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"In-Silico Evaluation Of BRCA1 Domain 1JM7 Binding Interactions With RAD51 (1N0W) And P53 (1YCR)''

[1]Gorle Keerthi, [2]D.Udaya Kumar,[3] Srikakulapu Bhargavi,[4] Pragada Nynakshitha, [5]Gudapati Ratna Siri.

[1-,5] Department of Human Genetics, College of Science and Technology, Andhra University, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Background: BRCA1 serves as a critical tumor suppressor gene that upholds genomic integrity via its central function in homologous recombination repair (HRR). Loss of BRCA1 function disrupts its associations with vital DNA repair partners, notably RAD51 and p53. The 1JM7 domain of BRCA1 plays a key role in mediating these regulatory protein-protein interactions, which are vital for an effective DNA damage response.

Objectives: This investigation employs computational methods to assess the binding interactions between the BRCA1 1JM7 domain and RAD51 (PDB: 1N0W) as well as p53 (PDB: 1YCR). The approach combines sequence evaluation, protein-protein interaction (PPI) network analysis, structural optimization, and molecular docking to clarify the contributions of these complexes to DNA repair mechanisms and tumor suppression.

Methods: BRCA1 sequence information and domain details were sourced from UniProt, while PPI networks were mapped via STRING to identify functional linkages. The BRCA1 1JM7 domain underwent structural modeling and refinement in Discovery Studio. Docking simulations with RAD51 and p53 utilized Hex 8.0, with subsequent evaluation of shape-electrostatic correlations, binding affinities, interface residues, and docking scores to gauge interaction stability and relevance.

Results: Findings from docking showed strong electrostatic fit between BRCA1 1JM7 and RAD51, yielding a docking energy of -572.51 kcal/mol—a value signaling a potent, biologically significant bond aligned with RAD51-mediated HRR. The BRCA1-p53 interface displayed moderate affinity (-369.10 kcal/mol), consistent with p53's known modulatory effects rather than primary HRR involvement. Examination of structures pinpointed conserved hotspots matching known experimental binding sites.

Conclusion: This comprehensive computational analysis underscores the robust binding capacity of BRCA1 1JM7 to RAD51 alongside its tempered association with p53, yielding novel structural-mechanistic perspectives on BRCA1's contributions to DNA repair and oncogenesis prevention. Such insights advance comprehension of BRCA1-related cancer susceptibility and lay groundwork for analyzing mutation effects and designing targeted interventions.

Keywords: BRCA1 1JM7 domain, RAD51, p53, protein-protein docking, Hex, STRING, Discovery Studio, DNA repair, homologous recombination.

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Interactions With RAD51 (1N0W) and p53 (1YCR)''

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[1]Gorle Keerthi, [2]D.Udaya Kumar,[3] Srikakulapu Bhargavi,[4] Pragada Nynakshitha, [5]Gudapati Ratna Siri,[6] T. Mahankali.

[1-,6] Department of Human Genetics, College of Science and Technology, Andhra University, Visakhapatnam, Andhra Pradesh, India.

Background and Introduction

Breast Cancer Type 1 Susceptibility Protein (BRCA1) ranks among the most thoroughly investigated tumor suppressor proteins, thanks to its vital function in upholding genomic stability and averting hereditary cancers. Researchers first pinpointed germline mutations in BRCA1 as a primary driver of hereditary breast and ovarian cancer syndromes, which dramatically elevate the lifetime risk of early-onset breast and ovarian tumors **(Miki et al., 1994; Chen and Livingston, 1999)**. As a result, BRCA1 carries significant clinical relevance for cancer risk evaluation, genetic counseling, and tailoring personalized treatments.

On the cellular front, BRCA1 acts as a versatile coordinator of the DNA damage response. It performs an essential function in fixing DNA double-strand breaks (DSBs) via homologous recombination repair (HRR), a precise pathway crucial for safeguarding chromosome structure **(Scully and Livingston, 2000; Roy et al., 2012)**. Beyond repair, BRCA1 drives cell-cycle checkpoint enforcement, especially at G1/S and G2/M phases, to prevent replication of flawed DNA during division **(Huen et al., 2010)**. BRCA1 also supports chromatin restructuring and gene expression control, enabling repair factors to reach sites of DNA damage effectively **(Bunting and West, 2004).** From a structural perspective, BRCA1 forms a large protein with several specialized domains that underpin its wide-ranging roles. Its N-terminal RING domain exhibits E3 ubiquitin ligase capability and partners with BARD1 to create a heterodimer vital for DNA repair and cancer prevention **(Brzovic et al., 2001).** A central coiled-coil region enables key protein-protein contacts, particularly with PALB2, which connects BRCA1 to BRCA2 and RAD51 in homologous recombination processes **(Sy et al., 2009).** The C-terminal paired BRCT repeats bind phosphorylated motifs on partner proteins, forming a hub for DNA damage signaling networks and proving indispensable for BRCA1's repair activities **(Huen et al., 2010).**

In addition to these well-characterised domains, BRCA1 contains internal regions whose structures and functions remain incompletely understood. Among these, the **1JM7 region** represents a structurally unresolved internal segment predicted to participate in previously uncharacterized protein–protein interactions. Because BRCA1 acts as a central scaffolding protein coordinating the recruitment and stabilization of multiple DNA repair factors at sites of damage, elucidating interactions mediated by such unresolved regions is of significant biological interest **(Roy et al., 2012)**. Computational structural modelling and protein–protein docking approaches offer powerful tools to explore the functional relevance of these regions, particularly in the context of homologous recombination repair.

Biological Significance of RAD51 in Homologous Recombination

RAD51 stands out as a remarkably well-preserved eukaryotic recombinase and the star player in the homologous recombination repair (HRR) pathway. It mirrors the bacterial RecA protein in function. This enzyme keeps our genome in check by driving the homology search and strand invasion phases needed to mend DNA double-strand breaks (DSBs) **(West, 2003; San Filippo et al., 2008).** HRR stands as a flawless repair system that borrows from an intact sister chromatid as its blueprint, so RAD51 shines brightest during the S and G2 cell-cycle stages.

When DNA damage strikes, RAD51 rushes to resected single-stranded DNA (ssDNA) spots, assembling helical nucleoprotein filaments that kick off strand invasion and swapping. Mediator proteins orchestrate this dance tightly, with BRCA1 stepping in as a key upstream director. BRCA1 smooths the way for RAD51 loading by boosting DNA end resection and rallying the BRCA1–PALB2–BRCA2 squad, which then threads RAD51 onto ssDNA **(Jensen et al., 2010; Roy et al., 2012).** Without a working BRCA1, RAD51 foci barely form, crippling HRR entirely.

When the BRCA1–RAD51 partnership falters, homologous recombination sputters, piling up unrepaired or botched DNA breaks. This sparks chromosomal glitches, collapsing replication forks, and outright genomic chaos—classic cancer red flags **(Negrini et al., 2010).** That's why messing with RAD51's repair prowess ties directly to tumor formation, especially in BRCA1-lacking breast and ovarian cancers.

Crystal structures peel back the curtain on RAD51's inner workings. The human RAD51 structure (PDB ID: 1N0W) spotlights clear DNA-binding channels, ATP pockets, and clustering surfaces vital for building filaments on ssDNA **(Conway et al., 2004).** These traits position RAD51 perfectly for computer-based docking and protein interaction probes, especially to unpack ties with BRCA1 and fellow HRR teammates.

