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RESEARCH REVIEW

Comprehensive overview of *BRCA1* in breast cancer: molecular mechanisms, multi-omics approaches, and therapeutic strategies

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BRCA1 is a tumor suppressor gene which is involved in repair of DNA, regulation of cell cycle, support of genome stability and other crucial physiological highlights. Numerous hereditary and natural variables are included in breast cancer advancement over different social orders. Among all of these factors in families with a history of breast cancer all through a few periods, hereditary genes, like inclining qualities to create this malady, ought to be considered more, since transformations within the *BRCA1* and *BRCA2* essentially increment the chance of breast and other cancer. Early discovery of transformation carriers in these genes, in turn, can play a vital part in its avoidance. Additionally, treatment approaches for *BRCA1*-associated breast tumors have demonstrated encouraging success, including PARP inhibitors, platinum-based chemotherapy, and newly developed targeted treatments. This review, summarize the molecular roles of BRCA1, its connection to the pathophysiology of breast cancer, existing therapeutic approaches, and recent multi-omics findings. It is anticipated that a more thorough integration of multi-omics data will enhance clinical outcomes and personalized treatment for patients with *BRCA1* mutated breast cancer.

Keywords: *BRCA1* protein, Missense mutation, Tumor Suppressor, Breast cancer, Transcriptomic, Proteomic, PARPi

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Introduction

Breast cancer (BC) is the most common malignancy all over the world and is the main cause of death, accounting for 11.7 percent of new cancer cases. In 2012, 1.7 million cases were reported worldwide by Globocan. In 2022, breast cancer was diagnosed in 2.3 million women worldwide; resulting in 670,000 deaths.[1] Genetic and familial cancer comes about around 10% of the cases, showing that 167,000 cases may be ascribed to a hereditary cause. Hereditary breast cancers occur approximately 15 to 40 % due to pathogenic variants (PVs) of breast cancer susceptibility gene 1 (*BRCA1*-17q21) and breast cancer susceptibility gene 2 (*BRCA2*-13q12 to 13).[2] Whole exome sequencing using next generation sequencing technology is considered to be a powerful method to identify genetic variants from larger cohort of patient populations. Approximately 10 % of the breast cancer cases occur in women who have a first degree relative with a history of breast cancer. However underlying inherited gene mutations, that could explain for familial clusters could only be identified in 20-25% of these families (genes that were tested *BRCA1, BRCA2, Tp53 PTEN, ATM, CHEK2* and *HRAS1*).[3] Most WES investigations focus on protein truncating mutations that represent the majority of disease-causing germline mutations in cancer genes. However missense mutations have been observed 98% of all genomic variants, therefore categorizing the pathogenicity of mutations/substitution in the disease susceptibility is still a challenging task. So, there are different in

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silico-based prediction tools that evaluate the amino acid substitutions on protein structure and function but validation of in silico prediction further requires support from in vitro based approach.

About *BRCA1* and *BRCA2*

The *BRCA1* was identified in 1994 based on its linkage to breast and ovarian cancer families.[4] The *BRCA1* encodes an 1863 amino acid protein with an apparent molecular mass of 220 kDa. Since its discovery, *BRCA1* has been found to participate in a variety of cellular processes, including the DNA damage response (DDR); regulation of transcription, cell cycle progression, and apoptosis and silencing of satellite DNA within heterochromatin. The *BRCA1* is located in human chromosomes 17q21.[5] In human, the full length *BRCA1* protein is encoded by 24 exons and several studies have investigated to understand that functional role of *BRCA1*.[4] *BRCA1* also comprises different functional domains such as *RING* (Really Interesting New Gene) finger domain at N terminus, an intrinsically unstructured DNA binding domain at central region and a tandem repeat of BRCT domain at the C- terminus.[5] The RING finger domain at the N- terminus is encoded by exons 2 to 7 that interacts with *BARD1* to forms a *BRCA1/ BARD1* heterodimer, which in turn increases E3 ubiquitin ligase activity of complex molecules.6 It has been reported that mutations identified in the RING finger domain of *BRCA1* impair the interactions with *RING* domain of *BARD1*, Hence the structural integrity of the *RING* domain becomes Essential for the proper functioning of *BRCA1*.[6] The C- terminal region of *BRCA1* has two tandem repeats of *BRCT* domain which recognizes the consensus sequence containing p Ser-x-x- Phe (p Ser - phosphoserine, x any amino acids) protein binding partners.[6] The central region of *BRCA1* which is not structurally well ordered contains two atomic localization signals in the exon 11 and a SQ cluster domain that interacts with distinctive DNA repair and cell cycle administrative proteins. The *BRCA1* BRCT domain interacts with a number of proteins including *BRIP1*, *CtIP*, and *CCDC98* and *ABRAXAS*, therefore recombinant DNA technology is used to generate the mutated proteins and furthermore expression and purification.

