

The Key Aspects of BRCA1 Interactome for Novel Breast Cancer Therapies

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Received: November 30, 2021

Published: January 12, 2022

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Abstract

In Feb 2021, World Health Organization (WHO) announced that breast cancer overtook lung cancer as the #1 cancer in the world. With over 2 million new cases and over 600,000 deaths in 2020, breast cancer is the most common cancer of women worldwide. About 10% of the breast cancer is familial (or hereditary), caused by mutations of Breast Cancer Susceptibility gene 1, commonly known as BRCA1. Located in chromosome 17, this gene has multiple functions, interactions, pathways and direct and indirect binding partners, contributing to the various hall marks of cancer, including cell cycle and other. It interacts with several genes and proteins and these interactions are studied using String diagrams. The goal is to obtain better insights of the various key aspects of these interactions and utilize them towards novel breast cancer therapies for familial breast cancer treatments.

Keywords: BRCA1; Breast Cancer; Familial; String Diagram; Gene Ontology; Pathways

Introduction

Cancer is a disease of somatic, chromosomal and gene mutations [1-10]. Inherited mutations in the BRCA1 (and BRCA2) genes are associated with hereditary breast and ovarian cancers, which is a disorder, marked by an increased lifetime risk of breast and ovarian cancers in women. Several other cancers have been associated with this, including pancreatic and prostate cancers, as well as male breast cancer [1-10]. The BRCA1 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, and chicken [9]. There are 293 organisms that have orthologs with human gene.

BRCA1 is a key gene in hereditary breast and ovarian cancers. BRCA1 mutation carriers are related to 70 - 80% of lifetime risk of hereditary breast cancer [1], while they are related to 50% of lifetime risk of ovarian cancer. They are also involved in the prostate cancer of Ashkenazi Jewish, with increased risk than normal people. Hereditary breast cancer accounts for only about 5 - 10% of all breast cancer [10], yet they have more propensity for tumor formation, and hence the occurrence of the other breast. Discovered in 1994 [11-13], BRCA1 encodes a 190 kD nuclear phospho-

protein [9], that plays a major role in maintaining genomic stability. It also acts as a tumor suppressor. Located in chromosome 17q21 [11-13], it interacts closely with its counterpart BRCA2 gene as well as a large number of a variety of genes, such as sensor, mediator, and effector positions [1]. The BRCA1 gene contains 22 exons spanning about 110kb of DNA, with 1863 amino acids [10]. The encoded protein combining with other tumor suppressors, DNA damage sensors, and signal transducers forms a large multi-subunit protein complex, known as BRCA1-associated genome surveillance complex (BASC) [13,14]. Table 1 shows the cumulative risk by age due to BRCA1 predisposing mutations [15].

Age (years)	Cumulative Risk (%)
30	3.2
40	19.1
50	50.8
60	54.2
70	85

Table 1: The cumulative risk by age due to BRCA1 predisposing mutations [15].

Table 2 shows the various BRCA1 functions and the domains, along with the various direct and indirect binding partners [1]. Literature [9,10,13] shows similar interactions with a number of other genes, which are studied in this research.

Function	Domain	Direct Binding	Indirect Binding
Recruitment to DNA damage sites	BRCT	Abraxas	RAP80
DNA end resection	BRCT and RING?	CtIP	MRN complex
G2/M checkpoint	BRCT BRCT SCD (S1423 and S1524 Phosphorylation)	Abraxas CtIP	RAP80 MRN complex
		ATM	MRN Complex
S-Phase checkpoint	SCD (S1387 phosphorylation) BRCT	ATM BRIP1	MRN complex TOPBP1
Repair during DNA replication	BRCT	BRIP1	TOPBP1
Homologous recombination	Coiled coil and S988 phosphorylation	PALB2	BRCA2

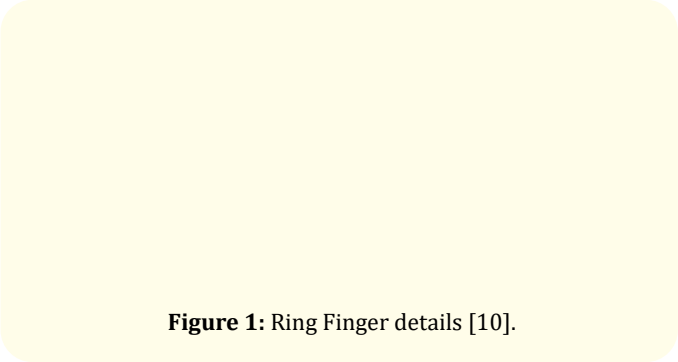
Table 2: BRCA1 Functions and its domains and direct and indirect binding partners [1].