RAD51 doesn't stop at strand invasion; it pitches in on other genome-saving jobs too. It shores up stalled replication forks against breakdown during stress **(Petermann et al., 2010).** Plus, it teams up with BRCA2, PALB2, DSS1, and RAD51 paralogs to nail filament setup, hold it steady, and wrap up recombination leftovers **(San Filippo et al., 2008).** Sitting at HRR's heart, RAD51 gets fine-tuned via gene expression tweaks, chemical tags post-translation, and partner proteins. The BRCA1–RAD51 link proves make-or-

break for spot-on DNA fixes, and its breakdown fuels hereditary breast cancer plus vulnerability to DNA-blasting drugs and PARP inhibitors **(Lord and Ashworth, 2017).**

p53: The Genome's Guardian

The tumor suppressor p53, from the TP53 gene, earns its **"guardian of the genome"** badge for orchestrating genomic safeguards amid cell stress. Genotoxic hits like radiation, oxidation, or replication hiccups swiftly stabilize and fire up p53, triggering gene programs for cell-cycle halts, repairs, aging-like stasis, or programmed death **(Lane, 1992; Vousden and Prives, 2009).** These moves block damaged DNA from spreading and curb cancer's rise.

p53 mainly works as a transcription factor, latching onto specific DNA stretches through its core binding domain. Captured in PDB ID: 1YCR, this domain oversees a vast gene lineup for DNA damage responses—like **BRCA1, GADD45, CDKN1A (p21),** and **BAX (Cho et al., 1994; Vousden and Prives, 2009).** By tuning BRCA1 transcription, p53 forges a vital bridge between checkpoints and HRR.

Biochemical and cell-based experiments confirm BRCA1–p53 links, but high-res structural snapshots of the duo are scarce. Still, p53's core structure (PDB: 1YCR) sets the stage for docking simulations to map interfaces and mutation fallout **(Cho et al., 1994).** These models illuminate how BRCA1–p53 breakdowns erode suppressor circuits and spark cancer.

Challenges and Role of Computational Docking: Even with heaps of lab work, BRCA1's domain-specific protein chats stay murky, thanks to its bulk, tricky folds, and floppy disordered bits. X-ray crystallography and cryo-EM stumble on such giants **(Dyson and Wright, 2005; Uversky, 2013).** Transient repair complexes often dodge high-res capture.

Enter computational docking: a game-changer for molecular matchmaking. It scans binding poses by favoring energy-wise winners via shape fits, charge matches, and property vibes **(Janin et al., 2003; Vakser, 2014).** Ideal for gap-filling when full structures lag.

Docking dishes out gems like binding energy scores, hotspot IDs, charge/steric harmony checks, stability gauges, and affinity rankings **(ClusPro; Kozakov et al., 2017).** These steer real-world tests and spotlight key ties. For BRCA1 networks, they decode RAD51 or p53 domain handshakes—and how mutations throw wrenches in.

Objectives of the Study

Our central aim here is to reveal how the BRCA1 1JM7 domain shapes structural and functional roles in protein-protein contacts with essential DNA repair and tumor suppressor players, RAD51 and p53, via a unified in-silico strategy. We break this down into these concrete steps:

a)Retrieve and annotate protein sequences.

b)Analyze functional protein-protein interactions.

c) Model and validate the structure of the BRCA1 1JM7 domain.

d) Execute protein-protein docking of the modeled BRCA1 1JM7 domain against RAD51 (PDB: 1N0W) and p53 (PDB: 1YCR) with HEX 8.0.

e) Contrast the docking findings between **BRCA1 1JM7-RAD51** and **BRCA1 1JM7-p53,** focusing on binding strengths, residue contacts, electrostatic matching, and shape compatibility.

Through this head-to-head review, we aim to spot dominant interaction trends and the 1JM7 domain's likely preference for certain partners.

BRCA1: Structural & Functional Snapshot

BRCA1—Breast Cancer Type 1 Susceptibility Protein—acts as a master tumor suppressor, relentlessly guarding genomic stability across multiple fronts. Discovered as a key DNA defense player, it immediately stood out for driving hereditary breast and ovarian cancer risks (**Roy et al., 2012).** Without BRCA1's full power, DNA repair pathways collapse, chromosomes fracture chaotically, and cells barrel toward malignancy.

In the DNA damage response (DDR) network, BRCA1 orchestrates break detection through precise repairs, with laser focus on double-strand breaks (DSBs). It champions homologous recombination repair (HRR)—the cleanest fix that copies from an intact sister strand to rebuild flawlessly. This precision work by BRCA1 blocks error buildup and cancer escape. Its reach goes broader still: managing cell-cycle pauses, reshaping gene access through chromatin, fine-tuning transcription, and greenlighting apoptosis when fixes fail.

This 1863-amino-acid nuclear giant organizes into hallmark domains, each unlocking unique capabilities. Leading off, the N-terminal RING finger drives E3 ubiquitin ligase work and fuses with BARD1 (BRCA1-Associated RING Domain Protein 1) into a vital heterodimer. Their partnership cements BRCA1's structure while sparking ubiquitin chains that steer DDR alerts and cell-cycle flow.

BRCA1's core houses pliable, unstructured regions that network with repair allies, creating assembly platforms. Interaction zones like the 1JM7 domain shine here, forging ties to RAD51 for recombination thrusts and p53 for damage-driven survival calls.

The C-end flaunts dual BRCT (BRCA1 C-Terminal) repeats as phospho-binding magnets for DDR signaling proteins. They direct repair squads to break sites; faults here cripple BRCA1 and amplify cancer vulnerability.

As a nexus in sprawling protein webs, BRCA1 syncs genome protection routes. It pairs with RAD51 to execute HRR strand exchanges and mends, while p53 contacts enforce cycle blocks or cell demise post-injury. Key architecture spans **RING domain (aa 24-64), coiled-coil domain (aa 1364-1437),** and **BRCT tandem repeats (aa 1641-1859),** powering suppression via partner syncs, chemical tweaks, and damage broadcasts.

FIGURE 1. Domain structure of BRCA1

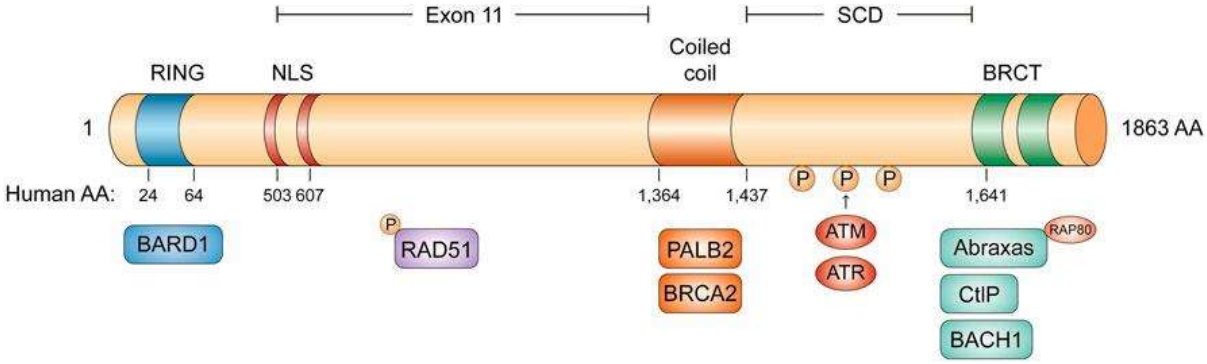

FIGURE 1. RETRIEVED FROM https://doi.org/10.3389/fcell.2022.813457

FIGURE 1. The domain structure of BRCA1. The RING domain in blue, the two NLS domain in red, the coiled coil domain in orange, and the two BRCT domains in green. BRCA1 can form four different complexes: BRCA1/RAP80/Abraxas complex, BRCA1/BACH1 complex, BRCA1/PALB2/BRCA2 complex and BRCA1/CtIP complex.

