

Synergism between BRCA1 Mutation and Impaired Estrogen Signaling in Oxidative Stress Modulation Makes Estrogen Responsive Tissues (Breast) More Susceptible to Develop Cancer

Aarifa Nazmeen and Smarajit Maiti*

Department of Biochemistry, Cell and Molecular Therapeutics Lab, Oriental Institute of Science and Technology, Midnapore, India

Abstract

Specific inherited mutations in BRCA1 increases the risk of female breast and ovarian cancers. BRCA1 critically maintains genome stability and cell cycle progression. BRCA1 is a well-known tumor suppressor gene; germline mutations in this gene confer increased susceptibility to developing breast and ovarian cancer. Though breast cancer associated with BRCA1 mutations were considered sporadic for mostly being Era(-). Significant numbers of Era(+) BRCA1 mutated breast cancer patients were also discovered. There are two questions prevailing with BRCA1 breast cancers. Why BRCA1 related patients have higher risk for cancer development mainly in estrogen responsive tissues such as breast and ovary. And the second is, the therapeutic approach for Era(+) BRCA1 breast cancers may not be same as Era(-) BRCA1 cancers. Recently BRCA1 in context with oxidative stress is been widely studied. The association of BRCA1 and cancers in estrogen responsive tissues may be explained by BRCA1, estrogen and ER cooperation mediated by oxidative stress.

Keywords: Oxidative stress; Oncogene; Cancer cells; Chemotherapeutics; Glycolysis

Introduction

BRCA1 loss encourages oxidative stress and impairs antioxidant status

BRCA1-mutation carrying breast tumor cells are more sensitive to oxidative stress than cells expressing normal BRCA1 [1,2]. BRCA1 is a known tumor suppressor gene and is allotted to DNA repair and cell cycle progression. Beyond the well-known functions, BRCA1 seemed specifically regulating the Tri-Carboxylic acid (TCA) cycle. Conversion of succinate to fumarate was promoted in SUM1315-BRCA1 cells by the up-regulation Succinate Dehydrogenase Complex (SDHC). This reaction results in ATP production and is essential to the electron transport chain. BRCA1 can markedly increase the cellular ATP levels. Now Succinate may accumulate in BRCA1-mutated cells as a result of low succinate dehydrogenase (SDH) level. This succinate can exit the mitochondria and activate Hypoxia Inducing Factor-1 α (HIF-1 α) [3]. Succinate inhibits HIF-1 α prolyl hydroxylases in the cytosol, leading to stabilization and activation of HIF-1 α [4]. Ultimately letting cells live under the control of HYPOXIA. HIF-1 α transcriptionally regulates nearly all the genes involved in glycolysis [5,6]. Normally, BRCA1 induces the expression of antioxidant genes such as glutathione-S-transferase conferring resistance to oxidative stress [7]. Normal BRCA1 expression promoted antioxidant signaling via inducing transcriptionally active Nuclear receptor factor-2 (Nrf2). One study reports an interaction between BRCA1 and Nrf2 which is responsible for degrading KEAP1 and enhancing Nrf2 stabilization. KEAP1-mediates ubiquitination of Nrf2 leading to Nrf2 degradation [8]. Expressing BRCA1 decreased Reactive Oxygen Species (ROS) levels and enhanced the survival of BRCA1- deficient mouse Mammary Epithelial Cells (MECs) [9]. Mutations or loss in BRCA1 impaired Nrf2 mediated activation of antioxidant genes in MEC. This process results in accumulation of intracellular ROS, leading to senescence and DNA damage reducing the repopulation potential and survival of MEC. Human BRCA1-mutant breast cancer cells exhibited impaired Nrf2 signaling, including low levels of the Nrf2-regulated antioxidants and elevated ROS [9]. Eventually, loss of Nrf2 along with activated

HIF-1 α may increase the sensitivity of these cells to oxidative stress induced by platinum-based chemotherapy. Though BRCA1 mutations are more engrained with ER-negativity, a study reports that out of 117 of BRCA1 mutated patients, 68 Era(-) and 49 were Era(+) [10]. The same therapeutic approach may not be working for the Era(+) BRCA1 mutation carrying breast cancers (Figure 1).

Literature Review

Role of estrogen, estrogen receptor α in BRCA1 mutated breast cancers

The question is why estrogen responsive tissues such as breast and ovary are more susceptible to cancers when BRCA1 is mutated. It is established that BRCA1 gene is an Estrogen-Estrogen Receptor (E-ER) responsive gene. However, contradiction lies in whether BRCA1 expression is directly regulated by ER binding to BRCA1 promoter. In MCF-7 cells BRCA1 expression appears after twenty four hours of estrogen treatment. Probably before BRCA1 expression, several other mediator genes are expressed. So, BRCA1 is not the direct or the first gene targeted by estrogen as described by Kininis et al. [11]. Epigenetically modified BRCA1 promoter appears to be strongly correlated with the absence of ER or progesterone receptor expression [12]. But in large number of instances, the response of cells towards estrogen is shown to be regulated by BRCA1 [13]. Premenopausal oophorectomy or treatment with tamoxifen [14,15] in BRCA1 mutation