Note: BRCT-breast cancer carboxyl-terminal domain.

Figure 1 shows the Really Interesting New Gene (RING) Finger details [10]. There are currently 1600 mutations in a truncated BRCA1 protein.

The majority of deleterious BRCA1 mutations are large deletions, rearrangements, splice-site, frameshift, or nonsense changes that result in a truncated protein [16]. However, a handful of proven deleterious BRCA1 mutations are missense changes that occur in key conserved protein domains such as the Ring finger domain and the breast cancer C-terminal domains. Figure 1 shows the Ring Finger details [10].

BRCA1 is a pleiotropic DNA damage response protein that operates in both check point activation and DNA repair [10]. BRCA1’s role in tumorigenesis is related to a number of cellular processes. They include double strand DNA repair, transcriptional regulation



of DNA repair-associated genes, and other. BRCA1 binds to BRCA2, TP53, and RAD51, in addition to other proteins associated with the cell cycle and DNA damage response genes. BRCA1 is involved in double-strand breaks (DSB) repair and play an important role in maintaining genomic stability [17,18].

A partial list of various human triple negative breast cancer (TNBC) cell lines, along with the ethnicity of the patients from whom they were derived that have BRCA1, and their molecular classifications are shown in table 3 [19].

Cell line	Ethnicity	Molecular classification
HCC 38	Caucasian	Basal B
HCC 1143	Caucasian	Basal A
HCC 1937	Caucasian	Basal A
HCC 2157	Black	Basal A
MDA-MB-157	Black	Basal B
MDA-MB-231	Caucasian	Basal B
MDA-MB-468	Black	Basal A

Table 3: A partial list of Human TNBC cell lines with BRCA1 [19].

BRCA1, a caretaker gene [20], is a tumor suppressor gene implicated in the predisposition to early onset breast and ovarian cancer [1-10]. Loss of the tumor suppressor BRCA1 function results in major chromosomal instability. As a tumor suppressor, BRCA1 exerts a pleiotropic effect, playing a role in the maintenance of genomic integrity. Several functions have also been ascribed to BRCA1, including double strand DNA break repair, participating in genome surveillance, transcription-coupled DNA repair, transcriptional regulation, chromatin remodeling, and ubiquitin ligation and cell cycle checkpoint arrests. In cells, loss of BRCA1 function leads to spontaneous chromosome breakage and sensitivity to DNA damage [1-10,21].

Although BRCA1 familial or hereditary breast cancer is only about 5 to 10% of all breast cancers, the incidence rate is higher for those family members [1-10]. It is of practical interest to explore this gene in detail, as it is involved in various other cancers also, such as prostate cancer and pancreatic cancer. It interacts with a large number of genes and proteins and these interactions are studies in this research.

Methodology

Google (MedLine, PubMed, and Google Scholar and images) was used to find various publications (1990 to 2021) that reported about BRCA1 and its various interacting genes, using terms, such as BRCA1, Notch. string-db.org [22] was used for generating all the string diarams and to study their interactions, the GO enrichment study, and the pathways.

BRCA-1 Interactions

With ring finger genes

Figure 2 shows the string interaction diagram [22] of BRCA1 with other Ring Finger genes, BRCA2, TP53, RAD51, and ATM, as shown in figure 1 [10]. It can be seen that there are more interactions (number of lines) between all of these genes, indicating the potency of BRCA1 to affect various cellular functions, along with these genes. Table 4 shows the top 5 GO enrichment terms for various Biological Processes (BPs), Molecular Functions (MFs), and Cellular Components (CCs). The various KEGG pathways include Homologous Recombination (HR), platinum drug resistance, p53 signaling pathway, breast cancer, cell cycle, apoptosis, and other.