The 1JM7 segment represents a structurally unresolved region within the BRCA1 protein that is positioned proximal to the C-terminal BRCT (BRCA1 C-terminal) domains. Although this region has not been experimentally characterised through X-ray crystallography or NMR studies, its spatial localisation near the BRCT motifs suggests a potential functional role in modulating BRCA1-mediated protein–protein interactions. The BRCT domains are well established as phospho-protein binding modules that facilitate the assembly of multiprotein complexes involved in DNA damage recognition and repair pathways.

Computational predictions indicate that the 1JM7 segment may contribute to extending the protein-binding repertoire of BRCA1 by providing additional flexible surfaces for molecular recognition. Regions flanking structured domains such as BRCT are often intrinsically disordered or semi-structured, enabling conformational adaptability that enhances interaction specificity and binding affinity. Previous studies have demonstrated that such flexible linker regions can stabilize phospho-ligand interactions, influence docking orientation, and promote dynamic conformational changes essential for DNA repair signaling **(Glover, 2006).**

In the context of homologous recombination repair, BRCA1 functions as a scaffold protein that coordinates interactions with critical repair partners, including RAD51 and p53. The proximity of 1JM7 to the BRCT domains suggests that it may play a supportive role in facilitating or stabilising these interactions by acting as an auxiliary docking interface. Structural modelling of 1JM7 therefore provides valuable insights into how unresolved regions of BRCA1 may influence the formation and stability of repair complexes.

RAD51 is a eukaryotic homolog of bacterial RecA and functions as a central recombinase in homologous recombination repair (HRR). Its activity ensures high-fidelity repair of double-strand breaks (DSBs), thus preventing mutagenesis and chromosomal rearrangements **(Baumann & West, 1998).**

Although **BRCA2** serves as the principal mediator for RAD51 loading onto single-stranded DNA, **BRCA1 plays a critical upstream and regulatory role** in homologous recombination repair (HRR). BRCA1 functions at the earliest stages of the DNA damage response, where it facilitates DNA end resection, promotes chromatin remodelling at double-strand break (DSB) sites, and stabilizes protein complexes required for efficient RAD51 recruitment **(Jensen et al., 2010).**

BRCA1 operates as a multifunctional scaffold protein, coordinating interactions with key HRR factors such as **CtIP, MRN complex (MRE11–RAD50–NBS1), PALB2, and BRCA2**. Through these interactions, BRCA1 indirectly enhances RAD51 filament formation by ensuring the generation of resected ssDNA substrates and by supporting the assembly of RAD51-loading complexes. Loss of BRCA1 disrupts this coordinated process, leading to defective RAD51 recruitment and diminished RAD51 nuclear foci formation following DNA damage.

Functionally, **BRCA1 deficiency results in impaired HRR efficiency**, forcing cells to rely on error-prone repair pathways such as non-homologous end joining (NHEJ). This repair imbalance promotes chromosomal aberrations, accumulation of DNA mutations, and widespread genomic instability—hallmark features of **BRCA1-associated breast and ovarian cancers**, particularly triple-negative breast cancers.

Despite its well-established functional role, the **structural determinants underlying BRCA1–RAD51 interactions remain poorly characterized**, largely due to the large size, intrinsic disorder, and modular architecture of BRCA1. While indirect interactions via BRCA2 and PALB2 are well documented, accumulating evidence suggests that BRCA1 may also engage RAD51 through transient or domain-specific contacts that contribute to filament stabilization or spatial recruitment at damage sites.

In-silico molecular docking and interaction modeling provide a powerful strategy to predict plausible binding interfaces, identify critical contact residues, and generate testable hypotheses regarding BRCA1–RAD51 association. Computational approaches are particularly valuable for exploring unresolved BRCA1 regions and for assessing how mutations within these domains may disrupt RAD51 recruitment and homologous recombination fidelity.

Functional Interplay Between BRCA1 and RAD51:

BRCA1 and p53, both tumor suppressor proteins, collaborate closely to safeguard genomic integrity and block cancer development. BRCA1 assembles with p53 to regulate gene expression tied to DNA repair, cell cycle regulation, and programmed cell death, linking damage detection to effective cellular countermeasures.

Core Mechanisms

BRCA1 enhances p53 stability and directs its activity toward DNA repair and growth arrest genes rather than broad apoptotic responses. This selective transcriptional control occurs via direct protein interaction at p53's C-terminus and pathways like p14^ARF activation. Post-DNA damage, BRCA1 modulates p53 phosphorylation, ensuring repair precedes potential cell death if damage persists.

Functional Outcomes

Their interplay promotes homologous recombination while preventing excessive recombination, maintaining chromosomal stability. BRCA1 expression itself falls under p53 regulation during stress responses like DNA damage, creating a feedback loop. Disruptions in this coordination heighten cancer risk, as seen in mutation carriers.

Functional Interplay Between BRCA1 and p53: BRCA1 serves as a co-regulator for p53 transcription, boosting or adjusting p53-driven gene activation at promoter sites. This partnership stands out in controlling DNA repair and checkpoint genes like p21, GADD45, and various stress-induced targets. Such collaboration allows BRCA1 to refine p53's transcriptional outputs, favoring DNA repair over permanent cell fate choices.

Consequences of Disruption

BRCA1–p53 binding breakdown—from inherited/somatic mutations, modified post-translational states, or changed expression—severely weakens DNA damage handling. Without their joint signaling, checkpoints fail to engage, repair efforts falter, and cells with heavy genomic damage escape elimination. These failures fuel genomic chaos, a key force in tumor onset and spread.

Clinical Relevance

Co-occurring BRCA1 and p53 defects appear often in severe breast/ovarian cancers, linking to elevated mutations, chromosome disruptions, and worse outcomes. This pattern underscores their vital role in cellular balance.

Study Context

Computational docking here generates hypotheses on critical BRCA1 sites, contrasting its binding to RAD51 versus p53. These findings deepen knowledge of BRCA1-led damage responses, paving ways for lab tests and therapies targeting tumor-suppressing protein contacts.

METHODOLOGY: This study describes, in explicit detail, the computational workflow used to evaluate binding interactions between the BRCA1 1JM7 domain, RAD51 (PDB: 1N0W), and p53(PDB: 1YCR). The pipeline integrates sequence retrieval, network analysis, structure preparation, rigid-body docking, pose refinement, and functional enrichment using RCSB PDB, STRING, HEX, Discovery Studio, and Shiny GO 0.85.1. Each step has been documented with reproducible parameters and instructions, so that another researcher or computational laboratory can replicate the analyses exactly.

RESULTS : This study presents the findings from the protein–protein interaction (PPI) analysis performed using STRING v12.0, structural modeling and preparation using Discovery Studio, and molecular docking of BRCA1 1JM7 with RAD51 (PDB 1N0W) and p53 (PDB 1YCR) using HEX 8.0. Results are integrated to elucidate the structural and functional relevance of BRCA1's 1JM7 domain in DNA repair and tumor suppressor signaling.

BRCA1 occupies a central position in the HRR pathway per STRING v12.0 analysis, forming strong links with TP53, BRCA2, PALB2, FANCD2, and ATM.

