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RESEARCH ARTICLE

KEY ROLE OF EGFR, ERBB2 AND PRPROTEINS IN GENE AND PROTEIN INTERACTIONS WITH VIMENTIN, FOXC1/2, FAK, AND THE BRCA1 IN PREVENTION OF TRIPLE NEGATIVE BREAST CANCER

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Abstract

Studies on protein–protein interactions and RNA–protein interactions between transcription factors and receptors that act as tumor suppressor proteins play key roles in designing new anticancer drugs for treatment. The BRCA1 RING domain exhibits protein–protein interactions with Vimentin, FOXC2, Focal adhesion kinase and EGFR, whereas the EGFR nucleic acid contig shows gene–protein interactions with Vimentin, FOXC2, Focal adhesion kinase and BRCA1. ErbB2 and the progesterone receptor play key roles in protein–protein interactions with the BRCA1 RING domain and ErB2 in TNBC, and the PR nucleic acid contig shows gene–protein interactions with vimentin, FOXC2, focal adhesion kinase and the BRCA1 RING domain, clearly indicating that the transaction of proteins occurs mostly although noncovalent interactions.

Introduction:-

BRCA1 (breast cancer gene 1) and BRCA2 (breast cancer gene 2) repair damaged DNA, and usually, offspring inherit the protein from their parents, with each gene being from their paternal or maternal partner. Mutated BRCA1 and BRCA2 are responsible for more than 60% of breast or ovarian cancers in inherited individuals. One of the important factors to be considered is genetic predisposition to the disease, and studies on mutations that genetically predispose BRCA1 and BRCA2 to mutations can prevent cancer-related deaths [1].

The nongenetic factors that are likely to contribute to breast cancer include early menopause, alcohol and tobacco consumption, exposure to radiation, obesity, decreased physical activity, urbanization, a sedentary lifestyle, a high-fat diet, frequent spontaneous miscarriages, lack of breastfeeding, hormone replacement therapy, aging, geographical location, socioeconomic conditions, reproductive events, exogenous hormones, breast density, and family history of breast cancer or other cancers [(2,3,4-14)].

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20-30% of cancers and can result in more aggressive cancers with a high recurrence rate and increased mortality.Trastuzumab is a HER2 receptor blocker used to treat most HER2-positive cancers, and emerging patterns of trastuzumab resistance have

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been recorded earlier; however, the development of therapeutic agents, such as monoclonal antibodies and other targeted therapies, can overcome trastuzumab resistance and help in the treatment of most HER2-positive breast cancers[15,16].

The progesterone receptor modulates estrogen receptor expression, and PR expression depends strongly on estrogen and can help improve the prognosis in most TNBC patients with a positive PR17. The estrogen receptor and progesterone receptor are mostly expressed in approximately 15-30% of luminal epithelial cells, and studies have shown that the PR also contains portions of ERα. Studies by Rachel Schiff revealed that ER+/PR- tumors share gene profiles with both the ER+/PR+ and ER-/PR- luminal subtypes, and patients with these genotypes have a poor prognosis concluded byPerou[18].

Methodology:-

Protein–protein interactions were studied using the PDB ids of RCSB through the H dock server by selecting protein option in the tab using accession numbers and FASTA sequence, and RNA–protein interactions were studied by developing nucleic acid contigs from the FASTA protein sequence and through the H Dock server by selecting ssRNAs. A model with a low positive free energy is selected from the top 10 predicted models, and receptor–ligand interface data with negative free energy are captured and in case of HER2 the data we constrained to first 300 amnoacids due to large data sequence.

The amino acid contig of EGFR:

SGSGEAPNQALLRILKETEFKKIKVLGSGAFGTVYKGLWIPEGEKVKIPVAIKELREATSPKANKEILDEAYV
MASVDNPHVCRLLGICLTSTVQLITQLMPFGCLLDYVREHKDNIGSQYLLNWCVFVCVQIAKGMNYLEDR
RHRDLAARNVLKTPQHVKITDFGLAKLLGAEEKEYHAEGGKVPIKWMALESILHRIYTHQSDVWSYGVTV
WELMTFGSKPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVMACWMIDWGDERMHLPSPTDSNFYRAL
MDEEDMDDVVDADEYLIPQQG

[RNA contig of EGFR generated with seq id 7EAI (RCSB PDB):

GGUUCUGGUGAAGCUCCAAAUGAAGCUCUUCUUAGAAUUCUUAAACAAACUAAUUUUAAAAAAAU
UAAAGUUCUUGGUAGUGGUGCUUUUGGUACUGUUUAUAAAGGUCUUUGGAUUCCUCAAGGUCAAA
AAGUUAAAAUUCCUGUUGCUAAAACAACUUCGUCAAGCUACUAGUCCUAAAGCUAAUAAACAAAU
UAAAGAUCAAGCUUAUGUUAUGGCUAGUGUUGAUAAUCCUCAUGUUUGUCGUCUUCUUGGUAUUU
GUCUUACUUAUGUACUGUUGAACUUAUUACUGAACUUAUGCCUUUUGGUUGUCUUCUUGAUUAUG
UUCGUCAACAUAAAUAUAAUAUUGGUUCUGAAUAUCUUUUAAACUGGUGUCGAGAUCGCCAAGGG
CAUGAACUACCUACCUACAGGAUCGACGGCUAGUGUUCUUCUAAAA

Amino acid contig of HER2/erB2:

MKFLVNVALVFM-
YYISYIYADYKDDDDKHHHHHHHHHHLEVLFQGPYPYDVPDYATQVCTGTDMKLRLPASPETHLDMLRH
LYQGCQVVQGNLEYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNG
DPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRAC
HPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCPALPTDCCHEQCAAGCT

{RNA Contig sequence of HER2/erbB2 generated with SNP id:9QBF:RCSBPDB: Due to the large size of the contig, I limited the writing of the RNA contig to first 276 aminoacids

