[Frontiers in Bioscience, Elite, 8, 72-83, January 1, 2016]

Critical role for BRCA1 expression as a marker of chemosensitivity response and prognosis

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1. ABSTRACT

Chemotherapy is still the leader option for cancer treatment. Nevertheless some patients develop chemotherapy resistance. One major research goal is to identify the critical genes involved in chemotherapy response to predict the best therapy option for patients. Germline mutations in the *BReast Cancer susceptibility gene (BRCA1)* are associated to increased risk of developing breast, ovarian and other types of cancers. However, due to harmful BRCA1 gene mutations are relatively rare in the general population, nowadays most researchers focused on BRCA1 expression downregulation and/or epigenetic inactivation in sporadic tumors as a prognosis tool for chemotherapy response in patients. Chemotherapy response can be dramatically different depending on BRCA1 expression status, tumor type and drug. Hence, the chemotherapy response could be dissimilar in breast, ovarian, uterine, prostate, esophageal, gastric and lung cancers. Additionally, differential BRCA1 expression in sporadic tumors shows different response to DNA-damaging agents, mitotic inhibitors or PARP inhibitors. In this review we will examine the response to different chemotherapy agents in several cancer types depending on BRCA1 expression status.

2. INTRODUCTION

The use of chemotherapeutics remains the predominant option for cancer therapy. However, one of the major problems for successful cancer therapy using these drugs is that patients often do not respond or eventually develop resistance after initial treatment. Therefore identification of genes involved in chemotherapeutic response is critical to predict tumor evolution and treat drug-resistant patients.

Mutations in *BReast Cancer susceptibility gene (BRCA1)* are responsible of 50% of inherited breast cancers and are associated to increased risk of developing breast and ovarian cancers and poor clinical outcome in prostate cancer (1-5). Though somatic mutations in BRCA1 are rare; BRCA1 mRNA and protein are down-regulated by epigenetic mechanisms in approximately 30% of sporadic breast cancers and 70% of ovarian cancers, but also occur in prostate, lung and other cancer types (6-8).

BRCA1 is implicated in multiple biological processes such as DNA damage response, transcription-coupled DNA repair, cell cycle and apoptosis (9-11). Due to its role on these cellular processes, BRCA1 is considered a key player that establishes chemotherapy sensitivity and should be considered for patient management. Hence, several researchers had been using pre-clinical and clinical studies to clarify BRCA1 role in response to DNA-damaging agents and other types of chemotherapy agents (12,13).

Chemotherapy drugs can be divided into several groups based on their mechanism of action, their chemical

structure, and their relationship to other drugs. Understanding how these drugs work is important in predicting side effects, efficacy and probable combination with other compounds for cancer therapy in patients. For instance, *DNA-damaging agents,* including alkylating compounds, directly damage the DNA to prevent cancer cells division. The platinum drugs (cisplatin, carboplatin and oxalaplatin) and antimetabolites (drugs that interfere with DNA and RNA replication: 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), hydroxyurea, methotrexate, etc) can be included into this group. Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in DNA replication. These drugs are also DNA-damaging agents, and consist of: daunorubicin, doxorubicin, epirubicin, idarubicin. Other anti-tumor antibiotics that are not anthracyclines include: actinomycin-D, bleomycin, mitomycin-C and mitoxantrone. Topoisomerase inhibitors interfere with the enzymes that help separate the strands of DNA so they can be copied, called topoisomerases. There are topoisomerase I inhibitors (topotecan and irinotecan) and topoisomerase II inhibitors (etoposide and mitoxantrone). *Mitotic inhibitors* are often plant alkaloids and other compounds derived from natural products. Examples of mitotic inhibitors include anti-microtubule agents, like taxanes (paclitaxel and docetaxel), epothilones and vinca alkaloids (vinblastine, vincristine and vinorelbine). Other agents are Poly(ADP-ribose) polymerase *(PARP) inhibitors* that primarily inhibit the PARP-1 and PARP-2 enzymes within the cell. Clinically, PARP inhibitors demonstrated activity in tumors which lack a functional HR system (BRCA1 and BRCA2 mutations) by forcing NHEJ repair. Several authors had reviewed BRCA1 role in chemotherapy response through the use of BRCA1 mutated cells. In addition, clinical studies have been carried out mainly in patients carrying mutations on the BRCA1 gene. However due to the low rate of BRCA1 mutations in the general population, nowadays the challenge is to understand the effect of BRCA1 expression downregulation and/or epigenetic inactivation in chemotherapy outcome in different populations and tissues.

