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The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers

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1. ABSTRACT

The Breast Cancer Susceptibility Genes, BRCA1 and BRCA2, are the dynamic regulators of genomic integrity. Inherited mutations in these genes are associated with the development of cancer in multiple organs including the breast and ovary. Mutations of BRCA1/2 genes greatly increase lifetime risk to develop breast and ovarian cancer and these mutations are frequently observed in hereditary breast and ovarian cancers. In addition, misregulation and altered expressions of BRCA1/2 proteins potentiate sporadic forms of breast cancer. In particular, both genes contribute to DNA repair and transcriptional regulation in response to DNA damage. Thus, deficiencies of BRCA1/2 functions lead to the accumulation of genetic alterations and ultimately influence the development of cancer. Studies since identification of both BRCA1 and BRCA2 have provided strong evidences for their tumor suppressor activities specifically for breast and ovarian cancer and this article aims to review the current state of knowledge regarding the BRCAs and associated cancer risk.

2. INTRODUCTION

BRCA1 and BRCA2 are two distinct tumor suppressor genes and they play an integral role in response to cellular stress via the activation of DNA repair processes (1-5). Germline mutations of BRCA genes predispose individuals to develop breast and ovarian cancer (6-8) and also incline the risk to develop other cancer types including pancreatic, and prostate cancer (9-13). These observations indicated that BRCA genes might function in tissue specific manners, at least in the breast and the ovary. However, detailed functional studies of BRCA1/2 have indicated that these proteins play role in many different organs to control chromatin remodeling, transcription control, cell cycle regulation, and DNA repair processes (6). They were found to interact with many DNA repair proteins (6-8, 14) and involved in Fanconi anaemia, a rare inherited disease caused by genetic defects in DNA repair proteins and characterized by genomic instability with increased cancer risk (15). Thus, the regulatory roles of BRCA1/2 genes to control cell cycle checkpoints and DNA repair mechanisms are highly correlated with their tumor suppressor activites,

although, the reason for development of breast and ovarian tissue specific tumorigenesis due to germline mutations of the BRCA1/2 is poorly understood (14, 16).

3. THE BRCA1 PROTEIN

The BRCA1 gene was cloned in 1994 and located in human chromosome 17q21 (17). In human, the full length BRCA1 protein is encoded by 24 exons and several studies have investigated to understand the functional role of BRCA1 (17-22). The BRCA1 is revealed as a multi-functional protein and known to interact with different protein partners in various cellular compartments to play essential roles in diverse cellular pathways such as DNA damage repair, cell-cycle arrest, apoptosis, genetic instability, transcriptional activation, and also in tumorigenesis (20-22). Mutations in BRCA1 are associated with increased lifetime risk of breast and ovarian cancers (17-19). In fact, many of the well-recognized risk factors and risk modifiers of tumorigenesis appear to operate similarly in BRCA mutation carriers (14).

In cancer patients, mutations in BRCA1 most frequently observed in three domains (23) called N-terminal RING domain encoded by exons 2-7 (amino acids 1-109), coding regions of exons 11-13, and BRCA1 C-terminus encoded by exons 16-24 (amino acids 1650-1863) or BRCT domain (23). These three domains are highly important not only for interaction with various partner proteins but also with BRCA1 subcellular localization. Structures of RING and BRCT domains have been solved (24-28), however, these two domains cover only a small part of the full length BRCA1 protein whereas exons 11-13 encode majority of BRCA1 protein and the structure of this region is still unknown.

The RING domain of BRCA1 consists of a RING finger motif correspond to residues 24–64, which is a highly conserved domain that plays key role in ubiquitination pathway. This domain interacts with another RING domain containing protein BARD1 (BRCA1 associated RING domain protein 1) (29). Yeast two-hybrid studies indicated that the RING finger motifs of both BRCA1 and BARD1 are required for their interaction (30) and the heteromeric complex identified as discrete nuclear foci on damaged, replicating DNA structures during S phase of cell cycle progression (31). The RING finger motif is responsible for the E3-ubiquitin ligase activity of BRCA1 (32) and the ubiquitin ligase activity of BRCA1 is dramatically increased by formation of the BRCA1/BARD1 heterodimer (33). Both BRCA1 and BARD1 knockout mice showed embryonic lethality (34-37) and BARD1 mutations are also prevalent in hereditary breast and ovarian cancers (38-40).