(AUGAAAUUUCUUGUUAAUGUCGCUCUCGUAUUCAUGGUUGUGUAUAUAAGUUACAUCUAUGCCGA
UUACAAGGACGACGACGAUAAACACCACCAUCAUCACCACCACCAUCAUCACCUACAAGUCCUCUU
UGAAGGUCCUUACCCAUACGUUCCAGACUAUGCCACGAAGUGUGUACUGGUACAGACAUGAAACUG
CGCCUACCUGCAAGUCCACAAACGCACUUAUGUUGCGACAUCUUUACGAAGGAUGUGAGGUAGUAG
ACGGAAACCUACAGCUAACAUAUCUGCCAACAAACGCCAGCUUCCUCGAAGACAUAGAACAGGUUG
AAGGAUACGUGCUGAUAGCUCACAACGAAGUUCGUGAAGUUCCUCUAGCGACUGCGUAUGCGUAU
UGUACGGCACAGAACUCUUUCAGGACAACUAUUGUGC

Amino acid contig of the PR:

GQDIQLIPPLINLLMSIEPDYAGHDHDHDNTKPDTSSSLLTSLNQLGERQLLSVVKWSKSLPGFRNLHIDDQI
TLIQYSWMSLMVFGLGWRSYKHVSGQMLYFAPDLILNEQRMKESSFYSLCLTMWQIPQEFVKLQVSQEEF

LCLLLLLLNTIPLEGLRSQTQFEEMRSSYIRELIKAIGLRQKGVVSSSQRFYQLTKLLDNLHDLVKQLHLYCL
NTFIQSRALSVEFPEMMSEVIAAQLPKILAGMVKPLLFHKK.

[RNA contig sequence of the progesterone receptor was built with a sequence id: 1A28: RCSBPDB:
GGCGAGGACAUUGAACUAAUACCACCGCUAAUAAAUCUACUGAUGUCAAUACAACCUGACGUCAUA
UAUGCCGGACACGAUAACACUAAACCAGAUACUUCUUCUUCUUCCCUACUCACCUCUGAACGAGCU
GGGCCAACGUGAACUACUCAGCGUUGUUAAAUGGAGCAAAAGUCUCCCUGGCUUUCGCAAUCUACA
UAUAUAUGACGAAAUAACACUAAUAGAAUAUAGUUGGAUGUCUCUAAUGGUCUUUGGCCUAGGCU
GGCGCUCAUAUAAACAUGUUUCCGGCGACAUGUUAUACUUUGCCCCCGACCUCAUACUUAAUCAAG
AACGUAUGAAGCAAUCUUCCUUCUAUUCUCUAUGUCUAACAAUGUGGGAAAUUCCUGAACAGUUU
GUUAAACUAGAGGUAUCAGAACAACAAUUCCUCUGUAUGAAGGUAUACUCCUGCUAAAUACUAUU
CCA

Results:-

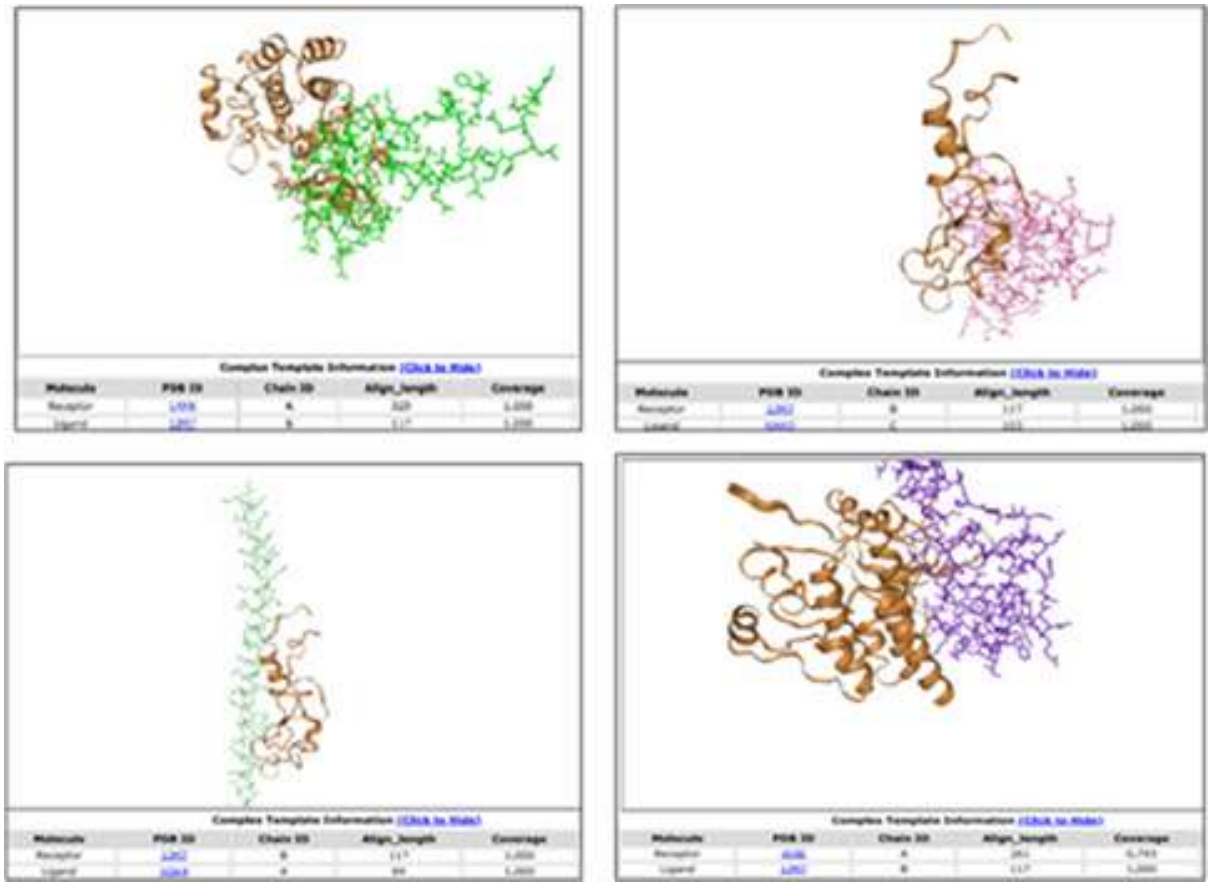


Figure 1 Protein–protein interactions between the BRCA1 RING domain and EGFR (A), FOXC2 (B), vimentin (C) and focal adhesion kinase (D).