Early studies using BRCA1 expression modulation showed that BRCA1 increases DNA-damaging agent resistance and anti-microtubule poisons sensitivity. However, afterward several studies showed the opposite response: BRCA1 loss of function increases DNA-damaging agents sensitivity. All these “contradictory” effects can be explained mostly if we take into account tissue type and different genetic background.

Hence BRCA1 expression status in different cancer types might be crucial to select the most efficient therapeutic strategy for patients. In this review we will examine the response to different chemotherapy agents in several cancer types depending on BRCA1 expression status. We will focus on BRCA1 expression role in DNA-damaging agents, anti-microtubule drugs and PARP inhibitors.

3. PRECLINICAL STUDIES FOR DNA DAMAGE-RESPONSE IN BRCA1-LINKED TUMORS

Preclinical and clinical data indicate that BRCA1 modulates the response to chemotherapeutic agents. First studies assessing BRCA1 role in response to DNA-damaging agents concluded that BRCA1 loss of function leads to increased sensitivity of tumor cells to DNA-damaging agents, such as cisplatin, bleomycin and etoposide (6,14-17).

Although most of these conclusions were obtained using BRCA1-mutated cells, other studies showed similar results after BRCA1 expression modulation. Thus, for example, *in vivo* studies using mice determined that breast tumors without BRCA1 and p53 expression showed increased sensitivity to double strand DNA damaging agents, olaparib and/or topotecan compounds (18). Additionally, it was observed that BRCA1 downregulation in MES (mice embryonic stem cells) showed an increased sensitivity to alkylating agents, such as mitomycine C and cisplatin (19). Moreover, the restitution of BRCA1 expression in MEF turned cells resistant to platinum derived agents (20).

Other authors using *in vitro* and *in vivo* research reported that BRCA1 hypermethylation in UACC3199 and HCC-38 cells conferred high sensitivity to platinum compounds (21). While the BRCA1 unmethylated and non-mutated cell line MDA-MB-231 showed increased resistance to these agents (21). Finally, in a screening to discover modulators of resistance to cisplatin, Husain *et al.* (16) found that resistance to cisplatin in MCF7 breast cancer cells induced by *in vitro* chronic exposure to this drug was associated to an increase in BRCA1 expression levels.

The concept of BRCA1 as a positive modulator of DNA damaging agents sensitivity is consistent with its function in DNA damage repair. Thus, cells with functional BRCA1 could be more efficient in double strand breaks repair by homologous recombination, then cancer therapy for BRCA1 defective patients could be improved by the administration of DNA damaging agents (13). However, opposite to this concept, other studies showed that BRCA1 expression increased sensitivity to DNA-damaging agents in other cell types. For instance, breast and prostate BRCA1 defective tumor cells are resistant to doxorubicin (22,23). Likewise, other *in vitro* studies demonstrated that breast cancer cells with BRCA1 diminished expression showed increased resistance to the topoisomerase II inhibitor, etoposide (14,24). Additional studies showed that BRCA1 increases sensitivity to doxorubicin, camptotecin and taxol in prostate cancer cells (25). Although these results seems to be contradictory, BRCA1 complexity and its numerous biological functions make reasonable the possibility that

BRCA1 final effect in chemotherapy sensitivity will be highly dependent of the tissue, its genetic background, the administrated drug and its multiple mechanism of action.

4. PRECLINICAL STUDIES FOR MITOTIC INHIBITORS-RESPONSE IN BRCA1-LINKED TUMORS

Anti-microtubule agents showed DNA-damaging agents opposite effect in BRCA1 mutated cells. Preclinical and clinical studies demonstrated that loss of BRCA1 causes cancer cells resistance to anti-microtubule agents, such as paclitaxel and docetaxel (26-31). Other authors demonstrated that BRCA1 increased sensitivity to taxol and other taxol derivates such as paclitaxel and vincristine (14,32). Tassone *et al.* assigned a positive role to BRCA1 in sensitivity to paclitaxel and doxorubicin in breast cancer cells (22). Additionally, it was reported that BRCA1 loss increases tamoxifen (Estrogen Receptor antagonist) sensitivity (33). Thus, depending on the type of chemotherapeutic compound, BRCA1 can have either a positive or a negative role in mediating chemosensitivity.