The *BRCA2* contains 27 exons with eight inside rehashed arrangement called BRC motifs, which considered to be the major domain to associated with *RaD51*.[7] In spite of the fact that there are few similarities between the exons structure of *BRCA1* and *BRCA2* there is no critical arrangement homology between them. Atomic localization signals in human *BRCA2* have been recognized and colocalized with *BRCA1* in sub nuclear foci in somatic cells. Like *BRCA1*, *BRCA2* is moreover vital as a transcriptional co-regulator.[8] *BRCA2* is also known to interact with *SMAD3* to form a complex that co-activate Smad3-dependent transcriptional enactment of plasminogen activator inhibitor-1 (PAI-1) and coordinates with histone acetyl transferases in androgen receptor -mediated transcription. The association of *BRCA2* with Rad51 demonstrated the inclusion of *BRCA2* in the repair of DNA harm by HR pathway.[9] The *BRCA2* also appears to participate in cytoplasmic division; when its function is disrupted, cytoplasmic division is impaired, and the incidence of binucleated cells is increased. All these discoveries recommended tumor suppressor role of BRCA2 via the maintenance of genome stability.[9] The schematic functional domains of *BRCA1* and *BRCA2* and multi-omics mechanisms underlying *BRCA1* dysregulation in cancer was showing in Figure 1.

Omics approaches in BRCA1 research

Breast Cancer risk associated with BRCA-1 mutation

Breast cancer is the most common malignancy all over the world, accounting for 11.7% of new cancer cases.[4] BC is the most commonly analyzed cancer and the driving cause of cancer passing among women in the Gulf Cooperation Council (GCC) locale, with an age-standardized frequency rate of 34.4 per 1 lakh and a mortality rate of 10.6 per 1 lakh in 2020. An essentially expanded hazard of breast cancer is too a highlight of a few uncommon hereditary disorders. These incorporate Cowden disorder, which is most regularly caused by changes in the *PTEN*; innate diffuse gastric cancer, which comes about from changes in the *CDH1*; Li-Fraumeni disorder, which is more often caused by changes in the *TP53*; and Peutz-Jeghers syndrome, which regularly comes about from transformations in the *STK11*. Mutations in *BRCA1* and *BRCA2* constitute the largest proportion of this genes.[10] The life time risk of breast cancers in carriers of a *BRCA1* mutation is up to 70% compared to around 12% in non-carriers. However, not everybody who acquires a change in the *BRCA1* will create cancer. Other hereditary, natural, and, way of life variables moreover contributes to a person's cancer hazard.

Administration of brca transformed early-stage breast cancer is possible through Role of multidisciplinary teams (MDT), genetic counsellor, diagnostic work up and treatment. The MDT approach and hereditary counseling is suggested by many international guidelines. MDT approach presents a critical affect on patient administration.

