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The Mechanisms of Tumor Susceptibility Associated with BRCA1/BRCA2 Genetic Mutations

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Abstract. BRCA1 and BRCA2 are highly conserved tumor suppressor genes, which have dispensable roles in maintaining genomic integrity and whose coordinated functions are mainly owed to DNA repair conducted by homologous recombination (HR) mechanisms. BRCA1/2 loss-of-function mutations cause defective repair of DNA double-strands breaks, destabilization of stalled replication forks, and instability of replication stress responses, leading to increased chromosomal instability and extensive genomic restructuring. BRCA1 deficiency is associated, at the molecular level, with alterations in the DNA end resection program, the checkpoint signaling program, and chromatin remodeling; BRCA2 dysfunction is associated with RAD51 loading and filament stabilization, and changes in the bias of cells toward error-prone repair programs. Besides these canonical repair errors, BRCA1/2 mutations have an effect on transcriptional regulation, chromatin structure and cell-cycle control which further promotes mutational gain and altered cell fate choices. A combination of faulty DNA repair, replication stress, and failure of genome maintenance form a permissive environment for oncogenic transformation. Such interactive molecular pathways can be used to explain the significant predisposition to breast, ovarian, and other solid tumors that are seen in subjects that carry pathological BRCA1/2 mutations.

Keywords: BRCA1, BRCA2, homologous recombination, PARP inhibitors, replication fork protection.

1. Introduction

Cloning and identification of BRCA1 and BRCA2 was the basis of learning the genetic basis of familial breast and ovarian cancer. BRCA1 was discovered by positional cloning and the discovery of the second main cancer predisposition gene, BRCA2, came next [1,2]. Later functional investigations defined BRCA1 and BRCA2 to have key roles in repairing DNA double-strand breaks (DSBs) especially using HR when a homologous template is present, and that lack of BRCA1 and BRCA2 function results in increased genomic instability and tumor formation [3].

As more is understood about the underlying molecular pathways, it is clear that BRCA1 plays a role in DSB end resection and also recruitment of DNA repair factors and controls chromatin rearrangements, transcriptional program and RNA metabolism which controls cell-lineage and gene expression across the genome. By contrast, BRCA2 has mainly molecular role, in forming RAD51 nucleoprotein filament on resected ssDNA to allow the strand of DNA for invasion during HR [4,5].

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These functions, both independent and combined, explain why BRCA deficiencies lead to multiple DNA repair deficiencies as well as how it covers the bigger network of regulating the cell.

And importantly BRCA1/2's far-outstanding consequence is beyond just typical HR deficiency. Replication fork safeguard interference, replication trouble responses and chromatin linkage governance are all driven toward a definite increase in genome disorder and form specific tumor predisposition, this is especially so for hormone influenced tissue, such as breast and ovaries. Although the above molecular flaws have been clinically used, it seems that genomic care pathways' constantly changing genetic landscape is a key aspect that might have an effect on disease development and outcomes [6,7].

This review will synthesize what has been known about BRCA1/2 mutations causing problems with many different parts of taking care of the parts of the cell and it will talk about how these problems happening together causes changes in a person's DNA and makes certain parts of their body more likely to develop tumors.

2. Molecular functions and regulatory mechanisms of BRCA1/BRCA2

2.1. Upstream regulation: DNA damage sensing and activation

After DNA damage, lesion sensing and signaling amplification are done by the phosphatidylinositol 3-kinase-related kinases (PIKK) family members, such as ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia- and -rad3-related (ATR), and the downstream effectors of these molecules. By ATM/ATR phosphorylation in a site-specific manner, BRCA1 reorganizes BRCA1-containing complexes functionally, and promotes DNA end resection and formation of repair competent ssDNA substrate for HR. At the same time, the BRCA1-BARD1 E3 ubiquitin ligase complex plays a role in local chromatin remodeling in sites of DNA damage and creates a permissive chromatin environment for the recruitment of subsequent repair factors [5].

Though BRCA2 is not controlled as strictly as BRCA1 through phosphorylation, its essential role in the DNA damage response still hinges on linking with PALB2. PALB2 acts like a molecular bridge between the damage signal that depends on BRCA1 and the damage signal that depends on BRCA2. It does this by bringing BRCA2 to the end of damaged DNA and putting it into RAD51 so that BRCA2 can fix the DNA when it gets damaged. BRCA1–PALB2–BRCA2 axis allows upstream damage signaling to link to the execution phase of homologous recombination so that it can efficiently go from receiving the signal to executing repair [3,8,9].