Figure 1A shows that the BRCAl RING domain participates in protein–protein interactions with epidermal growth factor receptor (EGFR) at the receptor–ligand interface with the amino acid pair ASP-ASN; ASN–PRO, ASN–VAL; ARG–PHE, ARG–CYS; SER-CYS; SER–PRO; PHE–PRO; PHE–ILE; and GLU–ARG, which are involved in major van der Waals interactions and ionic interactions. The amino acid pairs with low energy values were recorded to reduce the ambiguity in the data. Figure 1B shows the protein–protein interactions between BRCA1 and FOXC2 for the amino acid pairs CYS-SER, PRO–ARG, VAL-SER, VAL–PHE, CYS-GLY, THR-ASN, PRO-GLN, ASN-ASP, LEU-ASN, LEU-ARG LEU-ASP, HIS-ARG, and HIS-PRO at the receptor–ligand interface with van der Waals and ionic interactions. Figure 1C shows that the vimentin and BRCA1 ligand–receptor interfaces contain amino acid pairs such as ARG-VAL, ARG- GLU, LYS- TYR, ARG-GLU, ARG-TYR, LEU-TYR, LEU-HIS, ASP-

GLU, GLU-ILE, GLU-MET, LYS-ARG, GLU-ARG, and ARG-ASN with van der Waals and ionic interactions. Figure 1D Focal adhesion kinase (FAK) shows protein–protein interactions with BRCAl at interfaces containing amino acids such as ASP-ILE, PRO-ILE, GLN-ARG, VAL-ILE, LYS-ILE, TYR-ASN, ASP-ARG, GLN-ASP, ARG-LEU, SER-LYS, ALA-ARG, ARG-LYS, and GLN-GLN, which exhibit major van der Waals interactions and ionic interactions with few recorded hydrophobic interactions.

From the figure 1 &2 BRCA1 RING domain and BRCA1 show Protein -protein interactions with Vimentin, FOXC1/2 and FAK. Vimentin promotes invasion by driving the progress towards metastasis,FOXC1/2 and FAK are promoters of metastasis and mesenchymal transition may be by suppressing the gene expression of BRCA1 in normal cells there by converting them to tumor cells by progression through EMT. In addition, sequestration of protein in normal cells and loss of BRCA1 in cancer cells may cause most aggressive Triple negative breast cancers with poor prognosis. FOXC1/2 majorly activates PI3K/AKT pathway and drives the cellular program towards tumor metastasis by phosphorylation of BRCA1 Ser 1172 by AKT there by making the protein dispersed from repair foci and promotes cell division.

BRCA1/GATA3/FOXC1 Axis in the interconnected network regulates FOXC1 expression through BRCA1/GATA3 and loss of BRCA1 can leads to over expression of FOXC1/2 there by promoting the metastasis and tumorigenesis. Vimentin expression in TNBC can leads to more aggressive TNBC through metastasis to distant sites and FAK expression can lead to poor prognosis through increased cellmotility, invasionand resistance.

Figure 2A shows the results of protein interaction studies between the BRCA1 total amino acid contig and FOXC2, which revealed interactions between amino acids at the binding surface with low energy values recorded at HIS-ASN, HIS-LEU, THR-ASN, GLU-ASN, ASP-GLN, ASP-LYS, TYR-GLN, LEU-SER, and PRO-TYR, revealing ionic and van der Waals interactions. Figure 2B shows that the BRCA1 and vimentin pairs had low energy values for amino acid pairs such as LEU-LYS, THR-ASN, LEU-GLU, MET-MET, GLU-ARG, GLU-THR, PHE-GLY, GLU-GLN, TYR-LYS, ILE-GLN, ILE-VAL, GLN-VAL, and GLN-LYS through noncovalent interactions such as hydrophobic interactions, van der Waals forces and ionic interactions. As shown in Figure 2C, BRCA1 interacts with focal adhesion kinases at the amino acid positions ARG-HIS, ILE-HIS, GLN-LYS, GLN-HIS, LEU-HIS, THR-ARG, THR-HIS, GLY-ARG, GLU-ARG, VAL-SER, ARG-LEU, SER-THR, SER-ASN, and SER-LEU at the binding interface with vascular forces more strongly than with ionic interactions.

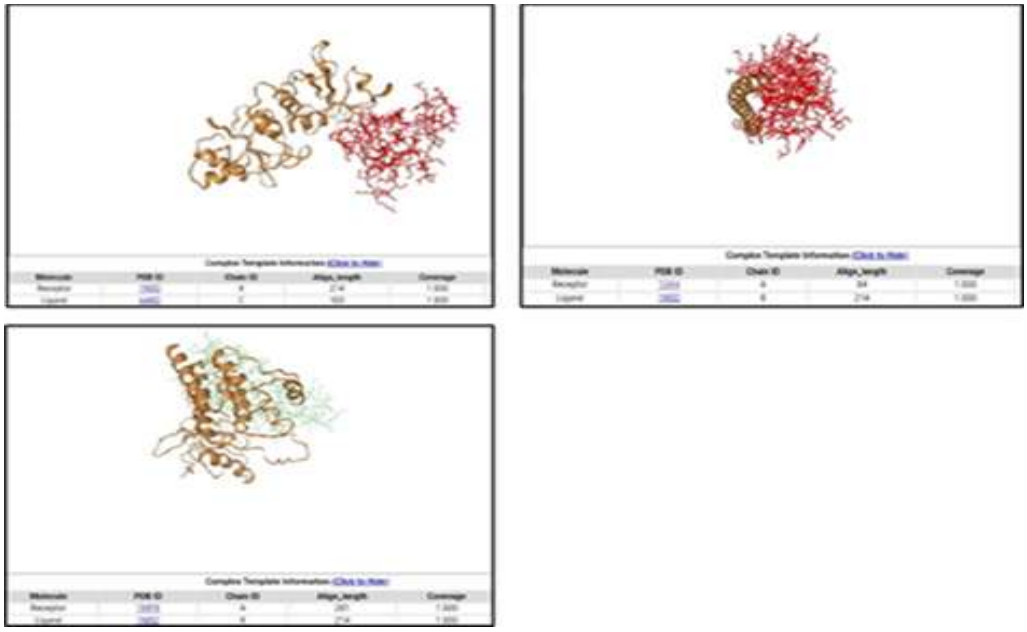


Figure 2: Protein–protein interactions of the total BRCA1 contig with FOXC2, vimentin and focal adhesion kinase.