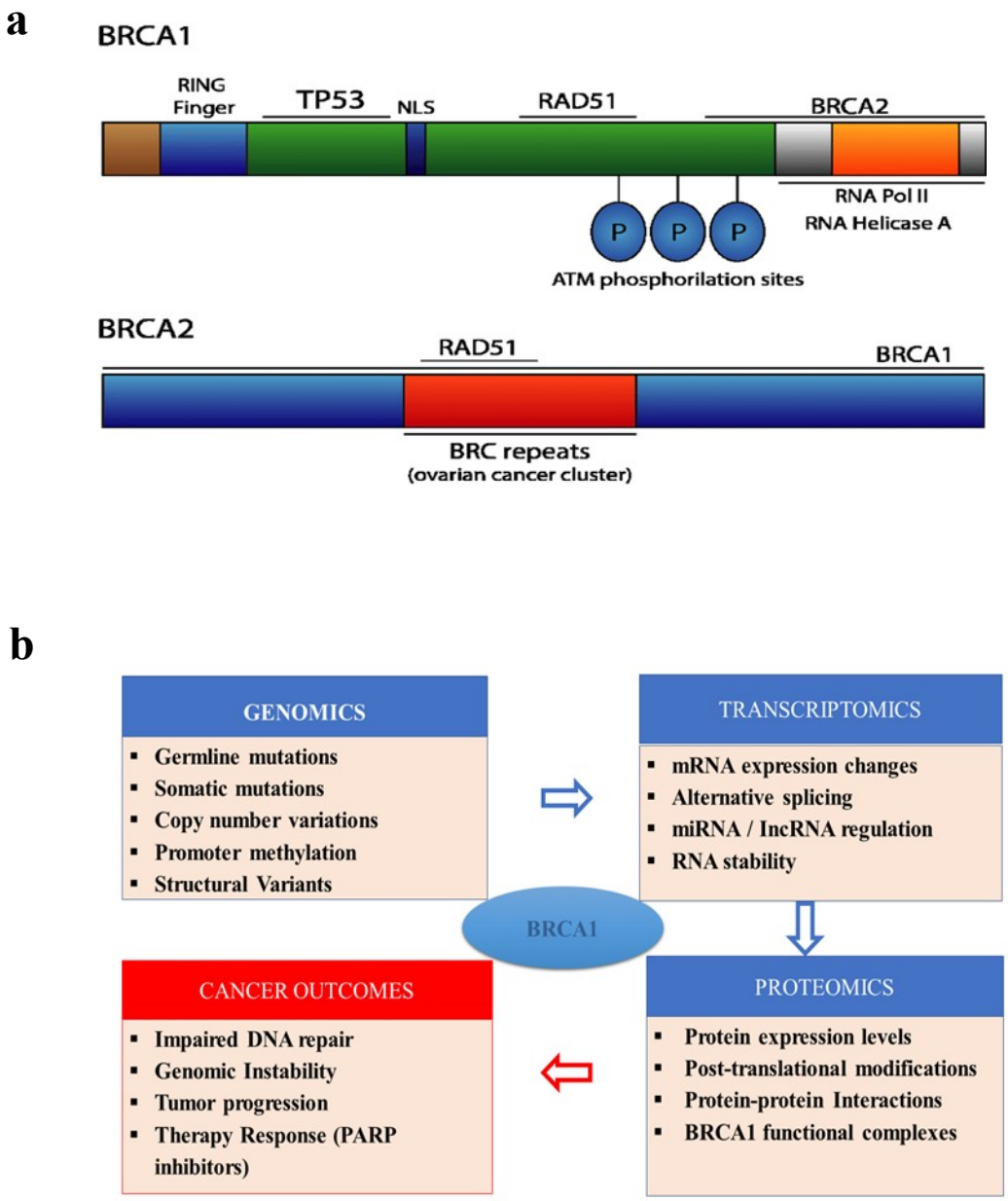

Figure 1. a. Schematic functional domains of *BRCA1* and *BRCA2*, **b**. Multi-omics mechanisms underlying *BRCA1* dysregulation in cancer. Overview of molecular mechanisms affecting *BRCA1* across genomic, transcriptomic and proteomic layers. This highlights how alterations at each omics level contribute to impaired DNA repair, genomic instability, and oncogenic transformation

