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Role of BRCA1 in Breast Cancer Metastasis

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Abstract

The role of BRCA1 in breast cancer metastasis is a less explored area that might have importance in increased aggressiveness of BRCA1 defective triple negative cancers. The possible influence of BRCA1 on apico basal polarity and ezrin, radixin and moesin (ERM) proteins are discussed in this review as a reason for cell metastasis. This might help in developing antimetastatic drugs that could help for better prognosis in BRCA1 defective breast cancers.

Keywords: BRCA1, ezrin, radixin, moesin, apicobasal polarity

1. Introduction

Breast cancer is the second largest cancer and the fifth major cause of death. There are many factors involved in breast cancer development and metastasis. Among the tumor suppressors that play a critical role in hereditary breast cancers, BRCA1 mutations are highly frequent, whereas loss of BRCA1 expression by promoter hyper methylation or allelic loss has frequently been noted in sporadic breast cancer [1, 2]. Mutation or loss of the functional BRCA1 expression in breast cancer is usually accompanied with TP53 mutations, ER/PR/HER2 negativity, and loss of ATM/CHK2, which, in turn, leads to a highly aggressive basal phenotype, which clearly possesses a therapeutic challenge [2, 3]. Specific malignant changes caused by BRCA1 mutations in the breast and the ovary remain a mystery till date.

2. BRCA1

BRCA1 is a multifunctional protein that is well known to be involved in multiple cellular processes by shuttling between nucleus and cytoplasm. Structurally, BRCA1 has three domains: (a) the RING domain; (b) the serine cluster domain (SCD); and (c) the BRCT domain. Potentially, four mutations are considered to be deleterious (5382insC, 5396+1G>A, 185delAG, and 2288delT) in the BRCA1 gene among the many mutations reported [4, 5]. The tumor suppressor function of BRCA1 is mainly attributed to the RING and BRCT domains of BRCA1, as women with hereditary breast cancer mainly possess mutations in one of the two domains.

Functionally, the RING domain of BRCA1 along with BARD1 possesses E3-ligase-mediated tumor suppressor activity, and any mutation in this domain would severely affect the heterodimerization and the stability of BRCA1 and BARD1, which, in turn, affects the tumor suppressor activity of BRCA1 [5]. The C-terminal BRCT domain is a phospho-protein binding domain known to interact with several partners and is reported to be critical for the localization of BRCA1 at the DNA damage site [6]. Furthermore, the tumor suppressor activity of the BRCT domain of BRCA1 has been reported using mouse models, although the exact mechanism is still debatable [7]. In short, functionally, BRCA1 is known to regulate multiple cellular processes such as DNA double strand repair, check point regulation, ubiquitination, and transcriptional regulation.

The RING domain, discovered as Really Interesting New Gene, spans from exon 2–7 of 24 exons of the BRCA1 gene. The RING domain of BRCA1 with a ring finger consists of seven cysteine and one histidine residues critically coordinate with Zn atoms, which actually stabilizes the RING structure [8, 9]. BARD1, a protein that is structurally homologous to the BRCA1 RING domain, interacts with the RING domain of BRCA1 and is critically important for the ubiquitin ligase activity, and it is reported to ubiquitinate several target proteins for degradation such as ER alpha, progesterone receptor, histone H2A, and CtIP [10-12]. It also modulates the nuclear import and export of BRCA1 [13, 14].

The core domain, which spans exons 11–13, is the largest domain of BRCA1 and is often called the serine cluster domain (SCD). It has two nuclear localization signals (NLSs), which control the nuclear import of BRCA1. Numerous proteins are reported to interact with this domain, and some of the notable binding partners are the retinoblastoma protein (RB), cMyc, PALB2, Rad50, and Rad51. The interaction between BRCA1 and RB is critically important for the BRCA1-mediated cell cycle regulation, as mutation in the binding region of BRCA1 failed to arrest the cell cycle progression [15]. PALB2, RAD50, and RAD51 interactions with BRCA1 are crucial for the BRCA1-mediated DNA repair. RAD50 and RAD51 mainly play a role in both homologous recombination (HR) and nonhomologous end joining (NHEJ) mediated by BRCA1, whereas PALB2 plays a role mainly in HR [16-18]. Mutations in any of the binding portions of this molecule severely affect the DNA repair capacity of BRCA1. Furthermore, BRCA1 is known to regulate the transcriptional activity of few oncogenic proteins reported till date. The well-studied example is that BRCA1 is known to downregulate the oncogenic transcriptional factor cMyc [19]. In addition, the serine clusters in this domain are reported to be phosphorylated by several kinases, including ATM/ATR during DNA damage, and this

phosphorylation is mandatory for the assembly of BRCA1 to the DNA damage site, and again, any mutation affecting the phosphorylation of BRCA1 could severely affect the DNA repair ability [20].