2.2. Core molecular functions and downstream effects: execution of homologous recombination

BRCA1 promotes DNA end resection to create ssDNA substrates that are first covered by replication protein A (RPA); following that, RAD51 is attached by BRCA2 with the involvement of PALB2. PALB2 interacts with both BRCA1 and BRCA2 to help find and fix where the DNA is broken (BRCA2 goes to the damaged DNA sites with BRCA2's help), and it also makes the important protein RAD51 easier to see at places where bad stuff happened and you want to fix it.

BRCA2 has four conserved BRC repeats and a DNA-bind domain that stabilizes RAD51 nucleoprotein filaments and stop RAD51 from falling apart too early, this leads to better strand invasion and gene repair. Because BRCA does not function properly, it can cause a drop in the amount of HR occurring and an increase in NHEJ due to the lack in HR and its error happening methods and creates larger changes to happen in the area and more mutations [3,9]

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In addition to its role in HR, BRCA proteins contribute to the stabilization of stalled replication forks by limiting excessive nucleolytic degradation by factors such as MRE11, thereby preserving fork integrity during replication stress [10,11]. And likewise, while replication fork protection is mechanistically related to HR, it is separate and different from it, and yet another level of genome maintenance, limiting the rate at which S phase DNA damage accumulates.

2.3. Crosstalk and feedback within DNA damage response networks

The BRCA pathway works in a complicated network consisting of DNA damage response components, in this network p53 signaling and FA signaling are important parts to make our genome stable. Between is laid down the concurrency with HR and replication fork protection, two complementary and functionally distinct, yet outcome-related pathways, which both restrain genomic instability clashes.

BRCA proteins and the FA pathway interaction: BRCA proteins and the FA pathway interaction is necessary for resolution of replication-related DNA lesions like interstrand and crosslinks. The main bit of FA like FANCD1/BRCA2, FANCN/PALB2 overlap right onto the BRCA axis and directly control replication stress sensitive RAD51 loading and replication fork stabilization. Breaking down this network messes up good repair and the wholeness of the fork and it leads to making aberrant chromosomal structures.

At the same time, BRCA-dependent p53 signaling control has a certain regulatory function on checkpoint and damage tolerance. Cell cycle regulates progress in response to replication stress. The BRCA loss is cutting this feedback weak, signal multiplying pressure, letting in the damaged ones pass the round. All together they make HR and fork instability more deficient, so genomic instability is much higher and the tumor becomes more vulnerable [12,13].

3. Functions of BRCA1/BRCA2

3.1. Tissue-specific functions of BRCA1/BRCA2

Breast and ovarian cancers have an especially high concentration of pathogenic BRCA1/2 mutations. BRCA1 mutations are more often times related to early-onset breast cancer and triple-negative breast cancer (TNBC), whereas BRCA2 mutations are also significant in cancer predisposition in more heterogeneous subtypes of breast cancer, as well as in pancreatic and prostate cancer. Germline and somatic BRCA1/2 mutations have different characteristics in terms of the lineage distribution, cancer risks, and genetic counseling implications. Mechanistically, germline mutations build a predisposing genomic instability framework throughout vulnerable tissues, whereas somatic mutations are more likely to indicate the selection pressures throughout tumor progression, as they enrich clones with impaired DNA repair function. Moreover, the screening plans and risk levels depend on the population and lineage-specific variations in the frequencies of variants [2,14].

All of these tissue- and lineage-specific patterns may indicate that BRCA-driven cancer predisposition is determined by not just mutation status per se but also by inherent variations in DNA repair needs, proliferative behaviors, and cellular context across tissues, as will be examined in the next section.

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3.2. Tissue-specific mechanisms: endocrine and microenvironmental influences

The fact that BRCA mutations mostly predispose people to breast and ovarian cancers is a question that has not been yet answered. One of these factors is that these tissues are hormone-driven and thus exposing cells to repeated proliferation-differentiation cycles and thus more replication stress and, thus, the chances of DSB formation. BRCA1 represses estrogen receptor alpha (ER-associated transcriptional programs) in an indirect manner, partially via regulation of ER-dependent transcription via ER. BRCA1 loss of function alters this regulatory constraint giving rise to persistent hormonal communication that increases replication stress and a genomic instability condition which aids in malignant transformation [6,15].

Besides endocrine effects, tissue-specific alterations in the expression of the HR cofactors, including RAD51, PALB2, and changes in cellular metabolic conditions are able to alter the effective capacity of the HR pathway. BRCA deficiency could reduce the repair failure threshold in tissues in which HR factor expression or metabolic support of DNA repair is constrained to provide windows of tissue specific vulnerability [14,16]. Hormones signal interactions, DNA repairing and microenvironmental conditions make effect of BRCA damage more powerful therefore it may cause certain part of our body to be continually damaged by gene and turning into cancer.