Studies have detailed that patient who are overseen by MDTs have made strides survival results and the relative risk of recurrence (risk proportion: 0.84; 95% CI, 0.70 to 0.99) and death (risk proportion: 0.89; 95% CI, 0.82 to 0.96) was altogether diminished compared to those who are not.[11] Hereditary counseling has been appeared to make strides understanding results with positive downstream impacts as patients are more prepared to share the outcomes about of hereditary tests with amplified families. The diagnostic strategy based on mammography, the affectability of ultrasound screening and Pathological diagnosis which is based on a core needle biopsy, ideally gotten by ultrasound or stereotactic direction. The standard treatment protocol for breast cancer patients typically includes surgery, radiation, chemotherapy followed by hormone therapy, targeted therapy, and immunotherapy.[12] At the genomic level, germline mutations in *BRCA1* (like 185delAG and 5382insC) lead to frameshift mutations that produce a shortened *BRCA1* protein and loss of homologous recombination (HR) repair.[13] These mutations are linked to a heightened risk of hereditary breast and ovarian cancer in a clinical context. Somatic mutations cause tumor-specific loss of *BRCA1* function, leading to genomic instability. These modifications indicate a likelihood of sensitivity to PARP inhibitors. Copy number loss (loss of heterozygosity, LOH) results from the deletion of the wild-type allele, causing a total loss of *BRCA1* function, and is linked to unfavorable outcomes in triple-negative breast cancer (TNBC). Hypermethylation of the promoter leads to epigenetic silencing of *BRCA1*, decreasing its transcription and playing a role in sporadic breast and ovarian cancers.[14]

Transcriptomic study in BRCA-1 mutated gene

The consider of all the RNA transcripts produced by the genome beneath specific circumstances is known as transcriptomics. Non-coding RNAs, mRNA, rRNA, and tRNA are examples of this. Recently, there has been more noteworthy intrigued in utilizing greatly parallel RNA sequencing (RNA-Seq) information to recognize quality combinations.[15] RNA-Seq has developed as an effective tool to profile the whole transcriptome at a level of detail unattainable by microarrays and it is able of creating single-end reads [SE] or paired-end reads [PE].[16] Repetitive gene combinations have been involved in a few shapes of breast cancer, such as ETV6-NTRK3 in secretory breast ductal carcinoma.

Role of BRCA1 in transcription activation and repression

The C- terminal region of *BRCA1* comprising 1646-1859 performs transcription activation function by binding to phospho-specific binding partners. However, different deleterious mutations at this region demonstrated the impaired Transactivation functions. The germ-line mutations such as brca1 Ala1708Pro, Gly1743Val, Arg1699Gln, Met1775Arg top identified in patients with breast or ovarian cancer abolished the transcription activity.[17] Furthermore, *BRCA1* is also known to stimulate Transcription activation function directly, it could stimulate transcription of the p53 responsive promoter, when overexposed without p53. The Transactivation domain of *BRCA1* suggests a mechanism induced growth inhibition through transcriptional regulation of p27kip1.[18] It can be assumed that Brca1 acts as a direct as well as indirect trans activator protein which performs its function in cell specific manner. *BRCA1 BRCT* interacts with *BRIP1* (*BRCA1* interacting protein), CtIP, whereas tumor associated mutations identified in *BRCA1 BRCT* motifs impair the protein-protein interactions (PPIs).[19] Role of *BRCA1* in regulation of estrogen receptors has revealed the tissue restricted tumor suppressing properties of *BRCA1*. In *BRCA1* insufficient human ovarian cancer cells, estrogen receptors shown ligand-independent transcriptional activity which was not watched in BRCA1 capable cells.[20] *BRCA1* is also able to perform repression function in ubiquitin dependent manner. The ubiquitin moiety interferes with the assembly of basal transcription factors at the promoter, and thus blocks the initiation of mRNA synthesis. Transcriptional repression causes mRNA down regulation at the transcriptomic level, which results in a more aggressive tumour phenotype and a decreased ability to repair DNA. Exon-skipping mutations created by alternative splicing result in *BRCA1* isoforms that are defective and may increase resistance to treatment. Poor survival outcomes are linked to miRNA regulation, such as miR-182, which decreases *BRCA1* expression at the post-transcriptional level.[21] Through competing endogenous RNA networks, lncRNA interactions modulate the stability of *BRCA1* and function as new biomarkers.[22] The *BRCA1* ring domain also helps in DNA repair and transcription regulation and it has E3 activity which is also involved in DNA repair. The *RING* domain allows *BRCA1* to cause a double-strand break, and is involved in tumor suppression.[23] Therefore, genomic integrity of the *RING* domain is essential for the function associated with protein-protein interactions. The *RING* domain is characterized by a conserved pattern that contains seven cysteine and one histidine residue, thus forming two distinct Zn2+ binding sites. This setup leads to the arrangement of a steady heterodimer