Exons 11-13 contain a large percentage of the clinically relevant mutations and highly important for the tumor suppressor function of BRCA1 (41). This middle region of BRCA1 is known to interact with several proteins involved in a wide range of cellular pathways such as transcription, DNA repair, and cell cycle progression and the interacting partners include retinoblastoma protein (Rb), c-Myc, RAD50, and RAD51 (4, 21). Exon 11 contains two nuclear localization sequences (NLS) and encodes nearly 60% of the BRCA1 protein (40, 42, 43). The NLS sequences are located in between amino acids 501-507 and 607-614 and facilitate to interact with importin-alpha, which mediates BRCA1 transport from the cytosol to the nucleus (44). Mutations of the NLSs result in a shift toward cytosolic localization of BRCA1 and subsequent increase in unrepaired mutations and chromosomal abnormalities in malignancies.

The C-terminal (BRCT) domain is spanned in between amino acids 1650-1863 and responsible for interactions with substrates of DNA damage-activated kinases such as ATM and ATR (45). This region of BRCA1 known to interact with various transcription regulators such as p53 and BACH1 as well as DNA damage repair proteins such as CtIP and CCDC98 (46-50). Multiple mutations in the BRCT domain, specifically mutation of hydrophobic residues destroy the ability to interact with phosphoproteins and recently reviewed extensively by Clark *et. al.* (23). These mutations have been observed in breast and ovarian cancers and indicate the involvement of BRCA1 C-terminus in tumor suppression (17, 19, 51, 52). The BRCT domain also reported to mediate DNA binding activity and interaction with other proteins (53).

Interestingly, BRCA1 was discovered as nuclear phosphoprotein in normal cells and in tumor cell lines from tissues other than breast and ovary, whereas, predominant cytoplasmic location of BRCA1 has been observed in the breast and ovarian cancer cells (54). However, several other studies also claimed BRCA1 localization mainly in the nuclei of both normal and cancer cells (43, 55, 56). In addition, studies also indicated that BRCA1 was a 190 kDa secreted tumor suppressor rather than 220-230 kDa proteins (57, 58). These opposing observations overall indicated the presence of functionally different alternatively spliced transcripts of BRCA1. In fact, alternative splicing of BRCA1 is very common and highly related to its function during tumorigenesis (59). A large number of splice variants of BRCA1 have been found in different tissues and cell types, although functional importance of majority of them are still unknown (60). Xu *et. al.* first indicated the presence of two possible exon 1 (exon 1a and 1b) representing two distinct BRCA1 transcripts (61). Although both of these transcripts are expressed in various tissues, the transcript with exon 1a are expressed in mammary glands and the transcript with exon 1b found in the placenta indicating possible tissue–specific distributions of BRCA1 transcript variants. Subsequent studies revealed that the wild type, BRCA1 $^{\Delta[9,10]}$, BRCA1 $^{\Delta 11b}$, BRCA1$^{\Delta\,[9,10,11b]}$, BRCA1-IRIS, and BRCA1 with exon 13A are highly abundant in various tissues and considered as the major BRCA1 transcript variants (6, 43, 62, 63). Recently, expression of BRCA1 $^{\Delta\,[14,15]}$ splice variant has been linked with radiation-induced DNA double-strand break (DSB) repair in MCF-7 breast cancer cells (64).