*Corresponding author: Smarajit Maiti, Department of Biochemistry, Cell and Molecular Therapeutics Lab, Oriental Institute of Science and Technology, Midnapore-721101, India, Tel: +91-9474504269; E-mail: maitism@rediffmail.com

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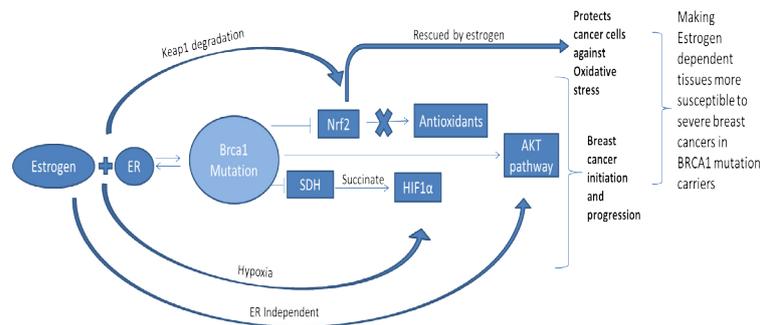


Figure 1: A cooperative connection between estrogen, estrogen receptor α and BRCA1 to regulate oxidative stress related factors like HIF1 α and Nrf2 to initiate breast cancer and promote its survival.

carriers noticeably reduces the risk of later carcinoma. Additionally, BRCA1 function is linked to ER expression and knockdown of BRCA1 leads to loss of ER expression [16]. A strong connection exists between menopausal status and the development of ER α (+) breast cancers in BRCA1 mutation carriers. In this regard, the role of BRCA1 in regulating HIF-1 α and Nrf2 seems to be valuable in oxidative stress-mediated cellular transformation. Estrogen is a well-known endogenous carcinogen with strong properties of cellular transformation also *via* oxidative stress. This leads to explore estrogens effect on HIF-1 α and Nrf2 with the hypothesis that combined effect of Estrogen (gain of function) and BRCA1 (loss of function) *via* oxidative stress makes estrogen dependent tissues more prone to cancer especially under BRCA1 mutation state [17]. Interestingly, Estrogen treatment partially rescued Nrf2 levels in BRCA1 deficient cells, suggesting that estrogen-dependent Nrf2 stabilization may counteract oxidative stress and promote the cancer. HIF-1 α is associated with aggressive phenotype of breast cancer like large tumor size, high grade, high proliferation, and lymph node metastasis. ER α -positivity and increased HIF1 α are also associated [18]. Hence, estrogen contributes in elevating *via* hypoxia or stabilizing HIF-1 α which is also the case in BRCA1 mutation carriers. This creates an imbalance between OS inducing and inhibiting factors in estrogen dependent tissues in BRCA1 mutation carriers. Estrogen rescuing Nrf2 function may be an important approach of cancer cells to protect against OS during disease severity. At severe disease condition the cancer cells remain extremely metabolically active generating significant amount of ROS. Excess ROS may also induce apoptotic pathways leading to cancer cell death. Estrogen stimulated Akt activation, in an estrogen receptor independent manner [19]. It suggests the possibility of ER independent estrogen function even in ER α (-) BRCA1 mutation carriers.

AKT can induce glycolysis *via* multiple mechanisms, including expression and activation of hexokinases (AKT can phosphorylate HK2) and activation of PFK enzymes. BRCA1 mutation seems to be correlated with high AKT phosphorylation levels [20]. This suggests that a mutation in BRCA1 could eradicate AKT inhibition and cause glycolysis to be upregulated enabling tumour cell transformation. If both estrogen and BRCA1 works in favour of high metabolism (AKT pathway), will provide sufficient energy along with oxidative stress mediated DNA damages which cannot be abrogated in BRCA1 mutated condition. In addition, E2 mediates up-regulation of cell proliferating factors (growth factors). Such a cellular environment is most likely to undergo cancerous transformation. BRCA1 has also been addressed as a molecular marker in lung cancer [21]. BRCA1 pathways function at multiple sites throughout the body, not just in breast or ovary. Known

interactions and relationships among BRCA-related pathways strongly support the idea that their inactivation provides growth or survival advantages for a variety of cancers. The risks for cancers in other parts of the body may be smaller than those for breast or ovarian cancer.