Figure 3A shows that BRCA1 interacts with EGFR at the 21st position Lys with the c1 position of adenine (588), the C1 position of uracil at the 654th position with ARG (24), the 27th position of ARG with the C4 position adenine, the 33rd position Arg with the N3 position cytosine (504), the 37th position Cys with cytosine at N2 (536) and the C3 position cytosine (537). At position 72, Ile with OP2 was adenine (547), and at position 83, Cys was adenine at position C6 (628).

From figure 3A mutations in BRCA1 may promotes phosphorylation at Ser 1172and may acts as a scaffold protein grouping all the kinases of Tyrosine receptor kinase signaling pathway there by causing over activation of EGFR signaling pathway. From figure 3B, 3C &3D EGFR, FOXC1/2, Vimentin and FAK shows positive correlation in TNBC progression and metastasis. EGFR/FAK pathway deregulation can lead to drug resistance and aggressive tumour formation to distant sites by vimentin over expression. FOXC1 acts as downstream regulator of EGFR-activated Akt/ERK/NF-κB axis and Vimentin and FAK are co-activators of downstream pathway of EGFR.

Figure 3B shows that EGFR interacts with vimentin at 31 Tyr with 28 cytosine residues, 35 Ile with 13 guanine residues and 14 cytosine residues, and the 38th position of LEU with 782,783 adenine and uracil residues. 39, Gln with 15 and 783 positions of uracil; 45, MET with 713 positions of adenine; 72, Thr with 887 positions of uracil; 75, Lys; and 76, Leu with 888 adenine and 867 guanine. The 76 position Leu with the 887-position uracil in the gene.

As shown in Figure 3C, EGFR interacts with FOXC2 at the 45th position of Gln with the 666th position uracil, at the 52nd position Arg with 160 and 161th positions cytosine and uracil, at the 53rd position His with adenine (136) and guanine (667), at the Ser (56) and Leu (57) with guanine (125) and at the Ser (56) with uracil (162), at the Leu (57) with uracil (135) and guanine (164), at the Glu (59) with uracil (134) and guanine (165), at the Lys (63) with uracil (162) and cytosine (163), at the Asp (82) with adenine (183), at the Arg (97) with uracil (171) and guanine (184) of the nucleic acid sequence.

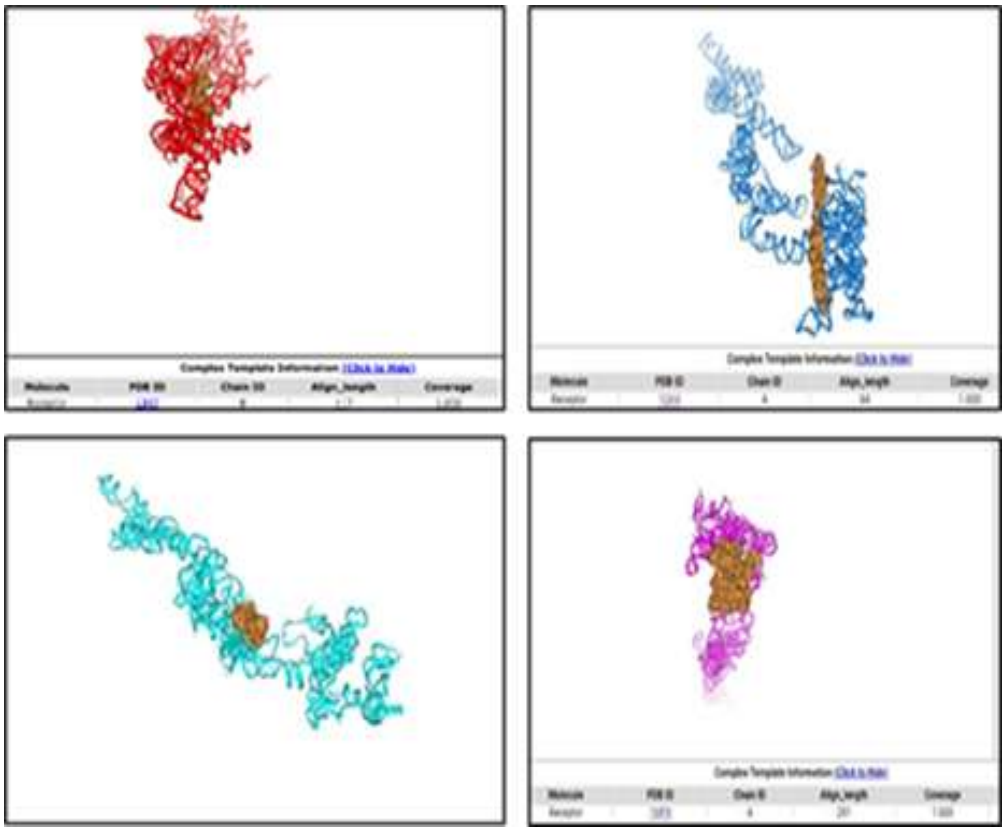


Figure 3 Protein–gene interactions between the BRCA1 ring domain and the EGFR contig (A), between vimentin and the EGFR contig (B), between FOXC2 and the EGFR contig (C) and between FAK and EGFR (D)

According to Figure 3D, EGFR interacts with focal adhesion kinase at sites such as Tyr (165) with adenine (760), Lys (176) with guanine (748), Ile (189) with uracil (749), and Arg (192) with guanine (748), and positions with a free energy change less than 2.0 are recorded and mentioned here.