4. FUNCTIONAL DIVERSITY OF BRCA1

BRCA1 regulates diverse cellular functions at different cellular compartments. During S-phase of the cell cycle or genotoxic stress, phosphorylated BRCA1

translocate to the nucleous and regulates DNA damaged repair processes, DNA replication, gene transactivation, and also X chromosome inactivation (65, 66). Analysis of BRCA1 protein level revealed that expression of BRCA1 remains low at G0 and G1 phases (56, 67), but increases from G1/S- phase checkpoint and maintained throughout S, G2, and M phase (68). BRCA1 undergoes hyperphosphorylation during S-phase, whereas dephosphorylated after the M phase (56, 67). DNA damage induces nuclear translocation of BRCA1 and become phosphorylated through DNA damage-activated kinases such as ATM, ATR, and Chk1/Chk2 (69-71). Nuclear translocation of BRCA1 is occurred due to the presence of two NLSs in exon 11 (44). An alternative pathway of BRCA1 nuclear localization is mediated through BARD1 as binding partner via the interaction through RING domain (72) and suggested possible mechanism of nuclear localization of the alternatively spliced variants of BRCA1 with spliced out exon 11 (73). Mechanistically, the N-terminus of BRCA1 also contains two nuclear export sequences (NES) that facilitate CRM1 (chromosome region maintenance protein 1) -mediated export of BRCA1 from the nucleous (74-76). BARD1 directly masks the NES signal of the BRCA1 and utilizes its own NLS for efficient import and nuclear localization of BRCA1. In addition, BRAP2 (BRCA1 binding protein 2) binds BRCA1 NLSs to facilitate cytoplasmic retention by disrupting interaction with nulear import receptor importin-alpha (77, 78).

In cytoplasm, BRCA1 regulates mitotic cell division, cytoskeletal rearrangement, apoptosis, and mitochondrial genome repair (21, 79, 80). The E3 ubiquitin ligase activity of BRCA1/BARD1 has a regulatory role in centrosome duplication and assembly of the mitotic spindle pole (81-83). In addition, BRCA1 has been implicated in the mitotic spindle checkpoint (84) and recently Bordie *et. al.* showed that mutation of the NES, or treatment of cells with leptomycin B, a CRM1 export inhibitor, caused a reduction in BRCA1 transport to the centrosome as well as its overall rate of exchange and retention (75). BRCA1 has also been reported to ubiquitinate another centrosomal protein, nucleophosmin (NPM1)(85) which is important for centrosome duplication (86). In addition, Bcl-2 and AKT1 have been reported to redirect BRCA1 to mitochondria and endoplasmic reticulum (87, 88). Thus, the translocation of BRCA1 between cellular compartments is common and highly related to its function in both normal and cancer cells.

The best-known function of BRCA1 is in DNA repair pathway and multiple, clinically observed, missense mutations arising throughout the entire BRCA1 gene were found to be nonfunctional in assays of DNA double strand break (DSB) repair (89-92). These observations indicate a link of efficient repair of DSB by BRCA1 to its tumor suppression activities. In fact, BRCA1 mutation carriers are relatively hypersensitive to platinum-based therapies (22, 93, 94) and tumor cells expressing high levels of BRCA1 are resistant to both ionizing radiation (IR) and chemotherapeutic agents (95, 96). BRCA1 contains a domain called the serine cluster domain located in exons 11–13 and this region contains several putative phosphorylation sites. ATM, ATR, and checkpoint kinases phosphorylate BRCA1 upon DNA damage (71, 97, 98) and hyperphosphorylated BRCA1 rapidly relocated to the sites of replication to recruit and organize multiple distinct protein complexes that recognize and repair damaged DNA and activate cell cycle checkpoints (4, 91, 92, 99). Serine cluster domains are common in ATM/ATR targets (100) and serine residues 988, 1189, 1387, 1423, 1457, 1524, and 1542 can all be phosphorylated by ATM, ATR, Chk1, or Chk2 (69-71, 92, 101, 102). Mutation of these serine residues have been observed clinically, and may affect localization of BRCA1 to the sites of damaged DNA and subsequent repair function (23). To facilitate DNA repair, BRCA1 recruits the RAD50-MREII-NBS1 complex to sites of DNA DSBs and this interaction requires BRCA1 exon 11 (103). BRCA1 also interact with PALB2, which acts as a scaffold to form a protein complex including BRCA1 and BRCA2 (Breast Cancer Susceptibility Gene 2) that involved in homologous recombination (HR) during DNA repair (104). In addition, BRCA1 is also known to interact with RAD51, another DNA repair protein involved in HR (4). Thus, the BRCA1 association with RAD50, PALB2, and RAD51 strongly suggests a role in both non-homologous end joining (NHEJ) and HR processes of DNA repair. Beside that, both BRCA1 and BARD1 have been detected at cellular mitochondria indicating a possible role of BRCA1 to regulate mitochondrial DNA repair also (105-107).