Correlation of BRCA1 with known oncogene in estrogen responsive tissue

Several oncogenes such as Myc, CCND1 (Cyclin D1) and ERBB2 (HER2/neu) plays an early vital role in sporadic breast cancer. Inactivation of BRCA1/2 by mutation is infrequent, as mutational inactivation requires both gene copies to be effectively mutated or deleted. However, hypermethylation of the BRCA1 promoter or binding of BRCA2 by EMSY (oncogene) are non-mutational functional suppression of BRCA1 [22]. Amplification of Myc oncogene contributes to tumor progression in BRCA1-associated breast cancers both in known deleterious germ-line BRCA1 mutations and sporadic cases which included one third of hypermethylation factor of the BRCA1 gene promoter [23]. The c-Myc can activate transcription of the human Telomerase Reverse Transcriptase gene (hTERT). BRCA1 and NMyC-interacting protein (Nmi) modulates c-Myc-induced hTERT promoter activity. Nmi functioned as an adaptor molecule to recruit c-Myc to a complex containing Nmi, c-Myc, BRCA1. Although, Nmi or BRCA1 alone had no effect on c-Myc induced hTERT promoter activity. BRCA1 together with Nmi significantly inhibited this c-Myc induced hTERT promoter activity (approximately 75% inhibition). Whereas, mutated forms of BRCA1 which occurs in familial breast cancers failed to suppress c-Myc-induced hTERT promoter activity. These results demonstrate a novel pathogenic mechanism whereby mutations in BRCA1 impair inhibition of c-Myc-induced hTERT promoter activity. This condition allows sustained activation of telomerase, a key enzyme in carcinogenesis [24]. EGFR expression was higher in normal tissues of BRCA-mutated patients, and was further increased in cancer tissues; EGFR levels were also significantly elevated in ovarian cancer with promoter hypermethylation-mediated inactivation of BRCA1. BRCA1 knockdown was an effective way to activate EGFR expression in ovarian cancer cells [25]. EGFR expression was prognostically significant among BRCA1 mutated cases [26]. Thus, interpreting a direct or an indirect influence of BRCA1 on EGFR expression in estrogen-dependent tissues like breast and ovary needs further explorations. Interestingly, IGF-1 was also found to be negatively regulated by BRCA1 in human breast cancer cells, at the transcriptional level. Knockdown of BRCA1 in MCF7 cells induces the expression of IGF-1 mRNA *via* estrogen receptor α (ER α). BRCA1 and ER α bind to the endogenous IGF-1 promoter region containing

an estrogen responsive element-like site. This suggests that a defect in BRCA1 turns IGF-1/PI3K/AKT signalling on. These signalling are significantly important in cell survival and proliferation [27]. BRCA1 seems to be an anti-growth promoting factor by inhibiting oncogenic expressions and whose deficiency lead to tumorigenic attributions. SOX2, an embryonic transcription factor remains gained in sporadic basal-like and BRCA1 germline mutated breast tumours. Sox2 showed a statistically significant inverse association with ER and PR and direct association with CK5/6, EGFR and vimentin [28]. SOX2 was strongly detected in the nucleus of breast carcinoma cells compared to weak or no SOX2 staining in normal, nontumorigenic mammary epithelial tissue. Further, knockdown of SOX2 expression in SKOV3 or HO8910 ovarian cancer spheroid cells decreased spheroid formation, cell proliferation, cell migration, tumorigenicity, the expression of stemness-related genes and epithelial to mesenchymal transition-related genes, whereas over-expression of SOX2 in SKOV3 or HO8910 ovarian cancer cells showed the opposite effects [29]. BRCA1 promoter hypermethylation was associated with low expression of pRb, and high/Intense p16, and the similar effects were noticed in BRCA1 mutated tumors (TNBC). Findings also demonstrate that epigenetic inactivation of the BRCA1 gene associates with RB/p16 dysfunction and promote TNBCs [30]. These studies clearly pictures out that in normal physiological condition BRCA1 is an important regulator of cell proliferation. BRCA1 keeps a grip on oncogenes and certain growth factors along with stemness related genes. This clearly evidences that mutated or hypermethylated BRCA1 may allow growth factors and oncogenes to be enhanced and suppress the expression of tumor suppressor genes.

Discussion and Conclusion

BRCA1 mutations make cells more prone to oxidative stress *via* HIF-1 α activation and Nrf2 inactivation. This along with estrogen and impaired BRCA1 tumor suppressive function increases chances of cellular transformation to cancer. Though, BRCA1 and E2-ER functions are interdependent, and normally Era(-) breast cancers are associated with BRCA1 mutations. A marked number of patients carrying BRCA1 are Era(+) which may make it vulnerable to treatment *via* the same therapeutic approach (oxidative stress inducing chemotherapeutics). The loss of Nrf-2 and gain of HIF-1 α functions could be the major factors that makes Era(-) BRCA1 mutations susceptible to such OS induced during chemotherapeutic interventions. On the other hand, if it's a Era(+) BRCA1 mutation the loss of Nrf2 is compensated by estrogen, thus becoming resistance to OS and associated chemotherapies. Expression of the HIF-1 α gene or a hypoxia metagene signature is associated with a poor outcome to endocrine treatment in Era(+) breast cancer. HIF-1 α was able to confer endocrine therapy resistance to Era(+) breast cancer cells. Unfortunately, a combined therapy including OS inducing chemotherapy plus endocrine therapy may be less worth in treating Era(+) BRCA1 mutation carriers. Despite being Era(+) or Era(-), BRCA1 mutation carriers are initially dependent on estrogen for developing breast cancers. Since, BRCA1 are tumor suppressor gene and not oncogenes. This suggest that there always exists some other initiator of cancer which is most likely to be estrogen in case of BRCA1 mutation carriers and oxidative-stress events seem to be the crosstalk pathway between estrogen and BRCA1.

Conflict of Interest

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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