Figure 2: Interactions of BRCA1 with Ring Finger Genes

Biological Process
Mitotic recombination-dependent replication fork processing
Establishment of protein localization to telomere
DNA damage response
Signal transduction involved in G2 DNA damage checkpoint
Telomere maintenance via recombination
Molecular Function
Identical protein binding
Cellular Component
Lateral element
Site of double strand break
Microtubule organizing center
Microtubule cytoskeleton
Nuclear chromosome

Table 4: Top 5 GO Enrichment for the Ring Finger genes string diagram.

With 23 other genes in [9]

Figure 3 shows the string interaction diagram of BRCA1 with other 23 genes, as given in [9]. It can be seen that there are more interactions between BRCA1, BRCA2, and CDK4, compared to MAP3K. This indicates that BRCA1 is a key gene interacting a number of other key genes, related to various cancers.

Figure 3: Interactions of BRCA1 with 23 other genes.

Table 5 shows the top 5 GO enrichment of BPs, MFs, and CCs [22]. The various sub-cellular localizations include Homomeric SMAD protein complex, Cyclin A1-CDK2 complex, Cyclin D1-CDk4,

BRCA1-C complex, and Cyclin A2-CDK2 complex. The salient KEGG pathways include cell cycle, Notch signaling pathway, and other. Figure 4 shows the Notch signaling pathway [23].

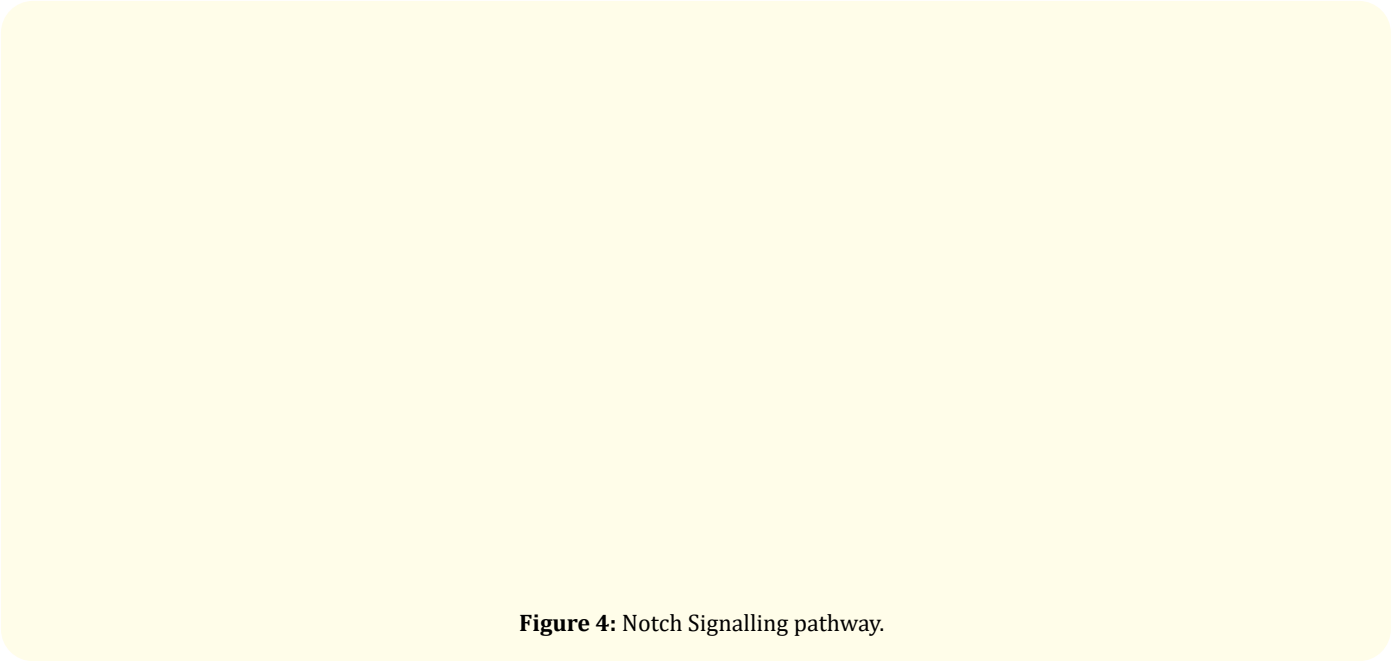


Figure 4: Notch Signalling pathway.