5. PRECLINICAL STUDIES FOR PARP INHIBITORS-RESPONSE IN BRCA1-LINKED TUMORS

Mounting evidence showed that BRCA1 and BRCA2-deficient cells are hypersensitive to PARP inhibitors, suggesting that these agents can be employed as novel therapeutic drugs to selectively treat BRCA1- or BRCA2-deficient tumors (34-36). Furthermore, several authors have recently found that BRCA1 CpG island hypermethylation predicts sensitivity to PARP inhibitors (21,37,38).

6. CLINICAL MANAGEMENT OF PATIENTS ASSOCIATED TO BRCA1

Identification of high-risk patients is the main concern in cancer prevention. Genetic mutations associated to cancer development are an evident marker for risk. Much effort has been made to reduce cancer mortality in this group of patients. However, is interesting that the gene mutations most commonly accountable for inherited cancers are not found in a large amount of cases in the general population, even when they share the clinical criteria for having inherited cancer (39). Hence, epigenetic alterations can explain for a significant proportion of cancers with the clinical/pathological features but not the characteristic mutations of inherited cancers.

Based on the critical BRCA1 role in determining sensitivity to chemotherapeutic agents, several clinical trials have been carried out in BRCA1-mutated patients. Early studies were consistent with a role of BRCA1 influencing DNA-damage agents and PARP inhibitors response. In fact numerous retrospective clinical studies support the pre-clinical data and demonstrated a notable increase in response to DNA damage-based therapy in BRCA1-linked breast and ovarian cancer (40-45). PARP inhibitors clinical trials have shown strong antitumor activities in breast, ovarian and prostate cancers with BRCA1 or BRCA2 mutations (46). Thus, these agents are the most established example of gene-mutation dependent cancer therapy. However, due to the low rate of mutations in BRCA1, most of these studies were performed in Ashkenazi´s population. Hence, BRCA1 is confined to a small subset of patients. Nowadays, the challenge is to understand the effect of BRCA1 expression modulation and/or epigenetic inactivation in a population without BRCA1 mutations. Thus, chemotherapy outcome can be also extensive to different ethnics and also independent of BRCA1 mutation status.

Next sections will discuss the latest findings in clinical trials and retrospective studies regarding BRCA1 expression effects in breast and ovarian cancer chemotherapy response but also uterine, prostate, esophageal, gastric and lung cancers.

6.1. Breast cancer

BRCA1 gene can undergo epigenetic inactivation in sporadic breast tumors (21,47-51) and ovarian tumors (50,52,53) by DNA methylation on its CpG island promoter sites. Specifically, BRCA1 promoter hipermethylation was identified in 9-32% of sporadic breast cancers (50,54,55). BRCA1 promoter methylation is associated with decreased expression of ER and basal-like phenotype (47,54). In addition, studies performed in Taiwanese breast cancer patients showed that BRCA1 promoter methylation correlates with triple-negative (ER-/PR-/HER2-) status and poor disease-free survival in women with breast cancer early-stage (56).

Interestingly, recent clinical studies revealed that BRCA1 could have a dual role in chemotherapy outcome in breast cancer increasing or diminishing sensitivity to chemotherapeutic agents according to the tumor subtype: patients with triple negative breast cancer might have more benefits receiving adjuvant chemotherapy when BRCA1 promoter is methylated, while in non-triple negative breast cancer patients BRCA1 methylation could be an unfavorable predictor for adjuvant therapy (57,58). Indeed, Xu *et al* performed a retrospective analysis in 1,163 unselected breast cancer patients to correlate BRCA1 promoter methylation with adjuvant therapy response (57). They found that the subgroup of triple-negative breast cancer patients treated with adjuvant therapy (anthracyclines followed by paclitaxel or methotrexate plus cyclophosphamide and 5-fluorouracil) had increased disease free survival rate when BRCA1 promoter was methylated (57). However

they found that BRCA1 methylation had the opposite effect in non-triple negative breast cancer (57).