Figure 4A shows that HER3 proteins interact with the BRCA1 ring domain at amino acid pairs such as Cys (41) - Asn (417), Asp (97) - Gln (425), Asp (97) - His (449), Glu (100) - His (416) &Asn (417), Pro (103) - Leu (415) &Asn (417), Arg (104) - Val (332), and Phe (108) - Leu (415) at the receptor–ligand interface through ionic interactions followed by van der Waals and dipole–dipole interactions.

As shown in Figure 4B, the ErbB2 gene interacts with the BRCA1 protein at various sites, such as Phe (45) with uracil (347), Cys (46) and Pro (59) with guanine (346), Thr (63) with guanine (367), Trp (66) with cytosine (750), Asn (88) with guanine (751), His (91) with adenine (344), and Asn (93) with uracil (343).

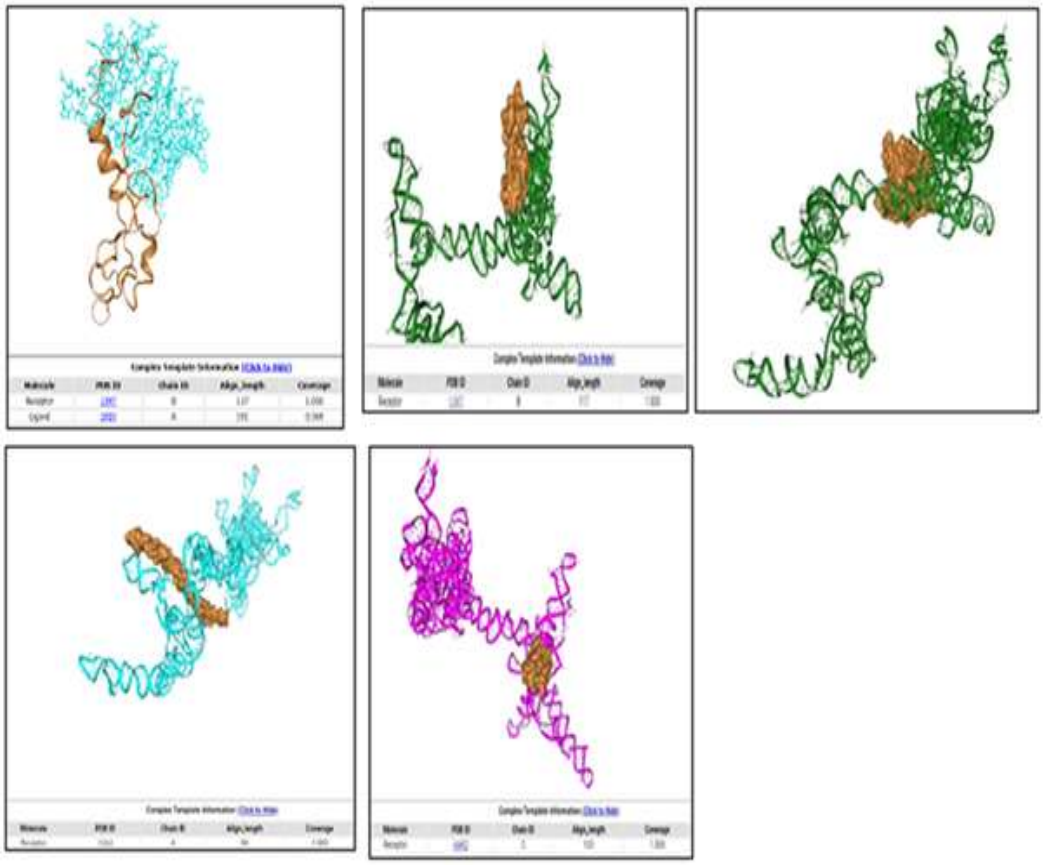


Figure 4 Protein–protein interactions between BRCA1 and HER3 (seq id:3P0Y) (A) and gene–protein interactions between erb2 and BRCA1 with seq.id 2A91 (B), between erbB2 and FOXC2 with seq.id 2A91 (C), between erbB2 and vimentin with seq.id 2A91 (D) and between erbB2 and FAK with seq.id 2A91 (E).

As shown in Figure 4D, the ErbB2 gene interacts with vimentin at sites such as Arg (15 and 18) at cytosine (162), Glu (27) at uracil (12), Tyr (31) at uracil (11), Tyr (31) at adenine (255) and guanine (256), and Gln (39) at guanine (260).

Figure 4E shows that ErbB2 and FOXC2 have gene–protein interactions at Tyr (165) with adenine (760), Lys (176) and Arg (192) with guanine (748), and Ile (189) with uracil (749). As shown in Figure 4C, Focal adhesion kinase interacts with ErbB2 at the nucleotide positions Phe (191) and uracil (554), Asn (224) and Asp (225) and adenine (449), Arg (229) and adenine (447), Glu (231) and uracil (555), Glu (234) and adenine (321) and uracil (446), and Met (238) and Tyr (247) with adenine (323), Tyr (256) and uracil (555).

Figure 5A shows that BRCA1 interacts with the progesterone receptor at positions 89 (Leu) with Tyr (23), Phe (45) with Asn (108) and Arg (111), Cys (46) with Ile (106), Pro (59) with Pro (103), Val (60) with Asn (28) Thr (63) with Tyr (23) Leu (89) with Tyr (100), His (91) with Val (94), and Ser (96) with Met (98) predominantly through van der Waals interactions and dipole–dipole interactions.