BRCA1 has been linked to cellular growth and proliferation and knockdown of BRCA1 accelerated the growth of normal and malignant mammary cells predominantly the breast and ovarian cancer cells (108, 109). In addition, introduction of wild-type BRCA1 into tumor cells inhibited cell proliferation (58). Study by Aprelikova *et. al.* showed that the BRCA1-mediated growth inhibition depends on Rb protein (110), a well-known tumor suppressor that controls growth by regulating progression through the cell cycle (110, 111). Exon 11 of BRCA1 known to interact with Rb and cells with wild-type Rb were sensitive to BRCA1-induced growth arrest (110). The transcription factor c-Myc also known to interact with BRCA1 (via exon 11) and the BRCA1 has two c-Myc binding sites (112, 113). The transformation activity of c-Myc/Ras and the transcriptional activity of Myc is inhibited by BRCA1 expression (113) indicating that suppression of the oncogenic activities of c-Myc may be associated with the tumor suppressor activity of BRCA1. BRCA1 also reported to interact with RHAMM (receptor for hyaluronan-mediated mobility), which regulate epithelial apicobasal polarization and ubiquitinated via the E3 ubiquitin ligase activity of BRCA1/BARD1 complex (114). RHAMM is linked to cancer metastasis and thus, indicated a yet to explore mechanism of BRCA1 tumor suppression activity specifically for sporadic breast cancer (115).

Since BRCA1 interacts with multiple transcription factors such as p53, ER-α, c-Myc, STAT1, CtIP, and ZBRK1 as well as with RNA polymerase II, it is obvious that BRCA1 plays a critical role in transcriptional regulation (113, 116-122). In fact, cancer-associated point mutations of BRCA1 disrupt its interaction with RNA

polymerase II indicating BRCA1 is a part of core transcriptional machinery (123). Recent studies indicated that BRCA1 autoregulates its own transription to maintain genome integrity in response to genotoxic stress (124, 125). BRCA1 also interacts with the RbAp46 (retinoblastoma suppressor associated protein), which is a component of the histone modifying and remodeling complexes (126) and BRCA1 is also found as a component of the human SWI/SNF-related chromatin-remodeling complex (127). Importantly, the BRCA1 interaction with different transcription factors occurred through the regions distributed both in N and C terminus. The transciption factors p53 and STAT1 interact through the N-terminal animo acid sequences 240 – 800, whereas, CtIP is known to interact with amino acids 1602-1863 in the C-terminus of BRCA1 (116, 118-120). Thus, it is clear that BRCA1 also functions as a transcriptional coactivator or corepressor representig a critical component of its overall role in tumor suppression, however, little is known about its target genes except for MAD2, ANG1, and BRCA1 itself (84, 124, 128, 129).

5. THE BRCA2

The BRCA2 gene was identified by Wooster *et. al.* in 1994 (130) and the gene contains 27 exons with eight internally repeated sequence called BRC motif, which considered to be the major domain to interact with RAD51 (131-134). Although there is some similarity between the exon structures of BRCA1 and BRCA2, there is no significant sequence homology between them (135). Nuclear localization signals in human BRCA2 have been identified (136) and colocalize with BRCA1 in subnuclear foci in somatic cells (135). Like BRCA1, BRCA2 is also important as a transcriptional co-regulator (8). BRCA2 is also known to interact with SMAD3 to form a complex that co-activate Smad3-dependent transcriptional activation of plasminogen activator inhibitor-1 (PAI-1) and cooperates with histone acetyltransferases in androgen receptor-mediated transcription (137, 138).