Similarly, Ignatov *et al.* observed that BRCA1 promoter methylation correlated with decreased BRCA1 expression and increased disease free survival in triple negative breast cancer patients receiving adjuvant anthracycline-based therapy (58). Furthermore in non triple negative breast cancer patients, BRCA1 methylation did not improve any clinical or pathologic parameter (58).

Finally clinical studies performed to explore the effect of BRCA1 expression on tumor response to taxane-based chemotherapy showed shorter time to disease progression in patients with BRCA1 depleted tumors than in BRCA1 expressing tumors, suggesting that BRCA1 is a good prognostic marker of patient progress with advanced breast cancer undergoing taxane-based therapy (59).

6.2. Ovarian cancer

BRCA1 expression is a well known prognostic and predictive marker in ovarian cancer. Thus, it was reported that low levels of BRCA1 expression are an indicator of better chemotherapy response in patients (60-62).

In ovarian cancer, clinical studies tend to confirm the classic concept of BRCA1 expression as a negative factor in DNA damaging agents-based chemotherapy. Thus, BRCA1 promoter hypermethylation is associated with BRCA1 expression decreases and, in turn, increases time to relapse and overall survival in patients with ovarian cancer treated with cisplatin (21). Other studies confirm these results; a study using a cohort of 292 patients showed that sporadic epithelial ovarian cancer patients have high chance of clinical response to chemotherapy compared with patients' absent/low BRCA1 expression regardless of treatment received (62). Moreover, absent/low BRCA1 expression in patients treated with platinum as chemotherapy had a better clinical response compared to patients with higher BRCA1 levels (62).

Furthermore, another study performed in epithelial ovarian cancer patients, showed that decreased BRCA1 expression is associated with improved survival when treated with intraperitoneal cisplatin and paclitaxel chemotherapies (63). Also patients with serous ovarian cancers had higher platinum sensitivity and longer progression-free survival when their tumors express high levels of miR-9 which correlates inversely with BRCA1 expression (64).

In agreement with these findings, it was reported that BRCA1-mutated patients show the opposite effect in chemotherapy response which might be explained by secondary mutations that restitute BRCA1 functionality. In fact, Swisher *et al* studied the occurrence of secondary genetic changes in BRCA1 that restored the reading frame of BRCA protein. They showed that 4 out of 6 recurrent platinum resistant tumors developed secondary mutations while none of platinum-sensitive recurrent tumors developed BRCA1 sequence alteration (65).

6.3. Endometrial and uterine cancer

Germline mutations in BRCA1 and BRCA2 have been implicated in the pathogenesis of endometrial cancer. One of the strongest evidence of this is a recent cohort study performed following 4,456 women with a BRCA1 or a BRCA2 mutation with endometrial cancer (66). This work showed that BRCA1 mutation carriers have a higher risk of endometrial cancer compared to the general population. Additionally, it was reported that BRCA1 mutation carriers with breast cancer that received tamoxifen treatment showed increased risk of endometrial cancer (66,67).

A particular cancer of the endometrium is uterine serous papillary carcinoma (USPC). Although this tumor originates in the endometrium, it shares similarities with serous papillary carcinoma of the ovary or the peritoneum. Furthermore, USPC responds to agents that are being used for carcinoma of the ovary and the peritoneum (68).

Thus, USPC could be considered a manifestation of the hereditary breast ovarian cancer syndrome, so studies in BRCA1 mutated carriers were performed to elucidate if BRCA1 is a risk factor for this disease. In fact, several authors showed a high rate of BRCA1 germinal mutations in Jewish patients with USPC compared to BRCA1 mutation incidence in general population (69-72).

BRCA1 expression effect of BRCA1 in uterine cancer has been subject of study in the last years. Recently it has been shown that the effect of BRCA1 expression on uterine serous carcinoma is similar to that observed in high grade serous ovarian cancer: low levels of BRCA1 are associated to a favorable prognostic (73). Therefore, BRCA1 expression could have implications in the clinical management of USPC patients. Regardless, this is an unexplored topic and further studies are needed to determine BRCA1 role in chemotherapeutic response in uterine cancer.

6.4. Lung cancer

Several studies have clearly stated BRCA1 as a prognostic marker in non small cells lung cancer (NSCLC). Interestingly, BRCA1 overexpression has been linked to poor survival in NSCLC patients (7).