Biological Process
Fungiform papilla formation
N-terminal peptidyl-lysine acetylation
SMAD protein complex assembly
Hair follicle placode formation
Establishment of protein localization to telomere
Molecular Function
Primary miRNA binding
NAD-dependent histone deacetylase activity (H3-K14 specific)
I-SMAD binding
Co-SMAD binding
R-SMAD binding
Cellular Component
Cyclin A1-CDK2 complex
Heteromeric SMAD protein complex
Cyclin A2-CDK2 complex
Activin responsive factor complex
SMAD protein complex

Table 5: Top 5 GO Enrichment for the 23 gene string diagram.

The Notch signaling pathway is a highly conserved pathway in most animals, from sea urchins to humans, and plays a key role in controlling the differentiation of breast epithelial cells during normal development [24]. The Notch signaling is dysregulated in various cancers, including triple negative breast cancers, which contributes to oncogenesis, renewal of stem cells, angiogenesis, and chemoresistance [25].

Buckley, *et al.* [26] reported that BRCA1 is involved in the activation of Notch signaling with implications for anti-endocrine treatment of breast cancer. They demonstrated that inhibition of Notch signaling decreased sensitivity of Tamoxifen, the anti-estrogen drug. Their findings suggest that BRCA1 transcriptional upregulation of Notch signaling is a key event in the normal differentiation process in breast tissue.

Notch pathway is involved in cell manipulation, differentiation, and apoptosis. Notch family is implicated in human breast cancer in different combinations [24]. The misregulated Notch ligand-receptor interaction in breast cancer could cause tumor growth initiation, progression, and maintenance by inducing aberrant tumor-

igenesis, while determining vascular integrity. It is reported that there could be a direct involvement of the Notch pathway in normal mammary gland growth and breast carcinogenesis. Breast cancer clinical outcome was accompanied by high expression of Notch-1, -3, -4 pathways and Notch-2 was identified as a tumor suppressor in many studies. There were multiple studies indicating association of high levels of Notch signaling with different subtypes of breast cancer. Notch family members involved in different types of breast cancers could be utilized to provide novel therapies by considering the potential therapeutic use of monoclonal antibodies inhibiting the notch pathway.

With genes in the pathway of Genome protection

Figure 5 shows the interactions of BRCA1 with a number of other genes discussed in [1], while figure 6 shows the partial pathway of BRCA1 [21], that illustrates the same. The functions of these and other interacting proteins are given in table 6 [27].

Figure 5: Interaction of BRCA1 with other genes in a common pathway of genome protection.

Figure 6: Partial BRCA1 Pathway [21].

BRCA1 interacting protein or complex	Function of interacting protein
RAD50	DSB repair
RAD51	DSB repair
BRCA2	DSB repair
BASC (ATM, BLM, MSH2, MSH6, MLH1, RCF	Mismatch pair
ATP	Mismatch pair
H2AX	Signals DNA damage
P53	Transcription factor; tumor suppressor
c-Myc	Transcription factor; oncogene
ATF	Transcription factor
STAT1	Signal transducer; transcriptional activation
E2F	Transcription factor; cell cycle regulator
Estrogen receptor	Ligand responsive transcription factor
Androgen receptor	Ligand responsive transcription factor
CtIP	Binds CtBP; transcriptional; co-repressor
Centrosome (p53, pRB, Nm23)	Chromosome segregation
BRAP2	Cytoplasmic retention
BARD1	Ubiquitin ligase
PALB2	DSB repair

Table 6: List of various BRCA1 interacting proteins or complexes and their functions [27].

This set of genes also have the same KEGG pathways as in figure 2. Table 7 gives the top 5 GO terms of BPs, MFs, and CCs.

Biological Process
Positive regulation of telomerase catalytic core complex
Establishment of protein-containing complex
Establishment of RNA localization to telomere
Telomeric 3 overhang formation
Establishment of protein localization to telomere
Molecular Function
Damaged DNA binding
Protein c-terminus binding
Identical protein binding
DNA binding
Protein binding
Cellular Component
Mre11 complex
BRCA1-A complex
Male germ cell nucleus
Lateral element
Site of double-strand-break

Table 7: Top 5 GO Enrichment for the above HSP string diagram.