complex with the *RING* domain of *BARD1*, a protein related with hindrance of 3′ end processing of mRNA precursor.[24]

Proteomic study in BRCA-1 mutated gene

Mass spectrometry-based proteomics innovations have developed to the degree that they can presently recognize and evaluate thousands of proteins.[25] Protein-based biomarkers may be of particular advantage in comparison with transcript-based and genomic markers, because they can be measured in routine assays. In addition, genomics and transcriptomics studies yielded a number of gene marks that were prognostic for survival, time to far off metastasis and reaction to treatment.[25] Two prognostic marks, Oncotype DX® and MammaPrint® have as of now been enlisted for clinical utilize. In a promising pilot think about utilizing SELDI-TOF-MS, serum peptide profiles seem recognize women with *BRCA1* transformations who created breast cancer from those who did not (carrier), typical volunteers, and women with sporadic breast cancer with great affectability and specificity.[26] Reduced *BRCA1* protein production at the proteome level results from translation inefficiency and/or accelerated degradation, impairing the DNA damage response (DDR) inhibitors may target BRCA1 phosphorylation, a post-translational change that controls homologous recombination (HR) repair activity and is mediated by ATM/ATR.[27] *BRCA1* ubiquitination encourages proteasomal degradation, which causes *BRCA1* instability and aids in the growth of tumors. E3 ligase activity is impaired when *BRCA1* protein complexes, especially the *BRCA1-BARD1* complex, are disrupted. This results in faulty DNA repair machinery and highlights possible therapeutic targeting options.[28] In a study conducted in 2017 performed a quantitative proteomics study of EOC patient tumor tissues and recognized changes in expression of a few key controllers of actin cytoskeleton/cell grip and cell movement (*CAPN1*, *PFN1*, *CFN1*, *14-3-3*, *CAPG*, *SPTBN1*,) related with misfortune of *BRCA1* work. Consistent with this pro-migratory function of *PFN1*, high cytoplasmic expression of *PFN1* has been reported to be associated with advanced stage and shorter disease-free survival in clear cell renal cell carcinoma.[29] At last, this built up a causal connect between *PFN1* and *BRCA1*- induced changes in cell movement in this way revealing a novel unthinking premise for *BRCA1*-dependent control of ovarian cancer cell movement. Full-length *BRCA1* rebuilding in immortalized human mammary epithelial cell line that harbors *BRCA1* transformation leads to change in the expression of a few proteins that are vital for start of intrusion and metastasis {E-cadherin, P-cadherin, caveolin and ID1 (inhibitor of differentiation-1)} with concomitant hindrance of cell relocation and invasion.[30] *BRCA1* suppresses motility of breast cancer cells through its ubiquitin ligase activity at least partly via regulating ezrin-radixin-moesin (ERM) protein content at the membrane.