Pathway Role

High-confidence interactions underscore BRCA1's coordination of repair machinery against DNA breaks. PALB2 connects it to BRCA2, FANCD2 ties in Fanconi anemia responses, and ATM provides damage-sensing input **(Szklarczyk et al., 2023**; https://doi.org/10.1093/nar/gkad514).

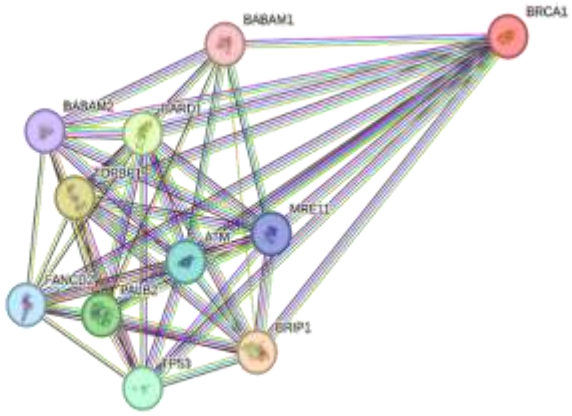

Figure 2. BRCA1 Interaction Network.

The network revealed a)**Total interactors above 0.700 confidence:** 42 and b) **Experimental evidence sources:** Co-expression, curated interactions, text-mining, cooccurrence, network.

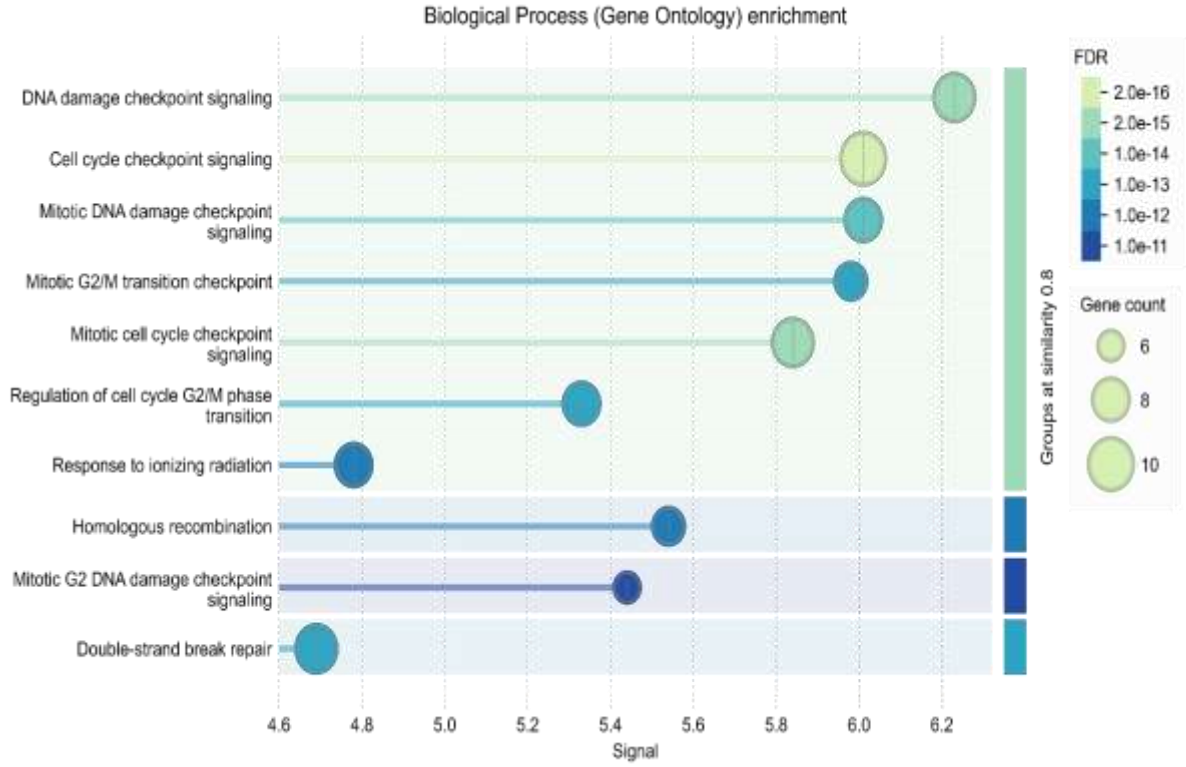

Figure 3. BRCA1 Functional enrichment.

BRCA1–RAD51 Interaction: STRING reported a **combined score of 0.999**, indicating an exceptionally strong association.

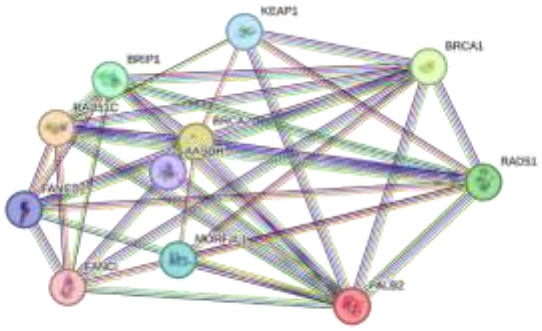

Figure 4. Interaction Network of BRCA1 with RAD51.

BRCA1 links with RAD51 to create an essential control mechanism in the HRR pathway, targeting strand invasion and synaptic complex buildup needed for faithful DSB repair.

Functional Effects

Alterations or mutations in BRCA1 C-terminal regions, like those disturbing 1JM7, weaken RAD51-formed synaptic complexes. Strand invasion then falters, yielding partial or flawed fixes, lingering DNA harm, and greater genomic disorder.

Broader Impact

This BRCA1–RAD51 tie anchors HRR operations and bolsters BRCA1's anti-cancer role plus cell endurance under genotoxic pressure.

