mouse models, would allow to generate improved specific inhibitory antibodies capable to recognise and eliminate cancer stem cells responsible for the maintenance of the cancer cell population (Perez-Caro and Sanchez-Garcia, 2006).

Understanding the mechanisms that underlie the self-renewal behavior of CSCs is of greatest importance for discovery and development of anticancer drugs targeting CSCs. During those pathways, Wnt, Notch and Hedgehog signaling pathways may play an important role in the recurrence and maintenance of cancer stem cell (Hu and Fu, 2012).

Finally, a recent study has identified the interleukin-6/Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signalling pathway in CD44+/CD24-stem cell-like breast cancer cells, as a potential therapeutic target, particularly in basal-like breast cancer (Marotta et al., 2011). The JAK1 and JAK2 inhibitor ruxolitinib is currently being investigated in a number of human malignancies, including solid tumours (http://www.incyte.com/drugs_product_pipeline.html 06.01.2012.).

Discussion

Breast cancer that effects many women in the world is complex and heterogeneous disease and is divided into many subtypes. In recent years, targeted therapy approaches take place of conventional therapies in breast cancer as in many other cancers. But unlike other subtypes, therapy of triple negative breast cancer is quite difficult due to absence of a variety of targets. For these reasons new targets are needed both in TNBC cells and in TNBC stem cells in tumor mass. Discovery of new targets will lead to develop of new and more effective drugs for the treatment.

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