Since BRCA1 expression has previously associated with differential sensitivity to cisplatin and antimicrotubule agents, the use of adjuvant therapies

with cisplatin has been taken into consideration for NSCLC patients. Recently Qin *et al* and Xian-Jun *et al* demonstrated that BRCA1 mRNA expression is associated with short progression free survival and overall survival of NSCLC patients treated with platinum-based chemotherapy suggesting that in this subset of patients BRCA1 decreases sensitivity to platinum agents (74,75).

Similar results were obtained with neoadjuvant gemcitabine/cisplatin chemotherapy. NSCLC patients with tumors with high BRCA1 expression showed shorter overall survival and progression free survival compared to low BRCA1 mRNA levels patients reflecting a worse therapeutic outcome for the first ones (6). Interestingly, Wang *et al* found that BRCA1 expression is negatively correlated with sensitivity to cisplatin but positively related to sensitivity to docetaxel (76).

Finally a meta-analysis confirmed that BRCA1 low levels are related to better clinical outcome to platinum based therapy. Meanwhile BRCA1 high expression correlates to a better response to toxal based treatment (77).

6.5. Esophageal and gastric cancer

BRCA1 expression is a known marker of prognosis and response to therapy in esophageal cancer. In this cancer type BRCA1 overexpression diminished chemotherapy sensitivity. Indeed recent findings showed that advanced and metastatic esophageal cancer patients with low expression of BRCA1 had increased response rate to cisplatin alone or in combination with radiotherapy. However, the opposite effect was observed in patients treated with docetaxel based therapy where BRCA1 expression improved therapy outcome (78). Previous studies demonstrated that BRCA1 is also relevant in chemotherapeutic response in gastric cancer. Patients without BRCA1 expression showed prolonged overall survival and better prognosis when receiving platinum based adjuvant chemotherapy (8).

6.6. Prostate cancer

Previous studies demonstrated that male BRCA1 and BRCA2 mutation carriers have an increased risk of develop prostate cancer (79-81). Other authors correlated *BRCA* mutation with clinical features and found that BRCA1 mutation may be associated to aggressiveness disease, including higher Gleason score, higher prostate-specific antigen (PSA) level at diagnosis, and higher tumor stage and/or grade at diagnosis, a finding that warrants consideration as patients undergo cancer risk assessment and genetic counseling (http://www.cancer.gov/cancertopics/pdq/genetics/prostate/HealthProfessional/page3#section_3.2.8) (3,4,82). Prostate cancer BRCA mutation carriers respond less well to conventional treatment, including surgery and/or radiotherapy and they also have a lower survival rate than BRCA1 mutation non carriers (83). Moreover, PARP inhibitors are currently in clinical trials for the treatment of prostate cancer (83). However, still there are no clinical data exploring the role of BRCA1 expression in chemotherapy outcome for prostate cancer patients. Future studies exploring this field might improve therapies for this group of patients.

7. CONCLUSIONS

BRCA1 expression diminution, as observed in some sporadic cancers, is important in modulating tumor response to chemotherapy. The concept of BRCA1 as a positive modulator of DNA damaging agent sensitivity is consistent with its function in DNA damage repair. Hence, cells with functional BRCA1 could be more effective in double strand breaks repair by homologous recombination, then cancer therapy for BRCA1 defective patients could be improve by the administration of DNA damaging agents.

General trend in the literature is that BRCA1 loss of function increases chemotherapy sensitivity in cell lines, thus BRCA1 mutation carrier patients will show higher sensitivity to these agents. However, several *in vivo* results using animal models concluded that BRCA1 depletion increases DNA damaging agent resistance.

Although this results seems to be contradictory, BRCA1 complexity and its numerous biological functions makes reasonable the possibility that BRCA1 final effect in chemotherapy sensitivity will be highly dependent and specific of the tissue, its genetic background and also the compound and its multiple mechanism of action.

8. ACKNOLWLEDGEMENT

The authors would like to report that no conflicts of interest exist with regards to this manuscript.

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Key Words: BRCA1, Chemotherapy, Cancer, DNA-damage, PARP-inhibitors, Mitotic Inhibitors, Review

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