Tumor-specific hyperphosphorylation of *ARID1A* (S363, S1184), driven by MAPK-related kinases, links chromatin remodeling dysfunction to impaired DNA repair and poor prognosis. In TNBC, TMT-based phosphoproteomics demonstrated that genistein suppresses cell growth by modulating phosphorylation networks governing DNA replication, mitotic progression, and ATR/BRCA1-mediated DNA damage response. Similarly, integrated phosphoproteomic and acetylomic profiling showed that safranal induces DNA damage, checkpoint activation, mitotic catastrophe, and epigenetic reprogramming to promote apoptosis. In invasive micropapillary carcinoma, integrative proteome-phosphoproteome analysis identified dysregulated protein homeostasis and activation of CDKs and mTORC1/S6K2 signaling, pathways closely linked to cell cycle and DDR control.[31] Plasma metabolomics-proteomics profiling of 216 participants identified 47 diagnostic metabolites with strong predictive accuracy (AUC = 1.0 training; 0.794 testing), while serum extracellular vesicle DIA proteomics (n = 126 patients) identified metastasis-associated biomarkers such as *TALDO1* with therapeutic potential. Additionally, proteogenomic approaches integrating key mutations (*TP53*, *PIK3CA*, and *BRCA1*/2) support personalized therapies with improved tumour reduction and reduced toxicity, and proteomics-guided biomarker discovery is particularly promising in TNBC management.[32] The overview of integrative multi-omics of *BRCA1* and their functional and clinical implications shown in the Table 1.

BRCA1 mutations in BC patients from Mizoram, India

Studies on breast cancer in the ethnically distinct Mizo population reveal a *BRCA1* variant spectrum that differs from those observed in mainstream Indian and Western populations. Targeted gene sequencing of Mizo breast cancer patients did not identify high-penetrance or truncating *BRCA1* mutations; however, eight BRCA1 polymorphisms were detected, including four synonymous and four non-synonymous variants. Notably, a novel synonymous variant, c.4772A>T (p.P1544P), was identified in exon 15, suggesting that traditional *BRCA1*-driven

Table 1. Integrative multi-omics alterations of *BRCA1* and their functional and clinical implications in cancer.

Omics layer	Type of Alteration	Molecular Mechanism	Functional Consequence	Clinical Relevance
Genomics [13,14]	Germline mutations (e.g., 185delAG, 5382insC)	Frameshift - truncated *BRCA1* protein	Loss of homologous recombination (HR) repair	Hereditary breast/ ovarian cancer risk
	Somatic mutations	Tumor specific	Genomic instabil-	Predictive for PARP
	Copy number loss (LOH)	Deletion of wild-type allele	Complete *BRCA1* loss	Poor prognosis in TNBC
	Promoter hypermethylation	Epigenetic silencing of *BRCA1*	Reduced transcription	Sporadic breast/ ovarian cancers
Transcriptomics [21,22]	mRNA downregulation	Transcriptional repression	Reduced DNA repair capacity	Aggressive tumor phenotype
	Alternative splicing	Exon skipping variants	Dysfunctional *BRCA1* isoforms	Therapy resistance
	miRNA regulation (e.g., miR-182)	Post-transcriptional suppression	Decreased BRCA1 expression	Poor survival correlation
	lncRNA interaction	Competitive endogenous RNA networks	Modulation of *BRCA1* stability	Emerging biomarkers
Proteomics [27,28]	Reduced protein expression	Translation inefficiency / degradation	Impaired DNA damage response	Predictive biomarker
	Phosphorylation (ATM/ATR-mediated)	Post-translational modification	Regulation of HR repair activity	Target for DDR inhibitors
	Ubiquitination	Proteasomal degra-	*BRCA1* instability	Tumor progression
	Disrupted protein complexes (*BRCA1–BARD1*)	Impaired E3 ligase activity	Defective DNA repair machinery	Therapeutic targeting potential

patients (13%). This study also reported co-occurring somatic alterations in ATM and STK11, along with dysregulation of the PI3K-AKT and MAPK signaling pathways.[34] Furthermore, the *BRCA1* variants rs1799966 and rs16941 have been shown to be significantly associated with an increased risk of TNBC in the Mizo population.[35] Collectively, the limited available data constrained by small sample sizes and underrepresentation in global variant databases support substantial genetic heterogeneity among breast cancer patients in Mizoram. While *BRCA1* appears to confer risk in specific clinical subgroups, particularly TNBC, it does not emerge as a consistently prevalent hereditary risk factor in this population. These findings highlight the need for larger, population-representative WES and WGS studies, functional characterization of novel variants, and the development of region-specific genetic testing panels.