The structure of the BRCA2 C-terminal domain has been solved and implicated to have DNA binding property (139). A large number of tumor derived mutations were observed in the BRCA2 C-terminal domain (65). The BRCA2, like BRCA1, colocalizes with RAD51 during meiosis on chromosome axes (135). The association of BRCA2 with RAD51 indicated the involvement of BRCA2 in the repair of DNA damage by HR pathway (65). Consistently, cells from BRCA2 mutant mice showed inefficient and aberrant chromosomal structures (3, 140). All these findings suggested tumor suppressor role of BRCA2 via the maintenance of genome stability.

6. BRCA MUTATIONS AND CANCER RISK

Mutations in the BRCA1 and BRCA2 genes are notably associated with inherited breast and ovarian cancers and nearly 30-40% of sporadic malignancies are associated with loss of BRCA1 expression (141, 142). The lifetime risk of breast cancer in BRCA1- and BRCA2-mutation carriers is 45–80% (143, 144) and for ovarian cancer, the lifetime risk is 45–60% and 11–35% for BRCA1- and BRCA2 -mutation carriers, respectively(143-145). BRCA mutation carriers are also at risk for other malignancies such as fallopian tube cancer, melanoma, endometrial, pancreatic, prostate, and colorectal cancer (11, 146-150). Compared to nonhereditary breast cancer patients, nearly 80% of BRCA1- mutation carriers are diagnosed with breast cancer prior to menopause (146, 151-153). In fact, for women with BRCA mutations, the risk of both breast and ovarian cancer development increased about 10-15 % in each decade after the age of 40 years (143). Additionally, BRCA1-mutation carriers develop ovarian cancer at a younger age than BRCA2-mutation carriers and sporadic cases (154).

In breast cancer, BRCA1 mutation predominantly observed in basal-like subtype (155-157) and nearly 70% of BRCA1-mutated breast cancers express basal cytokeratins and lack expression of estrogen receptor (ER) (156). BRCA2- associated breast tumors are predominantly ER positive and p53 negative whereas BRCA1-associated breast tumors are more often triple negative i.e. ER, progesterone receptor (PR), and epidermal growth factor 2 (HER2) negative and p53 positive (146, 158-160). Moreover, sporadic breast cancers with loss of BRCA1 expression also have a strong tendency to be of the basal-like phenotype (108, 161). On the other hand, tumors with functional BRCA1 are predominantly luminal type and associated with more indolent clinical courses, responsiveness to endocrine therapies, and improved survival (73, 162). Taken together, these findings suggest that loss of BRCA1 expression and/or function has a causal role in the development of the basal-like phenotype (14). A mechanistic understanding of how BRCA1 dysfunction contributes to the generation and pathogenesis of basal-like breast cancers is currently lacking but important to understand the molecular events that initiate basal-like malignancies (14).

7. TARGETED THERAPIES FOR BRCA-DEFICIENT CANCER

There is no single management strategy in reducing the risk of breast and ovarian cancer for BRCA mutation carriers and these issues have been reviewed recently in details by Bougie and Weberpals (163). The decision-making processes such as surveillance, risk-reducing surgery, and/or chemoprevention are very complex and differ from patient to patient due to their age, family history of female breast, male breast, ovarian, prostate, and pancreatic cancer in the risk stratification model. Thus clinical managements of patients with BRCA mutation carriers are highly challenging. In fact, there are no standard guidelines for recommending BRCA1 or BRCA2 mutation testing. Although surveillance strategies like mammography and breast magnetic imaging is helpful for breast cancer but there is no effective screening strategy has been developed for ovarian cancer (163, 164). Treatment options often depend on risk-reducing surgical procedures such as bilateral mastectomy and salpingo-oophorectomy (165). Chemopreventive strategies have been considered to reduce the risk of breast cancer only for

high-risk women (i.e. women aged 35 years and older) and involve the use of selective estrogen receptor modulators such as Tamoxifen, Raloxifene and aromatase inhibitors, whereas oral contraceptives have been used for chemoprevention of hereditary ovarian cancer (163-166).