4. Clinical implications and applications

4.1. BRCA1/2 mutations and cancer risk prediction

Clinical interpretation of BRCA1/2 variants depends on classification systems that divide variants into clearly dangerous, likely pathogenic, or values that need more care, along with the patient's family history, other tumors in the body, and information from working tests. But if one relies solely on sequence based annotation, the function of the VUS's will remain unknown, and this is particularly true for the missense variants which don't make much truncation. To do so, multigene testing and functional stratification methods are needed, like in vitro functional evaluation, deep sequencing and HR deficiency (HRD) scoring to understand how BRCA variants will interact with a patient's cells in real life; they will also help us decide if VUSs should be changed. Using functional evidence, genetic evidence, and clinical context can improve prediction [17].

4.2. Therapeutic sensitivity and resistance mechanisms associated with BRCA deficiency

In case of BRCA deficiencies in tumors they tend to become more sensitive to DNA repair mechanisms, this can be taken as target of intervention as well since it already seems to have a hard time dealing with situations involving replication caused DNA harms. This is due to the deficiency of HR and relying on other less correct repairs [12,13,18]. But when faced with continual selective force, BRCA deficient tumors may acquire some alterations to oppose this shortage.

By restoring a part of the HR capacity, one of the largest resistances is created. Mutations in BRCA1 or BRCA2 that change the open reading frame or restart a reading frame that wasn't open before can make it so second-time mutagenesis doesn't happen, and this shows us that having some ways to relieve stress when copying our DNA make it possible for the second round of making mistakes to not occur, even if there isn't BRCA2- or BRCA1-based repairing programs. Second, another group of resistance mechanisms will not replace HR, they would increase cell survival using another pathway that is different from HR. They stabilize stalled replication forks; they activate

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compensatory repair factors like RAD52; they limit excess DNA damage accumulation in order to maintain an HR deficiency [4,19,20].

Both of these types of adaptive responses highlight the plasticity of the genome maintenance networks within these BRCA-deficient tumors. Where the removal or sustainability of HR is symptomatic and reproducing under DNA damage induction while validate stress adaptations is a way for the cancer body to survive.

4.3. BRCA deficiency, tumor stemness, and recurrence

BRCA deficiencies lead to some kind of stem cell like states where there has been some modification of the way differentiation goes on and a capability to cope or persist for some period with genetic stress. Instead of turning into a stem cell, because constant mistakes in fixing DNA and keeping replication fork going create special conditions where only cells can live and grow whose pliability is better. These sorts of adaptive states are frequently accompanied by epigenetic modification, alternate use of DNA repair channels, plus the ebb and flow with the tumor environment as a whole, and that's what allows it to continue to go on in spite of ongoing, continuous onboard mutations.

As time passes, it is possible that these stress-bearing cells have an impact on the continuation of the tumor, the return of the tumor, and its tendency to spread. Even if this is true, it needs to be in line, the rest of the experimental evidence must be required, more in vivo and in patients must be performed before the cause of BRCA deficiencies is fully understood, the cell has changed, and how many years later a tumor evolved over time.

5. Challenges and perspectives

5.1. Current limitations in research and clinical translation

Although great progress has been made in BRCA studies, many problems still make it difficult for doctors to use this information when helping their patients: First, there is still many aspects about tissues specific type of cancer where the molecular aspects are still unexplored judge from its cancer cells preference in its' treatment for preferably breast and ovary. There are currently no comparative frameworks for cross-tissue; hormonal signaling and chromatin state have yet to be linked to the DNA repair process and BRCA-dependent genome upkeep. So, it is still hard to know which tissue-intrinsic things are making people more or less likely to get sick and which ones are just happening because the tumor got bigger.

Second, the genotype-phenotype information is unbalanced unequally over the populations, it leads to the systematic errors in estimating risks all around the world and screening process. Lastly, there are a lot of VUS and so there is a need to create more functional validation pipelines and methods of scalable annotation that are not completely based on the sequence's predictive power [14,17].

5.2. Future research directions and clinical strategies

The following areas are the priority areas that need to be conducted in the future. To begin with, the single-cell and epigenomic studies together with functional genomics integration will be necessary in order to clarify the impact of the tissue microenvironment and cell lineage conditions on BRCA pathway. These integrative frameworks could be used to elucidate context-specific differences between genome maintenance that result in tissue-specific cancer vulnerability.

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Second, multi-modal therapeutic approaches that act synergistically to target both replication fork protection and second-line repair processes, e.g., RAD52 inhibition, could offer a solution to limit adaptive survival in BRCA-deficient tumors and extend time to resistance.