Therapeutic strategies for BRCA1 mutation carrier patients

Platinum compounds (cisplatin and carboplatin) are compelling chemotherapeutic operators for ovarian cancers. Patients with ovarian carcinomas and *BRCA1*/2 transformations have longer recurrence-free interims than patients with

intermittent ovarian carcinomas, particularly when treated with platinum-based therapy. Similarly, the advantage of talazoparib was more pronounced in *BRCA1*/2-driven breast cancer patients who did not receive prior cisplatin or carboplatin.[36] Studies have suggested a few components that can lead to cisplatin resistance counting changes in transport of the sedate through changed expression of copper transporters and expanded glutathione expression. The best evidence on platinum efficacy compared to standard therapy to date in the TNT trial. The authors randomized carboplatin vs. docetaxel in patients with metastatic TNBC. They observed a carboplatin response rate of 68% vs. a docetaxel rate of 33% (P = 0.03) in the subgroup of 43 patients having *BRCA1*/2 mutations.[37] Advances in nanotechnology and nanoscience have facilitated the development of Pt NCs, representing an important research orientation for exploring platinum drugs with the precise structure to improve therapeutic effect and reduce systemic toxicity.

Poly (ADP-ribose) polymerase (PARP) was first discovered as a molecule in 1963. The first inhibitor of PARP was discovered in 1980 and was originally designed for possible use in chemotherapy sensitization. *BRCA1*/2-deficient cells are highly sensitive to PARP inhibitors. PARP inhibitors bind to PARP, inhibiting PARylation, and also trap inactivated PARP on DNA; thereby blocking replication forks, leading to their collapse and the generation of double-strand breaks.[38] Double-strand breaks form when single-strand breaks are not repaired. Both *BRCA1* and *BRCA2* proteins play critical roles in the HRR pathway. Double- strand breaks can be repaired either by the homologous recombination repair (HRR) pathway, using the sister chromatid as a template, or by the more error -prone template-independent mechanism of non-homologous end-joining.[39] Hence, restraint of PARP in HR-deficient cells, such as *BRCA1*/2-deficient cells, comes about in manufactured lethality, and promising results of clinical trials in *BRCA*-associated carcinomas have been detailed.[38] PARPi and Immune checkpoint inhibitors (ICIs) are the two emerging classes of drugs demonstrating specific clinical advantages in BC patients with gHRR and gMMR-PVs respectively. PARPi have been demonstrated to improve clinical outcomes in adjuvant and metastatic settings in gBRCA PVs BC and are currently approved by major regulatory agencies, including FDA and EMA. Currently, the PARP inhibitor, olaparib is endorsed for the adjuvant treatment of grown up patients with germline BRCA-mutated HER2-negative high-risk early BC who have been treated with neoadjuvant or adjuvant chemotherapy based on the comes about of the OlympiA trial.[40] The orderly writing audit recognized five considers that advise the address of the part of *BRCA1*/2 testing to direct the utilize of PARP inhibitors in the treatment of patients with HER2 negative breast cancer.

Conclusion

The development of hereditary breast cancer is closely linked to the malfunction of *BRCA1*, a crucial tumour suppressor that preserves genomic stability. Understanding *BRCA1*-driven carcinogenesis has been improved because of developments in omics technologies, such as transcriptomics, proteomics and integrated multi-omics techniques, these technologies have improved risk assessment, made it easier to find molecular biomarkers, and helped create focused treatment plans, such as those based on PARP inhibitors. Precision medicine approaches for *BRCA1*-associated hereditary breast cancer are anticipated to be considerably strengthened by continued technological improvements and integrative research, despite persistent difficulties with data integration, variant interpretation, and clinical implementation.

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Conflict of interests

The authors declare no competing interests.

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