Although the risk reducing surgical procedures are significantly protective for BRCA mutation carriers (167), targeted therapies for hereditary breast and ovarian cancer are highly desirable. In this regard, DNA defects, which are often necessary to develop tumourigenesis, also provide a therapeutically exploitable strategy when the cells become cancerous. Since BRCA1 deficiency leads to the deregulation of DNA repair pathways, tumor cells with BRCA1 deficiency are more vulnerable to DNA damaging agents such as platinum-based chemotherapeutics like Cisplatin and its derivative, Carboplatin (163, 165, 168). Inhibitors of Poly (ADP-ribose) polymerase (PARP), an enzyme critical in base excision repair and involved in the repair of single-stranded DNA breaks (SSBs), are also novel therapeutic option for the treatment of breast and ovarian cancers with defective BRCA function (169-171). Since BRCA1/2-mutated or deficient malignancies have intrinsic defects in HR-mediated DNA damage repair, ancillary DNA repair pathways dependent on PARP become critical (172). Cells with nonfunctional or deficient BRCA1/2 leads to genomic instability when treated with PARP inhibitors (163). Clinical trials using PARP inhibitors, such as Olaparib and BSI-201, are currently ongoing and show clinical efficacy in the treatment of BRCA1/2 -associated breast, ovarian, and prostate cancers, as well as sporadic basal-like breast cancers (173-176).

Recently, Stecklein *et. al.* showed that loss of heat-shock protein 90 (HSP90) function abolishes BRCA1-dependent DSB repair and that BRCA1-deficient cells are hypersensitive to 17-AAG (Tanespimycin) due to impaired G2/M checkpoint activation (177). The HSP90 protein regulate BRCA1 ubiquitination and proteasomal degradation and thus, inhibition of HSP90 resulted in compromised repair of ionizing radiation- and platinum-induced DNA damage. The HSP90 inhibition approach provides an opportunity to enhance sensitivity in refractory and/or resistant malignancies where BRCA1 is function is normal or even overexpressed (177).

8. NEW CHALLENGES

Loss of DNA repair mechanism promotes genetic instability and leads to tumorigenesis. However, defective DNA repair mechanisms alternatively provide cellular hypersensitivity to DNA damaging chemotherapeutic agents such as Cisplatin and Carboplatin as well as PARP inhibitors (154, 168, 178-180). Recently, it has been recognized that restoration of BRCA1/2 functions due to secondary mutations of BRCA1/2 in BRCA1/2-mutated tumors can occur and leads to resistance to Cisplatin and PARP inhibitors (181-184) (recently reviewed extensively by Dhillon and colleagues) (185). Several studies have suggested multiple mechanisms such as altered expression of drug transporters and cellular oxidative state (186), microhomology-mediated end-joining (187), and translesion synthesis (188) which can lead to this unexpected drug resistance. However, the detailed mechanism for acquisition of secondary BRCA1/2 mutations is still not clear. Thus, future studies are needed to explain this phenomenon and approaches may include the identification of a subset of BRCA1/2-expressing cells that may exist in the tumor prior to chemotherapy, mechanistic knowledge to understand the role of DNA repair in chemoresistance and generation of secondary BRCA1/2 mutations, as well as longer clinical studies to correlate secondary BRCA1/2 mutations with clinical outcomes. In addition, future research is also required to instigate drug sensitivity for the drug-resistant cancers with secondary BRCA1/2 mutations. In this regard, chemotherapeutic agents/PARP inhibitors in combination with proteasome inhibitors, CDK inhibitors, and HSP90 inhibitors provide an attractive approach since they are reported to inhibit RAD51 foci formation (189, 190) and successfully applied in Glioblastoma multiforme (GBM) (191). Moreover, the study by Stecklein *et. al.* also raise the possibility to treat drug resistant secondary BRCA1/2-mutated tumors by targeting HSP90 (177). Identification of novel strategies to prevent or overcome drug resistance in secondary BRCA1/2-mutated breast and ovarian cancer is a new challenge and success will improve patient survival immensely.

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