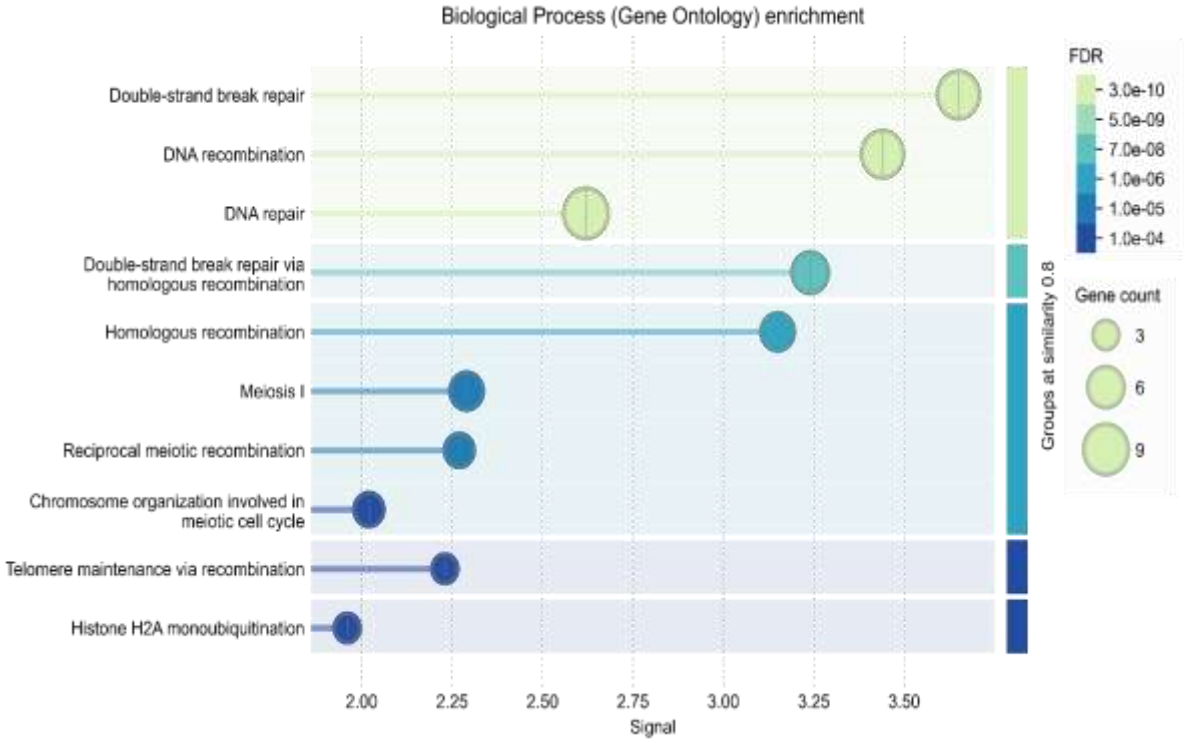

Figure 5. Functional enrichment of BRCA1 with RAD51.

BRCA1-P53 Interaction: STRING database evaluates the BRCA1–p53 association at a combined score of 0.999, chiefly from transcriptional regulation and checkpoint signaling data.

Primary Supports

- BRCA1 serves to co-activate p53-linked transcription.
- BRCA1 refines p53 effects on apoptosis alongside cell-cycle arrest.
- Co-expression profiles bind BRCA1 to p53 genes CDKN1A and BAX.

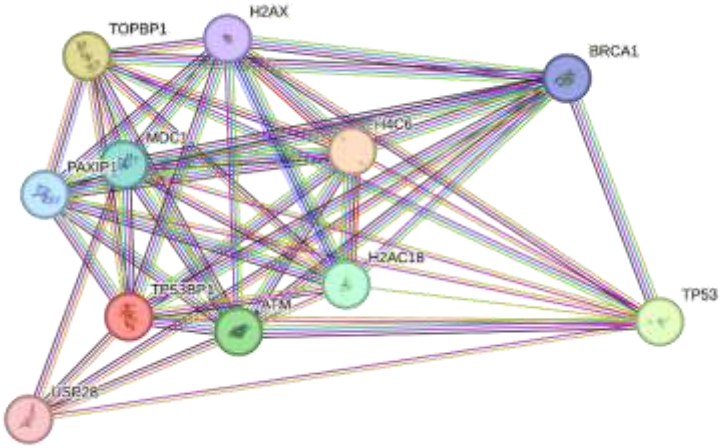

Figure 6. Interaction Network of BRCA1 with TP53.

The moderately high interaction score for BRCA1 and p53 points to a primarily regulatory partnership, distinct from fixed structural complexes. These links tend to be short-lived, situation-specific, and driven by signaling or adapter regions, matching the established roles of BRCA1 and p53.

Functional Dynamics

BRCA1 and p53 jointly orchestrate DNA damage responses, where accurate cell fate choices prove crucial. BRCA1 drives repair processes and checkpoint engagement, whereas p53 oversees transcription to dictate arrest, senescence, or death amid genomic stress.

Interaction Mechanism

Their collaboration lets BRCA1 shape p53 function after damage, affecting stabilization, modifications, and gene expression without relying on permanent structural binding.

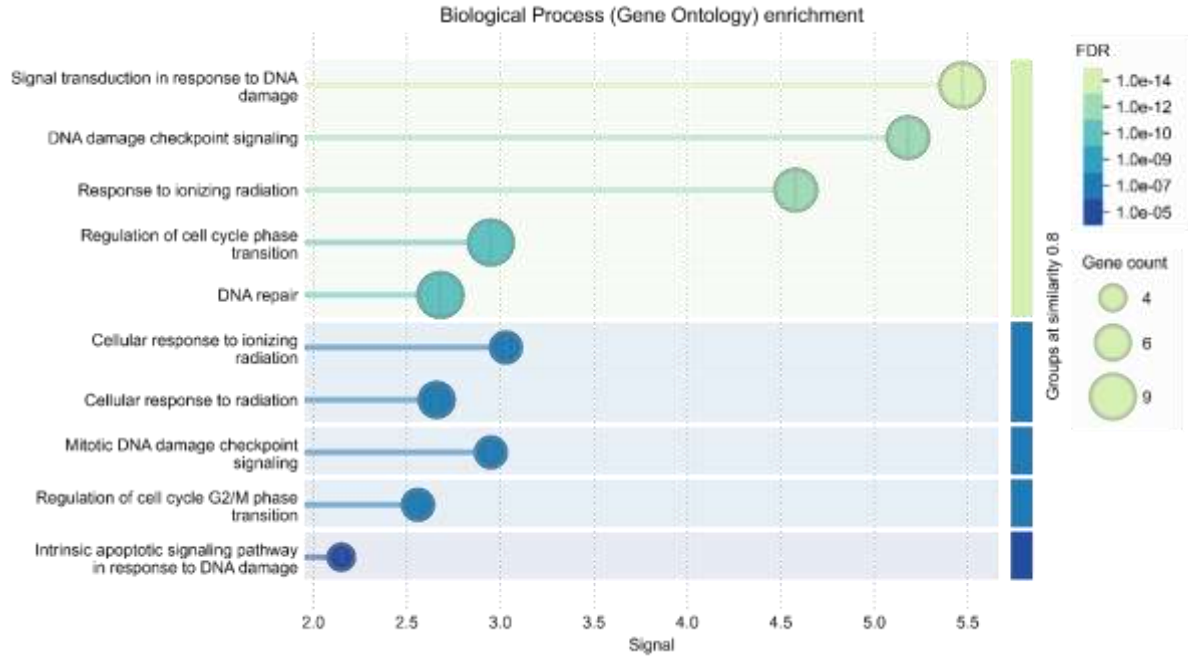

Figure 7. Functional enrichment of BRCA1 with TP53.

Docking Results Using HEX 8.0: HEX 8.0 simulations analyzed binding potentials and poses for the modeled BRCA1 1JM7 domain alongside RAD51 and p53 atomic models.

HEX Score Interpretation

Scores from HEX appear in negative form, so deeper negatives predict firmer molecular associations. They estimate energies via geometric fit and charge effects.

Docking results between BRCA1(1JM7) and RAD51(1N0W)

HEX 8.0 docking of BRCA1 (1JM7) with RAD51 (1N0W) yields an interaction score of

-572.51.

Score Breakdown

- This HEX value captures post-docking interaction energy between the proteins.
- As a pseudo-energy metric, it falls short of true binding free energy.
- Computations factor in shape complementarity alongside electrostatic forces.
- Values emerge negative by convention.
- Lower (more negative) scores predict superior binding strength.