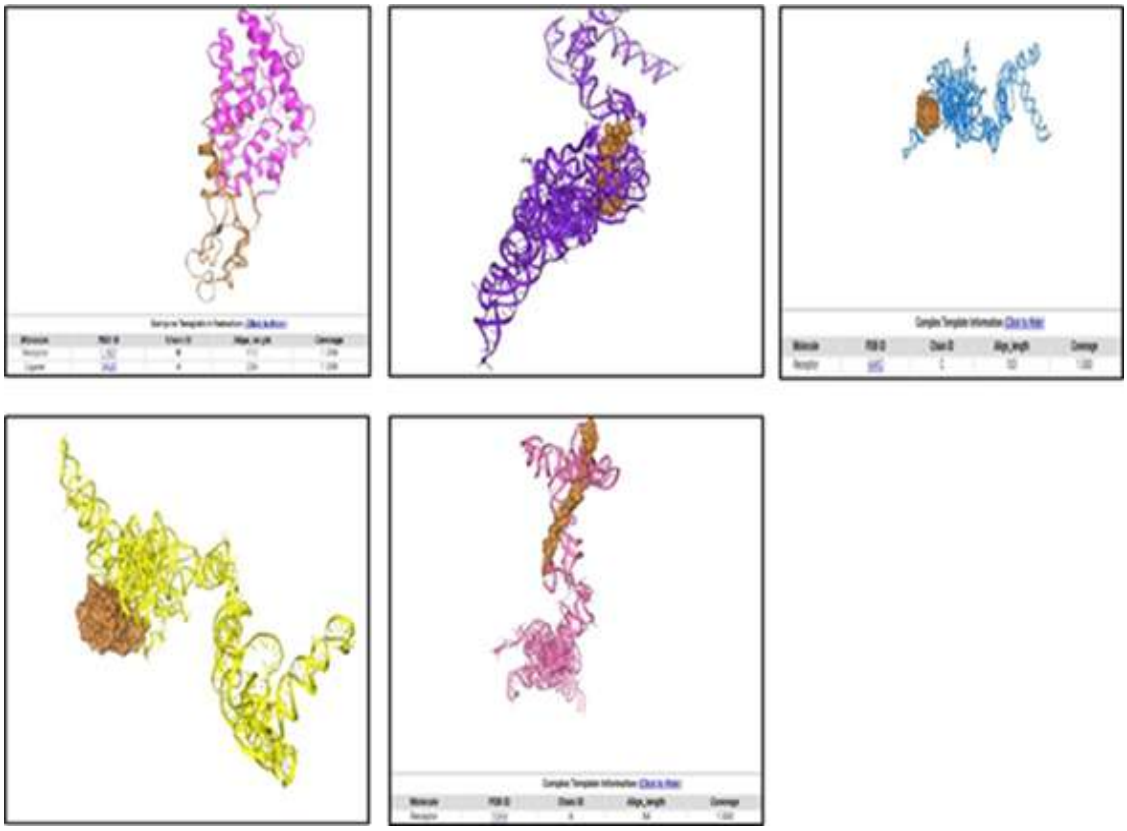


Figure 5: Protein–protein interactions between BRCA1 and progesterone receptor sequence 1A28 (A), and gene–protein interactions between PR and BRCA1 (B), between PR and FOXC2 (C), between PR and FAK (D) and between PR and vimentin (E).

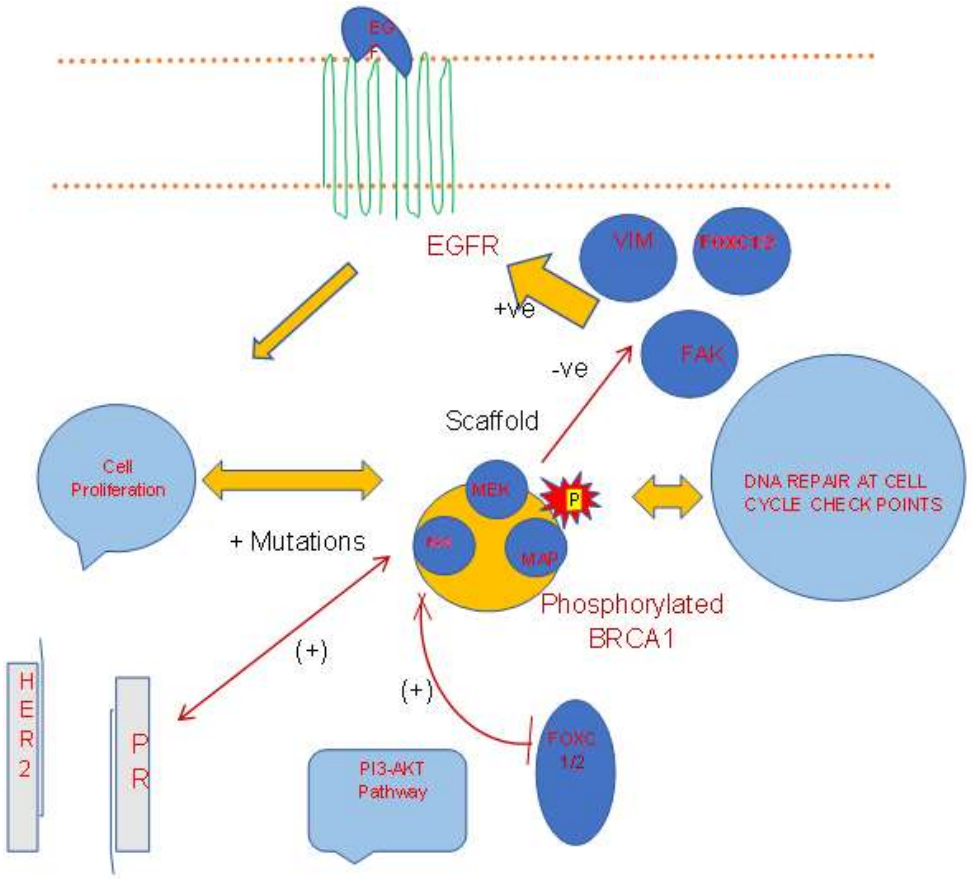
Figure 5C shows that the PR interacts with the FOXC2 protein via gene–protein interactions at position 3 (Lys) with guanine (405 & 406), with Pro (5) with uracil (357), with Tyr (8) with guanine (405), with Phe (39) with guanine (406), with Asn (43) with uracil (407), with Gly (46) and Trp (47) with guanine (406), with Asn (49), with Arg (52) with cytosine (307), with His (53) with cytosine (305 & 306), with Leu (57) with cytosine (305), with Glu (88) with uracil (396), and with Arg (97) with uracil (395).