Detection of DNA double-strand breaks involves sensor proteins of the MRN complex [8,13], composed of MRE11A, RAD50 and NBN (NBS1). Binding of the MRN complex to DNA DSBs activates ATM-dependent DNA damage signaling cascade, by promoting KAT5 (Tip60) mediated acetylation of ATM and subsequent ATM autophosphorylation. Activated ATM triggers and coordinates recruitment of repair proteins to DNA DSBs [3-10].

BRCA1 colocalizes in nuclear foci with RAD51, thereby implicating B1 in homologous recombination (HR) during meiosis and repair of DSBs [28]. These DSBs arise following exposure to ionizing radiation or free radicals and following DNA damage during replication at the site of replication fork. It is believed that DSBs are the main cause of genomic instability and chromosomal rearrangements that are hallmarks of cancer.

BRCA1-ATF is directly involved with homologous recombination (HR)-mediated repair of DNA double strand breaks [1]. It binds to DSBs through its association with the abraxas-RAP80 macro-com-

plex. BRCA1 is involved in processing DSBs through its interactions with CtIP and the MRN complex. BRCA1 is also required for RAD51 recruitment to the sites of DNA damage through its interactions with PALB2 and BRCA2.

BRCA1 interacts directly with estrogen receptor- α (ER- α), and Androgen receptor (AR); it represses ER- α and stimulates AR activity [12]. This and other findings correlate that BRCA1 mutations enhance the risk for several ER-positive cancers, including breast, uterine, and cervical and AR-related cancers, such as prostate cancer. In addition to stimulating tumor suppressor and growth inhibitor pathways, BRCA1 can inhibit oncogene activity. It binds to c-Myc oncogene, which is amplified or overexpressed in many cancers and inhibit its transcriptional and transformation activities.

All these interactions illustrate the different functions of the BRCA1 protein and their significance regarding developing different treatment options for patients who are BRCA1 mutant carriers or sporadic breast cancer patients with loss of BRCA1 expression in their tumors [3]. Similar results were also obtained with the BASC genes.

With genes in BASC super complex

BRCA1-associated genome surveillance complex (BASC) is a large complex of group of proteins that is associated with BRCA1 [13,14]. These include tumor suppressor and DNA damage repair proteins, such as MSH2, MSH6, and other. A string diagram of their interactions is shown in figure 7. The various KEGG pathways include non-homologous end joining, homologous recombination, mismatch pair, platinum drug resistance, and cellular senescence. Figure 8 shows the Homologous Recombination pathway [29]. Table 8 shows the top 5 GO enrichment terms.

The BASC super complex also contains PCNA, which is needed for DNA synthesis [13]. They all function in DNA metabolism and repair. Several of these also participate in cell cycle checkpoint functions to halt cell cycle progression when there is a damaged DNA.

HR is a critical pathway for DNA repair [28]. DSBs can be repaired using HR pathway. HR utilizes an undamaged sister chromatid as a repair template [30] to restore any damaged/lost sequence information at the DSB site. Since it requires a sister template to repair, HR pathways is only available during S/G2 phases of the cell cycle.

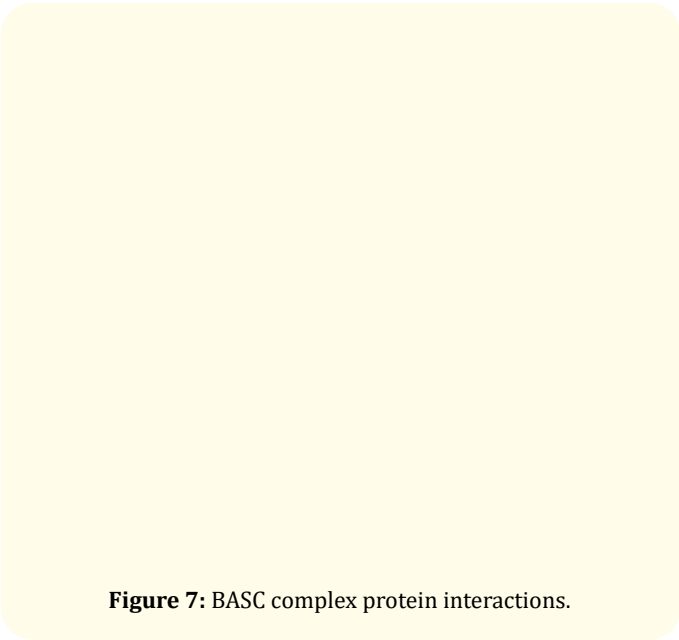


Figure 7: BASC complex protein interactions.