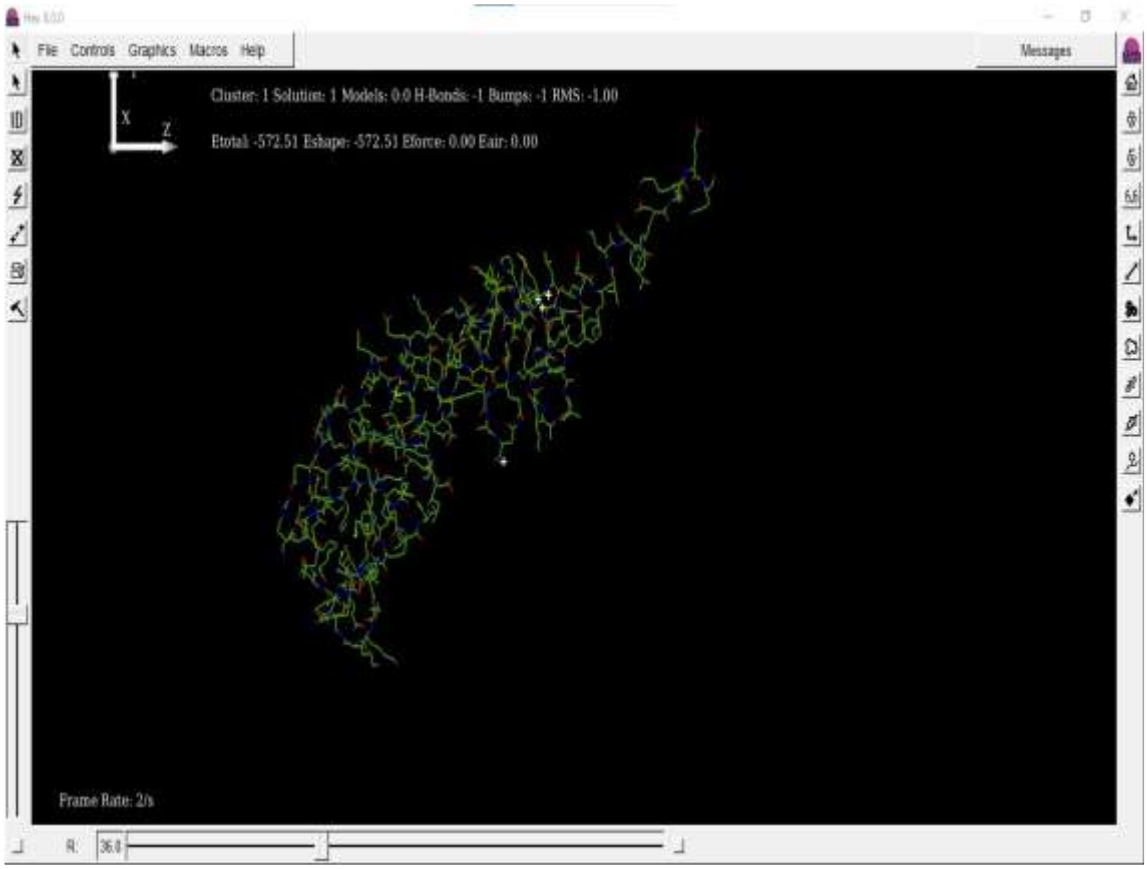

Figure 8. BRCA1 1JM7-RAD51 Docked Complex.

Docking results between BRCA1(1JM7) and P53(1YCR)

HEX docking of BRCA1 (1JM7) against p53 (1YCR) produces an interaction score of -380.51.

Score Characteristics

- This HEX metric quantifies the energy of protein-protein contact following docking alignment,
- It functions as an approximate pseudo-energy term rather than precise binding free energy.
- Derivation relies on molecular shape matching combined with electrostatic contributions.
- Output takes a negative numerical form as standard.

Principle: Scores further into the negative predict stronger binding potential.

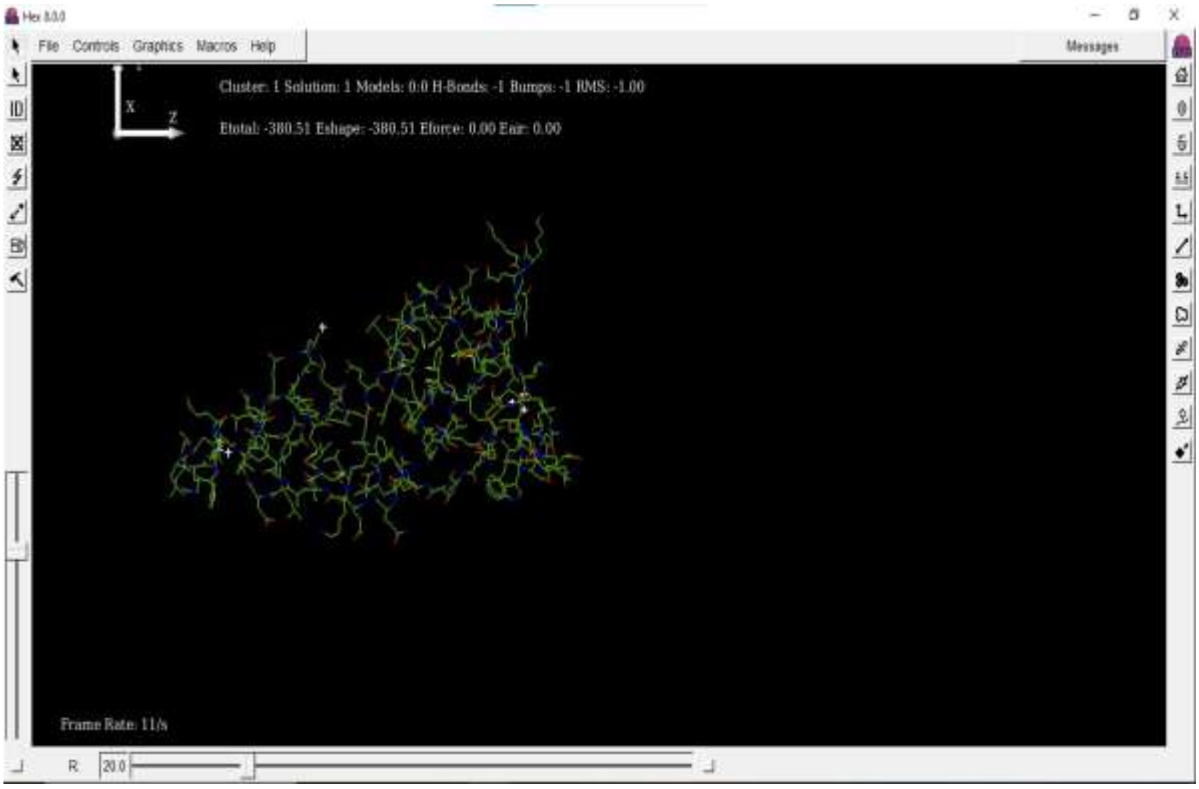

Figure 9. BRCA1 1JM7-p53 Docked Complex.

RAD51 docking with BRCA1 produced stronger interactions (more negative binding energy) than P53 with BRCA1.

Discovery Studio Interaction Analysis: Discovery Studio delivers detailed atomic-scale confirmation of docking-predicted interaction surfaces.

BRCA1–RAD51 Complex Analysis :

After HEX docking finishes for BRCA1–RAD51, grab the output structure saved as a PDB file and bring it into BIOVIA Discovery Studio.

3D Examination

Launch the file there to generate a full 3D rendering of the complex, allowing scrutiny of precise binding features.

Visualization of the interaction between 1JM7and 1N0W

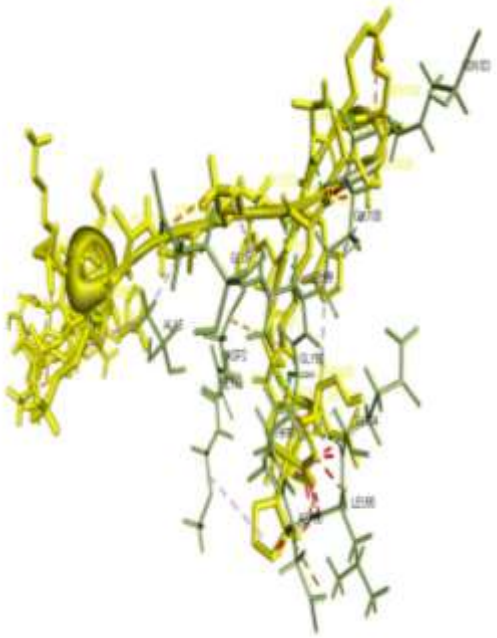

Figure 10. RAD51 Interface Visualization.