As shown in Figure 5B, the progesterone receptor interacts with BrCA1 at Arg (24) with uracil (443) and Asn (30) with cytosine (444), Ile (31) with uracil (707), Arg (33) with uracil (453) and adenine (706), Gln (81) with cytosine (455) and uracil (456), Ser (84) with adenine (705), Arg (87) with uracil (446) and adenine (705), ASn (88) with uracil (704), Leu (95) with adenine (701) and Asp (97) with adenine (689).

As shown in Figure 5D, the progesterone receptor interacts with focal adhesion kinase, which results in gene–protein interactions at various positions, such as Pro (39) with cytosine (16), Asp (57) with adenine (323), Arg (136) with adenine (337), Asp (153) with guanine (6), and Glu (266) with guanine (253).

Figure 5E shows that nucleic acid interactions with the progesterone receptor occur with the protein vimentin at Glu (2) with uracil (695), Glu (27) with uracil (490), Ala (29), Asp (33) and Gln (32) with cytosine (664), Asn (30) with uracil (490 and 491), Tyr (30) with uracil (490), Thr (34) with uracil (491), Arg (37) with uracil (491 and 492), Leu (53) and Gln (57) with adenine (551), Tyr (56) with uracil (505) and cytosine (506).

Often the PR and HER2 will show opposing interactions and FAK mRNA expression is higher in ER+/PR+/HER2- and HER2+ breast cancers,with the highest expression found in triple-negative breast cancer (TNBC). High PR expression is associated with lower histological tissue grade and high HER2 with high tumor grade finally causing increased motility, invasion and metastasis in TNBC.



Schematic representation of overall gene-Protein and Protein – Protein interactions between EGFR, ErbB2 and PRwith Vimentin, FOXC1/2, FAK, and the BRCA1 in prevention of triple negative breast cancer

Discussion:-

The roles of progesterone hormone and progesterone receptor in cancer treatment have been debated over the past several years, and by the early 20th century, it was determined that the presence of estrogen receptor alone cannot be a solution and that the PR is one of the targets of estrogen and the first baseline hormonal therapy for breast cancer[18].The human epidermal growth factor receptor 2 (HER2) receptor is a membrane protein tyrosine kinase that affects proliferation and growth when activated. The HER2 oncogene is located at chromosome number 17q12, and HER2 gene amplification is one of the major mechanisms responsible for HER2 overexpression, which is associated with most current HER2-positive cancers[19].

BRCA1 is a tumor suppressor gene that plays a key role in repairing DNA damage, regulating the cell cycle, maintaining genome stability and regulating several other physiological responses [20]. Women with BRCA1 mutations can develop not only most aggressive breast cancers, such as triple-negative breast cancer but also a high risk of exposure to other cancers, such as ovarian cancer[20].

Declarations:
Ethics approval: NA
Consent to participate: NA

Consent for Publication: NA

Availability of data and material:
Figure 1
FIGURE 1a: BRCA1-EGFR
ACCESSION NUMBER: 1JM7- BRCA1
ACCESSION NUMBER: 1XKK- EGFR
URL: RCSB PDB - 1JM7: Solution structure of the BRCA1/BARD1 RING-domain heterodimer
URL: RCSB PDB - 1XKK: EGFR kinase domain complexed with a quinazoline inhibitor- GW572016
FIGURE 1B: BRCA1- FOXC2:
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: FOXC2 - 6AKO
URL: RCSB PDB - 1JM7: Solution structure of the BRCA1/BARD1 RING-domain heterodimer
URL: RCSB PDB - 6AKO: Crystal Structure of FOXC2 DBD Bound to DBE2 DNA
FIGURE 1C: BRCA1 VIMENTIN:
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: VIMENTIN-1GK4
URL: RCSB PDB - 1JM7: Solution structure of the BRCA1/BARD1 RING-domain heterodimer
URL: RCSB PDB - 1GK4: HUMAN VIMENTIN COIL 2B FRAGMENT (CYS2)
FIGURE 1D: BRCA1-FAK:
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: FAK-4I4E
URL: RCSB PDB - 1JM7: Solution structure of the BRCA1/BARD1 RING-domain heterodimer
URL: RCSB PDB - 4I4E: Structure of Focal Adhesion Kinase catalytic domain in complex with hinge binding pyrazolobenzothiazine compound.

Figure 2
Figure 2A: BRCA1-FOXC2:
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: FOXC2 - 6AKO
URL: rcsb.org//entry/1JM7/display>1JM7_1|Chain A|BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN|Homo sapiens (9606)
URL: RCSB PDB - 6AKO: Crystal Structure of FOXC2 DBD Bound to DBE2 DNA
FIGURE 2B: BRCA1 VIMENTIN:
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: VIMENTIN-1GK4
URL: rcsb.org/fasta/entry/1JM7/display>1JM7_1|Chain A|BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN|Homo sapiens (9606)
URL: RCSB PDB - 1GK4: HUMAN VIMENTIN COIL 2B FRAGMENT (CYS2)
FIGURE 2C: BRCA1-FAK axis
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: FAK-4I4E
URL: rcsb.org/fasta/entry/1JM7/display>1JM7_1|Chain A|BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN|Homo sapiens (9606)
URL: RCSB PDB - 4I4E: Structure of Focal Adhesion Kinase catalytic domain in complex with hinge binding pyrazolobenzothiazine compound.

Figure 3
Figure 3 A: BRCA1-EGFR:
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: EGFR-7AEI
URL: rcsb.org/fasta/entry/1JM7/display>1JM7_2|Chain B|BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1|Homo sapiens (9606)
URL:rcsb.org/fasta/entry/7AEI/display>7AEI_1|Chain A|Epidermal growth factor receptor|Homo sapiens (9606)
Figure 3B: EGFR-VIMENTIN:
ACCESSION NUMBER: EGFR-7AEI

ACCESSION NUMBER: VIMENTIN-1GK4
URL: rcsb.org/fasta/entry/7AEI/display>7AEI_1|Chain A|Epidermal growth factor receptor|Homo sapiens (9606)
URL: RCSB PDB - 1GK4: HUMAN VIMENTIN COIL 2B FRAGMENT (CYS2)
Figure 3C: EGFR- FOXC2
ACCESSION NUMBER: EGFR-7AEI
ACCESSION NUMBER: FOXC2 - 6AKO
URL: rcsb.org/fasta/entry/7AEI/display>7AEI_1|Chain A|Epidermal growth factor receptor|Homo sapiens (9606)
URL: RCSB PDB - 6AKO: Crystal Structure of FOXC2 DBD Bound to DBE2 DNA
Figure 3D EGFR-FAK
ACCESSION NUMBER: EGFR-7AEI
ACCESSION NUMBER: FAK-4I4E
URL: rcsb.org/fasta/entry/7AEI/display>7AEI_1|Chain A|Epidermal growth factor receptor|Homo sapiens (9606)
URL: RCSB PDB - 4I4E: Structure of Focal Adhesion Kinase catalytic domain in complex with hinge binding pyrazolobenzothiazine compound.