Finally, the BRCA1 C terminal domain (BRCT) is reported to modulate its interactions with phosphoproteins that are critically important for the tumor suppressor activity of BRCA1 in particular nuclear localization and assembly at the DNA damage sites [21]. Several mutations have been reported in the BRCA1 gene portion that interfere with several cellular processes, and sometimes, they can be highly lethal [22]. Interestingly some of the mutations in the BRCA1 gene portion (for example, C61G RING mutation) are hypomorphic, i.e., it does not lose its complete DNA repair ability but still maintains the residual unknown DNA repair mechanism [5, 23]. From the therapeutic point of view, BRCA1 mutations with residual tumor suppressor activity clearly pose a complexity in the treatment compared with BRCA1-proficient or BRCA1-deficient breast/ovarian tumors.

3. BRCA1 defect and pathological condition

Clinically, BRCA1 is reported to be functional in different organs of the body apart from its cardinal role in the breast and the ovary. Recently, BRCA1 has been reported to play an immense role in brain development [24]. In addition, its role as a regulator of metabolic function in skeletal muscles has been reported [25]. It also plays a huge role in Alzheimer disease, although the exact role is still unclear [26]. Recently, BRCA1 has been reported to act as a transcriptional cofactor during HIV infection [27]; again, the evidence is still preliminary. The function of BRCA1 as a tumor suppressor is crucial in the breast and ovarian tissue, and mutations in BRCA1 usually predispose to breast or ovarian cancer as discussed earlier. Apart from that, BRCA1 mutations are also reported to develop cancers in the prostate, fallopian tube, peritoneal, and pancreas, the specificity being unclear [28, 29]. Acute myeloid leukemia and the Fanconi anemia subtype has been reported if BRCA1 mutations are inherited from both parents [30-32]. Although BRCA1 has been studied for 20 years, its multiple facets are still undiscovered to a larger extent, which makes BRCA1 the molecule of attraction in current research. The role of BRCA1 in metastasis is one of the novel functions evidenced very recently.

4. BRCA1 in migration/invasion

Although there are no evidencing reports regarding the role of BRCA1 in ovarian cancer metastasis, its role in breast cancer metastasis is clearly an emerging subject with a few reports. The RING and BRCT domain of BRCA1 has been reported to be critically important for controlling the cancer cell migration and motility in the breast or the ovary [7, 33], although the complete mechanism is ill understood. In addition, restoration of full-length BRCA1 in 3450delCAAG mutated breast cancer cells is reported to block the cell invasion and motility induced by that particular mutation [34]. Furthermore, BRCA1 has been implicated to play a

key role in epithelial to mesenchymal transition, again the exact mechanism being unclear [35]. In this review, we discuss the possible mechanistic role of BRCA1 in the migration and invasion of BRCA1-defective breast tumors, which is less explored till date. Currently, there are two evident mechanisms through which BRCA1 could control the migration and invasion of breast cancers that will have immense potential in the futuristic breast cancer treatments. First, the mechanism deals with the role of BRCA1 in maintaining the apicobasal polarity. The second mechanism deals with the role of BRCA1 in regulating the ERM complex that maintain the cytoskeleton.

4.1. BRCA1 and apicobasal polarity

Apicobasal polarity is a unique polarity feature of the epithelial cells that refers to the apical membrane on one side and the basolateral membrane on other side, separated by tight junctions. It is a critical feature of cytoskeletal reorganization in the epithelium of the breast and plays a key role in maintaining the integrity of cell-cell connections by maintaining the adherent junctions through microtubule organization [36]. In addition, it is known to be regulated by several signaling pathways such as WNT signaling, TGF β , and integrin-mediated signaling. Furthermore, it is critically important for the differentiation of the breast epithelium, whereas the loss of epithelial polarity is often considered a hallmark of EMT and cancer [37-39]. Frequently, the loss of expression or mislocalization of the molecules of polarity complex such as SCRIB, Crumbs, and PAR has been implicated in the carcinogenesis of the breast [40-42]. Recently, BRCA1 has been reported to play a key role in the cytoskeletal organization and polarity of the breast tissue [43]. Probably, the loss of polarity in BRCA1-mutated breast tumors results in the loss of cell-cell adhesion and, hence, the movement of cancer cells from the primary to the distant site.