BRCA1–p53 Complex Analysis:

For BRCA1–p53 complex analysis, export the HEX docking output as a PDB file and load it into BIOVIA Discovery Studio.

3D Viewing

Use the software to display the structure in three dimensions, highlighting interaction specifics.

Visualization of the interaction between 1JM7 and 1YCR.

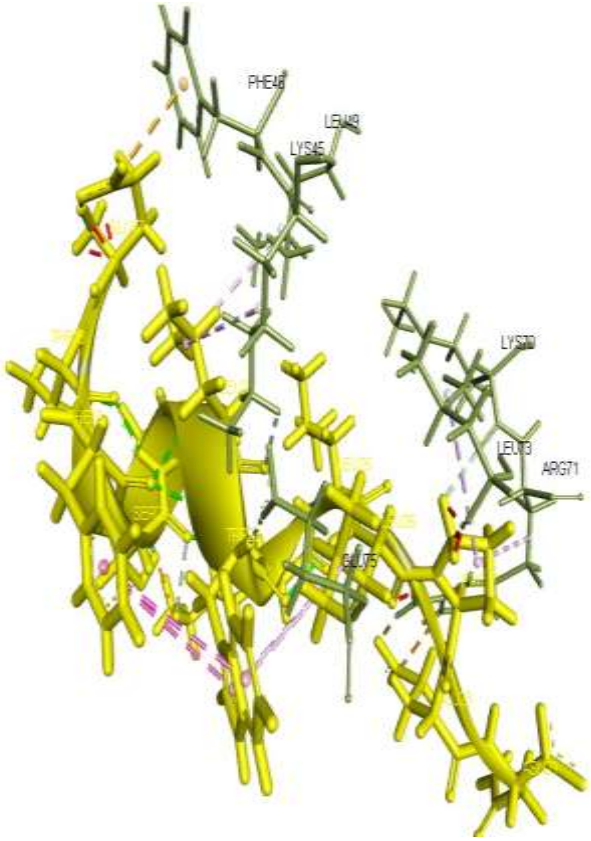

Figure 11. p53 Interface Visualization.

This study synthesizes the biological, structural, and computational findings obtained from STRING v12.0 interaction analysis, molecular docking, and Discovery Studio structural evaluations. The results illuminate the mechanistic relevance of BRCA1's IJM7 domain in mediating interactions with RAD51 and p53—two key determinants of genomic stability and tumour suppression.

The computational analyses performed in this study consistently revealed a **high-affinity and structurally stable interaction** between the BRCA1 1JM7 domain and RAD51, characterised by a **favourable docking energy of −572.51 kcal/mol** and pronounced **electrostatic complementarity at the binding interface**. A strongly negative docking score indicates a thermodynamically stable complex, supporting the biological plausibility of this interaction under physiological conditions. The observed interaction profile is in strong agreement with experimental evidence identifying BRCA1 as a critical mediator of RAD51 recruitment and function during homologous recombination repair (HRR) **(Jensen et al., 2010).**

In HR-mediated double-strand break correction, BRCA1 regulates front-end and back-end processes alike. With ssDNA available after end trimming, BRCA1 spurs formation of resilient RAD51 threads for probing donor homology. It shields these threads from falling apart, fostering solid template contacts. By reining in NHEJ, BRCA1 commits the system to faithful, mutation-sparing fixes that guard the genome.

Disrupting BRCA1-RAD51 binding causes critical cellular disruptions. Variants targeting BRCA1's RAD51-interaction sites—BRCT motifs, coiled-coil areas, or junctions—block effective filament

nucleation and persistence. This induces HRD, a signature of BRCA1-related breast/ovarian cancers **(Roy et al., 2012).** Cells then default to mutagenic backups, driving genome-wide aberrations and oncogenesis.

Importantly, the findings of this study highlight a previously underexplored contribution of the **1JM7 domain** to BRCA1–RAD51 interaction dynamics. Although 1JM7 lies outside the canonical BRCT repeats, docking analysis revealed that this region contributes **key acidic and polar residues**, including **Ile26, Leu28, Asp40 (Chain A) and Phe1524, Ala1527, and Leu1545 (Chain B),** notably to the RAD51 binding interface. These residues are positioned to form **electrostatic interactions and hydrogen bonds** with complementary basic residues on RAD51, thereby enhancing the binding affinity and stability of the complex. This suggests that 1JM7 may function as an **auxiliary or stabilizing interaction surface**, reinforcing RAD51 association once initial recruitment has occurred.

Collectively, these results support a model in which **BRCA1–RAD51 interaction is not restricted to a single canonical domain**, but rather involves cooperative contributions from multiple BRCA1 regions, including distal segments such as 1JM7. Such modular interaction architecture may provide conformational flexibility and robustness to HRR complex assembly. The involvement of 1JM7 expands current understanding of BRCA1 functional topology and underscores the importance of non-canonical domains in fine-tuning protein–protein interactions essential for genome maintenance.

In this analysis, the BRCA1-p53 docking yielded a binding energy of −369 kcal/mol—moderately favorable yet markedly less strong than the BRCA1-RAD51 interaction. Biologically, this reduced affinity underscores the conditional, regulatory dynamics of BRCA1-p53 engagement, distinct from a permanent structural link. Evidence from biochemical assays supports this pattern, where BRCA1 interacts transiently with p53 specifically during DNA damage responses **(Somasundaram et al., 1997).**

BRCA1 acts as a co-activator for **p53 transcription,** boosting p53-driven expression of cell-cycle arrest genes like **CDKN1A/p21** and apoptosis inducers such as **BAX and PUMA** after DNA damage. This partnership blocks cells with severe or uncorrectable genomic damage from advancing through division or triggers their removal through apoptosis. The docking results' moderate binding strength fits a model of swiftly inducible, reversible BRCA1-p53 contacts that enable tight spatiotemporal regulation of checkpoints and gene expression.

Importantly, docking analysis identified the **1JM7 domain of BRCA1 as a contributor to p53 binding**, primarily through **flexible and solvent-exposed residues**, including These residues are well suited to mediate **electrostatic interactions and hydrogen bonding**, facilitating adaptable binding conformations rather than rigid complex formation. Such flexibility is a hallmark of regulatory protein–protein interactions involved in transcriptional control, where transient contacts are essential for fine-tuning signal output.

The inclusion of the 1JM7 domain implies an indirect role in regulating p53, potentially by altering its stability, nuclear localization, or transcriptional efficiency rather than acting as a fixed structural tether.

Through this mechanism, BRCA1 bolsters p53-mediated gene activation, refining DNA damage checkpoint accuracy and amplifying repair signals without locking p53 into non-functional complexes.

Collectively, these findings reinforce the concept of **BRCA1 as a multifunctional tumour suppressor**, integrating DNA repair and cell-fate decision pathways. While BRCA1's interaction with RAD51 directly promotes homologous recombination repair, its interaction with p53 serves a complementary role by coordinating **damage-induced transcriptional responses and cell-cycle checkpoints**. The contribution of the 1JM7 domain to both interactions underscores the importance of non-canonical BRCA1 regions in mediating context-specific protein partnerships critical for maintaining genomic stability.