Biological Process
Telomeric 3overhang formation
Regulation of mitotic recombination
Positive regulation of isotype switching to iga isotypes
Negative regulation of telomere capping

Positive regulation of helicase activity
Molecular Function
Guanine/thymine mis pair binding
Mismatched DNA binding
G-quadruplex DNA binding
Damaged DNA binding
DNA secondary structure binding
Cellular Component
Mre11 complex
MutSalpha complex
Mismatch repair complex
Lateral element
DNA repair complex
Subcellular localization compartments
MutSbeta complex
MutSalpha complex
MutLalpha complex
Mre11 complex
MutS complex

Table 8: Top 5 GO Enrichment for the BASC Proteins string diagram.

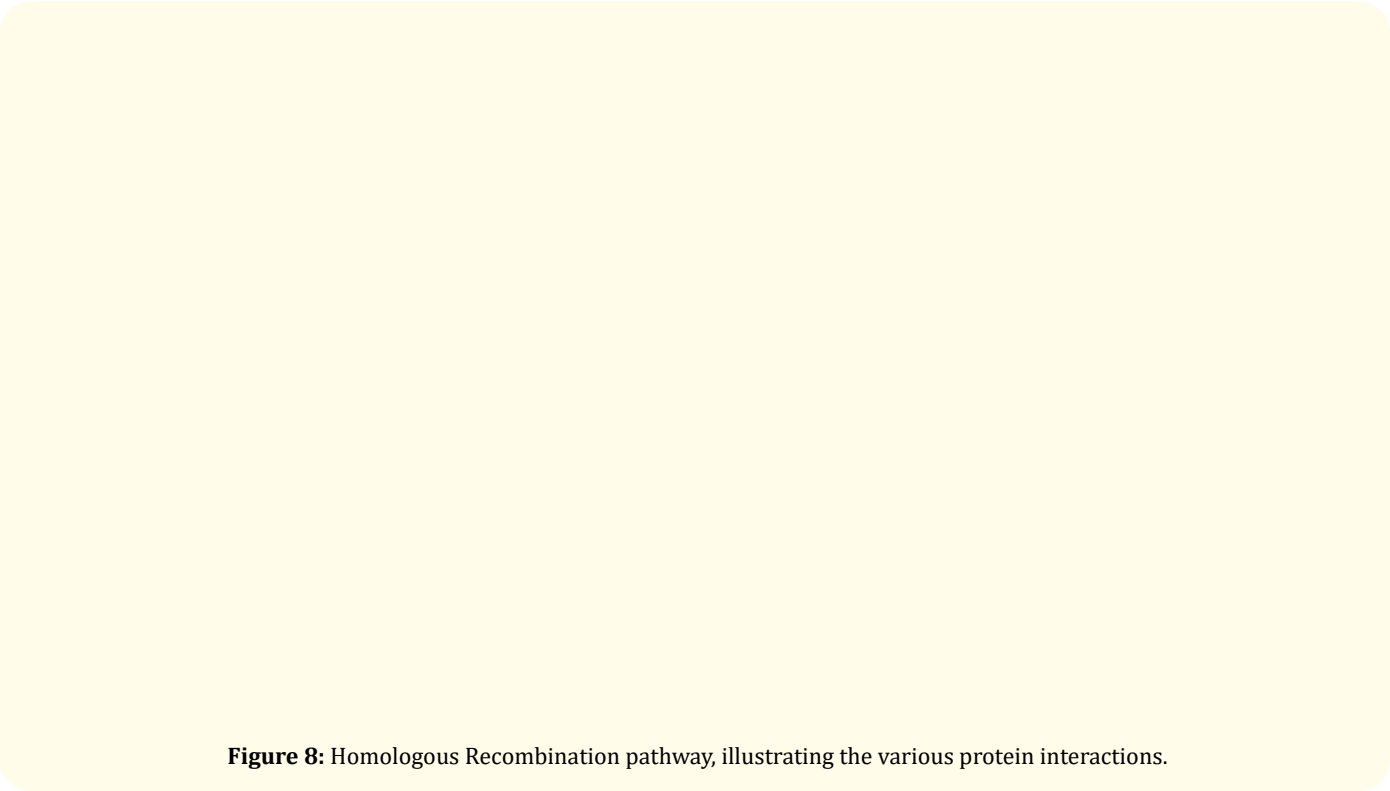


Figure 8: Homologous Recombination pathway, illustrating the various protein interactions.

PARP inhibitors for BRCA1 breast cancer

In addition to surgery, and chemotherapy using Taxanes and platinum-based compounds, use of Poly (ADP-ribose) polymerase (PARP) inhibitors have received major attention as therapeutic agents for the treatment of breast cancers with or without mutations in BRCA1, due to its DNA repair mechanisms [10,28]. Thus, it can be effectively used for TNBC, with possible BRCA1 mutation as, BRCA1 mutation could cause TNBC, with basal-like subset of breast cancers [2,31], which lack the conventional receptors that many chemo drugs attack. Veliparib, a PARP agent is used as a 2nd line of treatment along with platinum compounds. The efficacy of Veliparib, as an anti-cancer drug was studied in our research [32], using MDA-MB-231, human triple negative breast cancer cells. A concentration of 1 to 500 μ M was used for this purpose. Figure 9 shows the viability results at various doses.

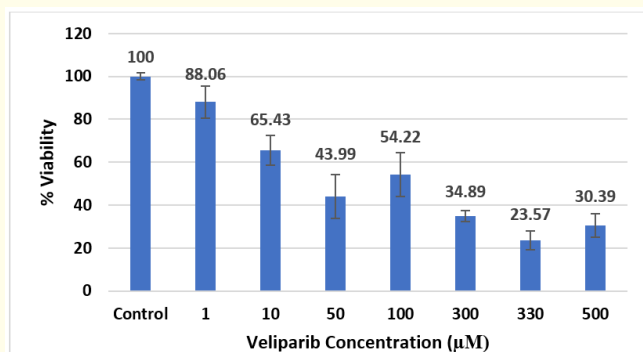


Figure 9: Viability of MDA-MB-231 cells at various Veliparib doses.