Mechanistically, BRCA1 regulates the polarity and, hence, the differentiation of breast cancer cells by regulating the expression of Hyaluronan-Mediated Motility Receptor (HMMR), a low-penetrance breast cancer susceptibility gene product that is usually over expressed in BRCA1-related tumors and results in poor prognosis [43-45]. The early report comes from a linkage association study where the genetic variation at chromosome 5q33-34, which is actually the gene location of HMMR, is clearly associated with the risk of breast cancer among BRCA1 mutation carriers [46]. Furthermore, it was confirmed by a pilot study conducted in Spain and Italy, where HMMR rs299290 variation among BRCA1 mutation carriers clearly posed a risk of breast cancer [47]. In addition, BRCA1-related breast cancers, which are generally ER negative but not ER positive, are associated with the HMMR genetic variation. Further knockdown of BRCA1 has clearly impaired the polarization by modulating the cytoskeletal components and its organization. For instance, the cytoskeletal molecule vimentin is increased, and CCD49f is decreased upon BRCA1 knockdown. Maxwell et al. (2011) have shown that BRCA1, through the non-centrosome-dependent assembly of microtubules, maintains the polarity of the breast epithelium and the loss of BRCA1 clearly impair the cytoskeletal reorganization, as observed by increased levels of intermediate filament proteins such as vimentin. Furthermore, BRCA1 is reported to maintain the polarization of breast epithelium by directing the proteasome-mediated degradation of the BRCA1 target, HMMR [47]. Sup-

porting evidence shows that proteasome inhibition and BRCA1 depletion clearly induced the expression of HMMR, which might be the probable reason why an overexpression of HMMR and polarity loss is frequently observed in BRCA1-related breast cancer than BRCA1-unrelated breast cancer [47]. Further accumulation of microtubule-associated factors TUBG1 by HMMR at the centromere in BRCA1-mutated breast tumors was reported to have impaired the polarity and hence induced the basal phenotype [43, 48]. Overexpression of TUBG1 and HMMR has clearly impaired the polarization, even in the presence of BRCA1, suggesting that the upregulation of microtubule-associated factors together with the depletion or mutation of BRCA1 and proteasome inhibition is the prime event in the loss of polarity in BRCA1-related breast tumors. Further overexpression of Aurora kinase A (AURKA) is reported to regulate the HMMR-mediated polarity loss, and HMMR is shown to negatively regulate AURKA. The depletion of AURKA is also known to reduce the abundance of HMMR, and the abundance is restored to the normal level in AURKA- and BRCA1-depleted conditions [43]. Clearly, a strict balance exists between BRCA1, HMMR, and AURKA, and probably, the polarity is completely dependent on the interactions between these molecules.

PAR is a polarity complex of par3, par6, and aPKC known to regulate cell plasticity by localizing at the tight junction [14]. Par6 is critically regulated by TGF β signaling, and its misregulation leads to the highly aggressive breast tumorigenesis. Further correlation of the par6 expression and BRCA1 mutation has recently been reported. Although no direct regulation has been established between par6 and BRCA1, par6 has been shown to be over expressed in BRCA1-mutated breast tumors, which, in turn, have been linked with the high expression of basal markers such as cytokeratin 5/14 and vimentin. Alternatively, a positive association was reported between the activation of PAR6 pathway and the expression of basal cytokeratins in BRCA1-mutated breast tumors [40, 49, 50].

Starita et al. (2004) have shown that BRCA1 inhibits the expression of gamma tubulin by direct ubiquitination and is reported to maintain the centrosome number, and probably, the mutation in BRCA1 has readily increased the tubulin expression and polymerization and, hence, might induce the metastasis of breast cancer cells.

It clearly shows that BRCA1 sustains the polarity of breast cancer cells by maintaining a tight regulation with centrosome pathway components and the loss of BRCA1 in BRCA1-mutated breast tumors, leading to impaired polarization, which, in turn, results in the basal-like phenotype of breast cancer cells. Furthermore, the loss of polarity induces the EMT process [51-53], which might promote the migration and invasion of BRCA1-related breast cancer cells. Here comes the question of how the cancer cell migrates in a condition where BRCA1 is a wild type. Probably, the epigenetic silencing of BRCA1 as reported in many sporadic breast tumors might prevail in such situations, which needs future experimentations.