FIGURE: 4
FIGURE: 4A: BRCA1-ErB2
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: ErB2- 2A91
URL: RCSB PDB - 1JM7: Solution structure of the BRCA1/BARD1 RING-domain heterodimer
URL: RCSB PDB - 2A91: Crystal structure of ErbB2 domains 1-3
FIGURE 4B: BRCA1: HER2/ErB2
ACCESSION NUMBER: BRCA1- 1JM7
ACCESSION NUMBER: HER2/ErB2-9QBF
URL: rcsb.org/fasta/entry/1JM7/display>1JM7_2|Chain B|BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1|Homo sapiens (9606)
URL: rcsb.org/fasta/entry/9QBF/display>9QBF_1|Chain A|Receptor tyrosine-protein kinase erbB-2, Green fluorescent protein|Homo sapiens (9606)
FIGURE 4C: HER2/ErB2: FOXC2
ACCESSION NUMBER: HER2/ErB2-9QBF
ACCESSION NUMBER: FOXC2 - 6AKO
URL: rcsb.org/fasta/entry/9QBF/display>9QBF_1|Chain A|Receptor tyrosine-protein kinase erbB-2, Green fluorescent protein|Homo sapiens (9606)
URL: RCSB PDB - 6AKO: Crystal Structure of FOXC2 DBD Bound to DBE2 DNA
FIGURE 4D: HER2/ErB2: VIMENTIN
ACCESSION NUMBER: HER2/ErB2-9QBF
ACCESSION NUMBER: VIMENTIN-1GK4
URL: rcsb.org/fasta/entry/9QBF/display>9QBF_1|Chain A|Receptor tyrosine-protein kinase erbB-2, Green fluorescent protein|Homo sapiens (9606)
URL: RCSB PDB - 1GK4: HUMAN VIMENTIN COIL 2B FRAGMENT (CYS2)
FIGURE: 4E: HER2/ErB2: FAK
ACCESSION NUMBER: HER2/ErB2-9QBF
ACCESSION NUMBER: FAK-4I4E
URL: rcsb.org/fasta/entry/9QBF/display>9QBF_1|Chain A|Receptor tyrosine-protein kinase erbB-2, Green fluorescent protein|Homo sapiens (9606)
URL: RCSB PDB - 4I4E: Structure of Focal Adhesion Kinase catalytic domain in complex with hinge binding pyrazolobenzothiazine compound.

FIGURE 5
FIGURE 5A BRCA1:PR
ACCESSION NUMBER: 1JM7- BRCA1
ACCESSION NUMBER: 1A28 - PR
URL: RCSB PDB - 1JM7: Solution structure of the BRCA1/BARD1 RING-domain heterodimer
URL: RCSB PDB - 1A28: HORMONE-BOUND HUMAN PROGESTERONE RECEPTOR LIGAND-BINDING DOMAIN
FIGURE 5B: BRCA1-PR

ACCESSION NUMBER: 1JM7- BRCA1
ACCESSION NUMBER: 1A28 – PR
URL: rcsb.org/fasta/entry/1JM7/display>1JM7_2|Chain B|BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1|Homo sapiens (9606)
URL:rcsb.org/fasta/entry/1A28/display>1A28_1|Chains A, B|PROGESTERONE RECEPTOR|Homo sapiens (9606).
FIGURE 5C: PR-FOXC2
ACCESSION NUMBER: 1A28 – PR
ACCESSION NUMBER: FOXC2 - 6AKO
URL:rcsb.org/fasta/entry/1A28/display>1A28_1|Chains A, B|PROGESTERONE RECEPTOR|Homo sapiens (9606).
URL: RCSB PDB - 6AKO: Crystal Structure of FOXC2 DBD Bound to DBE2 DNA
FIGURE 5D: PR-FAK
ACCESSION NUMBER: 1A28 – PR
ACCESSION NUMBER: FAK-4I4E
URL:rcsb.org/fasta/entry/1A28/display>1A28_1|Chains A, B|PROGESTERONE RECEPTOR |Homo sapiens (9606).
URL: RCSB PDB - 4I4E: Structure of Focal Adhesion Kinase catalytic domain in complex with hinge binding pyrazolobenzothiazine compound.
FIGURE 5E: PR-VIMENTIN
ACCESSION NUMBER: 1A28 – PR
ACCESSION NUMBER: VIMENTIN-1GK4
URL:rcsb.org/fasta/entry/1A28/display>1A28_1|Chains A, B|PROGESTERONE RECEPTOR |Homo sapiens (9606).
URL: RCSB PDB - 1GK4: HUMAN VIMENTIN COIL 2B FRAGMENT (CYS2)

The first Author/Corresponding Author Dr. Eswari Beeram will be contacted to obtain the raw data.
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Author contributions:
Author: 1: The first author performed the experimental work and wrote the manuscript.
Author: 2 Second author reviewed the manuscript
Author: 3 Third author reviewed the manuscript
Author: 4 Fourth author reviewed the manuscript
Author: 5 Fifth author reviewed the manuscript.

Limitations statement:

The amino acid sequence is encoded at only 100-300 amino acids due to the large size of the contig in the case of eErb2/HER2. When predicting SOX10 expression, the methodology used for the study was limited because the data generated represented by some protein IDs ultimately limited the study to only 8 proteins instead of 10 proteins, and I am unable to study all the proteins and genes involved in TNBC.

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