With control normalized to 100% viability, the viabilities range from 88% for 1 μ M to 65.43% at 10 μ M. The viability was reduced to 43.99% at 50 μ M. However, it increased to 54.22% at 100 μ M and reduced to 34.89 for 300 μ M. The lowest viability of 23.57% was obtained for 330 μ M. An increase in viability is observed with increase in dosage of Veliparib with 30.39% viability for 500 μ M. This increase in viability could be attributed to the saturation of the drug, which correlates with the results obtained in another study by Jung-Min Lee., *et al.* [33], where they report the 11% of cell kill at 50 μ M concentration of Veliparib [33].

Conclusion

Conserved from chimpanzee, Rhesus monkey, dog, cow, mouse, rat, and chicken, and discovered in 1994, BRCA1, a caretaker gene, is very important and versatile molecule that links, binds, and in-

teracts with a number of other proteins related to DNA damage. These were illustrated by the numerous interactions with a number of other proteins, using various string diagrams, showing its strong, intermediate, and weak interactions with these.

Based on its associations and physical interactions with other proteins, BRCA1 has been implicated in a wide array of cellular functions, including cell cycle regulation, DNA damage response, maintenance of genomic stability, transcription regulation, replication, and recombination as well as higher chromatin hierarchical control. Identification of BRCA1 has led to major changes in the treatment of women with inherited breast and ovarian cancers. Nevertheless, it is unclear which loss of function contributes to cancer initiation and progression.

The Notch signaling pathway, with major participation and playing multiple roles in breast cancer progression could be a critical part of BRCA1 therapy, inhibiting which could provide innovative therapeutic options.

PARP inhibitors are other potential candidates to treat BRCA-1, triple negative and other breast cancers. More research is needed to utilize the great discovery of the BRCA1, for the benefit of breast cancer patients.

Acknowledgements

None.

Conflict of Interest

None.

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