4.2. BRCA1 and ERM complex

Ezrin, radixin, and moesin, together known as ERM, are three functionally homologous adapter proteins consisting of an N-terminal FERM domain and a C-terminal ERM associated the F-actin-binding domain (C-ERMAD) that is linked to the N-terminal FERM domain through the intermediate alpha helical region. Activation of ERM has been reported as an

important process in the functioning of ERM. ERM remains in the closed conformation until it is activated by the phosphorylation of threonine residues in ezrin, moesin, and radixin [54]. Activated ERM helps in linking the actin cytoskeleton to the plasma membrane through the FERM and F-actin-binding domain [55]. Further activated ERM is reported to interact with transmembrane proteins such as receptor kinases, CD43, and CD44 [56]. Functionally, ERM has been critically implicated in the normal physiological as well as in the cancer conditions. In particular, ERM is known to be involved in three key events: (a) epithelial morphogenesis; (b) migration; and (c) adhesion. Changes in the above-mentioned events are observed during cancer, and it is a clear indication of cancer. Basically, polarity is maintained by ERM in normal physiological conditions and the overexpression of ERM during cancerous conditions leads to a more mesenchymal nature of the cells, and hence, it promotes the event of metastasis by probably interacting with EGFR, CD44, and HGFR [57, 58].

Abnormal expression and localization of ERM has been reported in different types of cancer, and it is clearly known to regulate the cellular signaling and the cytoskeleton during cancer progression, which, in turn, affects the migration and motility behavior of cancer cells. The ERM complex is known to be directly or indirectly phosphorylated by many kinases, which, in turn, activate many signaling pathways involved in cell adhesion, migration, morphology, and proliferation during tumorigenesis [58, 59]. Further overexpression of ERM molecules together or individually was reported to be a clear indication of the EMT process [60, 61]. All the above-mentioned activities of ERM were also highly pronounced in breast cancer [62-64]. In addition, moesin was associated with poor relapse-free survival in breast cancer patients. Although the role of ERM in breast cancer progression was well studied over the years, its relation with BRCA1 during metastasis was ill understood, with only a few recent reports [33]. ERM has been reported to be associated with the ER-negative basal phenotype, and the expression of ERM was also reported to be high in BRCA1-related basal breast tumors compared with BRCA1-unrelated or sporadic breast tumors [65], which, in turn, could contribute to the migration and invasion of cancer cells. Recently, its relation with BRCA1 during migration has been revealed in breast cancer cell lines. Although ERM acts through multiple pathways to promote cancer cell migration and invasion, the presence or absence of BRCA1 was found to be highly significant in ERM-mediated cell motility and migration of breast cancer cells [33]. As previously discussed, the tumor suppressor activity of BRCA1 mainly lies in the BRCT domain, as the mutation of BRCA1 leading to the expression of truncated protein is frequently associated with breast and ovarian cancers [7]. Interestingly, BRCA1 was found to localize at the leading edges and focal adhesion sites of the plasma membrane and reported to control the breast cancer cell spreading and cell motility [33]. Furthermore, the BRCT domain of wild-type BRCA1 was found to co-localize with F-actin, ezrin, moesin, and radixin in the plasma membrane of breast cancer cells and hence controls the breast cancer cell motility in an unknown manner. In addition, a detailed study on this will give an idea on the exact localization of BRCA1 in the plasma membrane and its contributions to inhibit metastasis. Further stable expression of the BRCT coding domain of BRCA1 in breast cancer cells was found to co-localize with ERM and F-actin along with wild-type BRCA1. The BRCT coding domain acts as a dominant negative factor by gradually displacing the endogenous wild-type BRCA1 at leading edges and focal adhesion sites, thus promoting the motility and migratory capacity of breast cancer cells. Probably, BRCA1, by interacting through its BRCT domain, might reduce the ERM protein levels by ubiquitinating it through the E3

ubiquitin ligase activity and hence reduce the motility of breast cancer cells. Alternatively, mutation in the BRCA1 gene at the BRCT domain fails to reduce the levels of ERM at the leading edges, and hence, the motility behavior of breast cancer cells was increased. In addition, this might be one of the reasons why ERM is highly overexpressed in BRCA1-related basal breast tumors than BRCA1-unrelated tumors [65]. It was also reported that not only the BRCT domain but also the E3 ubiquitin ligase activity of BRCA1 are required for complete tumor suppressor function [33], further supporting the above-mentioned speculation, although it was contradictory to previous reports. This will have immense potential in tumor metastasis in BRCA1-defective cancers which the researchers have overlooked. Further studies are warranted to elucidate the exact signaling pathways and the biological consequences associated with ERM in BRCA1-related and BRCA1-unrelated breast tumors.