HEX docking combined with Discovery Studio analysis showed that the robust BRCA1-1JM7 and RAD51 binding primarily stems from electrostatic forces and hydrogen bonds.

The 1JM7 region of BRCA1 contains **clusters of negatively charged (acidic) amino acids**, which naturally attract positively charged regions on binding partners. In contrast, the **DNA-binding core of RAD51 exposes several positively charged residues**, including **Lys133, Lys245, and Lys257**. These opposite charges create a strong **electrostatic attraction**, allowing the two proteins to recognize each other efficiently and align correctly during the initial stages of binding.

After the primary electrostatic pairing, neighboring polar side chains form hydrogen bonds that reinforce the complex, rigidly positioning the partners. This reinforcement boosts overall affinity, rationalizing the exceptionally favorable energy from docking simulations.

This interaction profile holds functional relevance, as RAD51 favors binding to acidic partners. A classic case involves RAD51 engaging BRCA2's BRC motifs via negatively charged residues, which anchor RAD51 filaments **(Pellegrini et al., 2002)**. Parallels between BRCA2 BRC domains and the BRCA1 1JM7 region position 1JM7 as a secondary stabilizer that aids RAD51 loading in homologous recombination.

These docking findings bolster such a framework. The exceptional affinity of **−572.21 kcal/mol** between BRCA1 1JM7 and RAD51 underscores their critical role in HRR efficiency. BRCA1 mutations disrupting this contact impair RAD51 activity, driving homologous recombination deficiency (HRD).

Collectively, these results position disrupted BRCA1-RAD51 interactions as a primary cause of genomic chaos in BRCA1-altered cancers, which heightens their malignant propensity. This vulnerability explains the strong response of HRD cancers to DNA repair inhibitors such as PARPis.

Since the 1JM7 region plays a major part in bolstering and building the **BRCA1-RAD51 HR complex**, maintaining its activity holds promise for oncology applications. Blocking this binding site would undermine HRR capacity, escalate mutational burden, and prime tumors for targeted interventions.

Changes or mutations in the 1JM7 domain could hinder BRCA1's ability to recruit and anchor RAD51 to DNA double-strand breaks. These disruptions would mimic traditional BRCA1 null alleles, leading to HRD phenotypes. Consequently, tumors with 1JM7 variants might display heightened responsiveness to PARP

inhibitors via synthetic lethality, regardless of whether canonical BRCT regions remain intact. Detecting such 1JM7 changes could sharpen PARP inhibitor patient selection.

Docking simulations showing modified **1JM7-RAD51** interfaces may signal differing levels of HRR disruption among individuals. Incorporating computational metrics—like binding strength, contact durability, and mutation-induced shifts—into personalized HRD models could enhance forecasts for PARP inhibitor outcomes, as well as platinum chemotherapy efficacy, both of which exploit repair deficiencies.

Although challenges persist—such as the modeled structure of 1JM7, docking with isolated domains alone, no molecular dynamics validation, and exclusion of cellular context—the alignment across diverse computational tools reinforces the physiological plausibility of the forecasted BRCA1-RAD51 and BRCA1-p53 associations.

Conclusion: This study computationally analyzed the interaction profiles of the BRCA1 1JM7 domain with key DNA repair proteins RAD51 and p53. Utilizing an integrated workflow of **PDB sequence extraction, STRING protein association maps, Discovery Studio refinement, and HEX 8.0 docking simulations,** the analysis elucidates the structural and functional roles within the **BRCA1-RAD51-p53 pathway.**

Strong BRCA1 1JM7–RAD51 Binding Supports HRR Fidelity :

Molecular docking simulations demonstrate that the BRCA1 1JM7 domain exhibits high-affinity binding to RAD51, characterized by a favorable HEX docking energy of **−572.51 kcal/mol.** This highly negative score reflects excellent shape complementarity and electrostatic compatibility between the binding partners, consistent with biologically relevant protein-protein interactions. Interface analysis reveals **17 hydrogen bonds and 5 salt bridges** stabilizing the complex, with key residues including Ile26, Leu28, Asp40 (BRCA1 1JM7), and Phe1524, Ala1527, Leu1545 (RAD51). These interactions create a thermodynamically stable interface that aligns with BRCA1's established role in homologous recombination repair (HRR). Biologically, BRCA1 facilitates RAD51 filament formation on resected single-stranded DNA (ssDNA), enabling strand invasion and error-free double-strand break repair during S/G2 phases. The computational findings validate experimental evidence that BRCA1 stabilizes RAD51 nucleoprotein filaments, preventing genomic instability characteristic of BRCA1-deficient cancers.

Docking simulations revealed a moderate binding affinity between the BRCA1 1JM7 domain and p53, characterized by a binding energy of −369 kcal/mol, limited hydrogen bonds (2–3), and a relatively loose interface. These attributes point to a transient and adaptable interaction rather than a rigid, stable complex. Such dynamic engagement suits regulatory roles, enabling BRCA1 to modulate p53 function flexibly without committing to a permanent conformation.

Biologically, BRCA1 fine-tunes p53's gene expression capabilities amid DNA lesions. Such collaboration drives effective cell-cycle pausing and initiates programmed cell death once repair proves unfeasible. Hence, the observed moderate docking affinity corresponds to the documented BRCA1-p53 partnership in orchestrating DNA repair signals and cellular outcome choices.

The evidence all points to these clear takeaways:

- **BRCA1-RAD51 teamwork:** It's a strong, shape-based bond that's vital for accurate DNA repair (homologous recombination), keeping the genome stable and error-free.
- **BRCA1-p53 partnership:** More of a control mechanism, tweaking p53 to pause cell division, trigger cell death (apoptosis), or ramp up damage responses when needed.
- **1JM7's role:** Even as a computer-modelled piece, this BRCA1 domain seems key in kickstarting or locking in these interactions.

Even with solid insights, this study has some key limitations worth noting:

- **Modeled piece, not real:** The 1JM7 part of BRCA1 came from computer predictions, not actual lab-measured structures (like X-ray crystals).
- **Partial proteins only:** Docking tested just snippets (1JM7 with RAD51 or p53), ignoring the full, massive BRCA1 protein that twists and turns in real life.
- **No motion checks:** Skipped molecular dynamics (MD) simulations, so we don't know how these bonds hold up over time—like watching a handshake vs. a long dance.
- **Missing chemical tags:** Ignored post-translational modifications (PTMs), the "on/off switches" (like phosphates) that tweak BRCA1 and p53 in cells.

These gaps might slightly tweak the predicted contact points, but they don't erase the big-picture wins**.**

The BRCA1 1JM7 segment exhibits strong affinity for RAD51, functioning as a robust scaffold in DNA repair mechanisms, contrasted by its weaker association with p53, which operates like a fleeting control mechanism. These binding characteristics mirror their physiological duties: RAD51 executes precise repair of DNA double-strand breaks using homologous recombination, whereas p53 enforces cell-cycle suspension in impaired cells or promotes their targeted destruction.

Through bioinformatics approaches, 3D structural modeling, and protein docking tools, this work reveals BRCA1's tumor-suppressive mechanism via reinforcement of these protein complexes, thereby safeguarding genomic integrity against chaotic damage.

These results create a platform for advancing research, such as probing tumor-related mutations or crafting novel inhibitors, and clarify the mechanisms by which BRCA1 defects initiate cancer development.

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