5. Screening and diagnosis of BRCA1 mutated breast and ovarian cancers

The major annoying fact about BRCA1/2 mutation is that the inheritance of BRCA1/2 mutation increases the risk for breast cancer by about 20–25% [66, 67]. Women who inherit BRCA1 mutation have 55–65% risk of getting breast cancer [68, 69]. In addition, BRCA1 mutations are quite frequent among a particular ethnic population; e.g. Ashkenazi Jews have a high prevalence of BRCA1 mutation than any other population. Particularly, 2288delT and 5382insC mutation in the gene portion of BRCA1 is highly prevalent in Ashkenazi Jews, with a frequency of 1.1% and 0.1–0.15%, respectively [22, 70]. High prevalence has also been reported among the Dutch and Norwegian populations. In addition, the prevalence highly varies within the population, e.g., the US population based on their different ethnic origin [22, 71, 72]. Early clinical breast examination is the best possible method of diagnosing and treating breast tumors [73]. There are many screening tools in the current scenario that particularly assess the family history and its probable association with BRCA1 mutation [74]. However, the screening is mainly recommended for those who have a family history of breast/ovarian cancers [74]. The other specific tissue where inherited BRCA1 mutations usually predispose cancer is the ovary. Estimated data show that women who inherit BRCA1 mutations have 39% of developing ovarian cancer [68, 69]. Women with Ashkenazi Jewish heritage or familial history of breast cancer have increased risk of three to six times than the general public, and women with BRCA1 mutations have more than six times greater risk than the general population to develop ovarian cancer. Screening is usually done by analyzing serum markers such as CA-125 and/or transvaginal ultrasound, and in the case of BRCA1-related ovarian cancer, the screening starts early at the age of 30.

6. Management and therapy of BRCA1 mutated cancers

Surprisingly, a survival advantage for BRCA1 mutation carriers is growing now, although it is still under controversy. An improvement in the survival rate was observed in BRCA1 mutation carriers of the Ashkenazi ethnicity upon platinum-based chemotherapy compared

with BRCA1 non-mutated patients [75]. In addition, many studies from different parts of the world have substantiated the survival advantage among BRCA1 mutation carriers of ovarian origin, although the exact reason is not yet clear [76-78]. However, there are reports which indicates in the case of breast cancer, BRCA1 mutation does not pose any survival advantage; instead, it poses a clear challenge to chemotherapy. In the treatment point of view, the hormone therapy usually fails as BRCA1-mutated breast and ovarian cancer tends to be triple negative in general. The commonly used drugs are either insensitive or have developed resistance in BRCA1-mutated conditions. The only promising drug that is effective in treating BRCA1-mutated breast and ovarian cancer is the PARP inhibitor. The well-studied PARP inhibitor, Olaparib, has been found to be effective in treating BRCA1-mutated breast, ovarian, pancreatic, and prostate cancer. The loss of DNA repair by homologous recombination in BRCA1-mutated conditions activates the alternate method of single-strand DNA repair by poly(ADP-ribose)polymerase [79-81]. The rescue of DNA repair by PARP clearly imposes a chemotherapeutic challenge, and the inhibition of PARP during this condition has improved the benefit rate by 63% [82, 83]. Although it is not completely evaluated as a drug for treating BRCA-related cancers, significant clinical activity has been demonstrated in BRCA1-mutated breast and ovarian cancer during phase trials. There was suspicion that the PARP inhibitor alone or in combination could be an effective drug alternative in treating BRCA1-mutated breast and ovarian cancer. However, recent information has shown that the PARP inhibitor may not be clinically successful as drug resistance against the PARP inhibitor is also observed. As of now, we do not have an effective treatment for BRCA1-related cancers. Designing drugs considering BRCA1 interaction with metastasis-related proteins would be an effective strategy to treat BRCA1-related cancers.

7. Conclusions

It is very clear that BRCA1 is a multifunctional protein that exerts its function from the nucleus to the cytoplasm to the plasma membrane. BRCA1, by controlling apicobasal polarity and by interacting with ERM proteins, is supposed to be involved in cancer cell metastasis. If the link between BRCA1 and migration/invasion is completely unraveled, then we could revolutionize the treatment modalities for controlling metastasis in BRCA1-defective breast tumors.

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