Third, use scaled deep mutational screens with differing combinations of CRISPR based functional screens provides facilities to deploy systematic ways of sorting variants of uncertain significance and use functional impact in the interpretive domain.

Lastly, also with the increase in the ancestry diverse groups as well as the longitudinal monitoring of the circulating tumor DNA (ctDNA), it is able to pick up the BRCA reversion mutations earlier on and enable the use of adaptive treatment as the disease progresses [8,21].

6. Conclusion

BRCA1 and BRCA2 are major guardians of the genome, and alteration of their functions becomes important action for building tumors with multiple integrated routes. All of the above are defective HR repair, defective stalled replication fork stability and widespread chromatin architecture and transcriptional regulation changes. It's a single path that mutations in BRCA1/BRCA2 don't use—instead they affect many levels of genome maintenance at once. The result of these flaws is continuous genome variations which create a friendly atmosphere for malignant transformation, mainly in a particular tissue environment where regulatory demands and cell structures change from organ to organ.

Review points out DNA repair failure, response to replication stress, tissue restricted regulation, they all meet to generate the BRCA related cancer risk. These overlapping processes account for both the broad effect of BRCA dysfunction on genome integrity as well as the selective sensitivity of certain tissues to cancer development. Researchers could also take advantage of the vulnerabilities present within BRCA defective cells, such as those displayed with Synthetic Lethality techniques; yet because genome preservations networks have the ability to adjust themselves it is challenging for us to achieve desired long term clinical success. Tumors can activate alternative pathways that reduce long-term treatment efficacy.

In the next five years, it will be expected of this field as a combination of functional genomics and epigenetic profiling as well as longitudinal molecular monitoring. Such strategies will be important to understanding how BRCA dysfunction leads to cancer risk that is tissue type-specific. At the end of the day, it's going to make it better when it comes to evaluating cancer risks, detecting them early, and gaining a deeper understanding of how these cancers caused by BRCA come about-this can strengthen the connection between molecular pathologies and targeted cancer care.

References

[1] Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P. A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., Bennett, L. M., & Ding, W. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science, 266(5182), 66–71. https: //doi.org/10.1126/science.7545954

[2] Wooster, R., Bignell, G., Lancaster, J., Swift, S., Seal, S., Mangion, J., Collins, N., Gregory, S., Gumbs, C., & Micklem, G. (1995). Identification of the breast cancer susceptibility gene BRCA2. Nature, 378(6559), 789–792. https: //doi.org/10.1038/378789a0

[3] Powell, S. N., & Kachnic, L. A. (2003). Roles of BRCA1 and BRCA2 in homologous recombination and therapy. Oncogene, 22(37), 5785–5793. https: //doi.org/10.1038/sj.onc.1206678

[4] Foo, T. K., & Xia, B. (2022). BRCA1-dependent and independent recruitment of PALB2–BRCA2–RAD51 in the DNA damage response and cancer. Cancer Research, 82(17), 3191–3197. https: //doi.org/10.1158/0008-5472.CAN-22-1535

DOI: 10.54254/2753-8818/2026.PJ31585

[5] Poorbagher, M. R. M., & Santarosa, M. (2025). Beyond repair: expanding roles of BRCA1 in RNA processing and cancer. Biochimica et Biophysica Acta – Reviews on Cancer, (ahead of print). https: //doi.org/10.1016/j.bbcan.2025.189499
[6] Schlacher, K., Wu, H., & Jasin, M. (2012). A distinct replication fork protection pathway connects Fanconi anemia tumour suppressors to RAD51–BRCA1/2. Cancer Cell, 22(1), 106–116. https: //doi.org/10.1016/j.ccr.2012.05.015
[7] Schlacher, K., Christ, N., Siaud, N., Egashira, A., Wu, H., & Jasin, M. (2011). Double-strand break repair-independent role for BRCA2 in blocking stalled replication fork degradation by MRE11. Cell, 145(4), 529–542. https: //doi.org/10.1016/j.cell.2011.03.041
[8] Xia, B., Sheng, Q., Nakanishi, K., Ohashi, A., Wu, J., Christ, N., Liu, X., Jasin, M., & Livingston, D. M. (2007). Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. Nature Genetics, 39(2), 159–161. https: //doi.org/10.1038/ng1942
[9] Sy, S. M. H., Huen, M. S. Y., & Chen, J. (2009). PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proceedings of the National Academy of Sciences, 106(17), 7155–7160. https: //doi.org/10.1073/pnas.0811159106
[10] Foray, N., Marot, D., Randrianarison, V., Picard, D., Perricaudet, M., Favaudon, V., & Jeggo, P. (2003). A subset of ATM- and ATR-dependent phosphorylation events requires the BRCA1 protein. The EMBO Journal, 22(11), 2860–2871. https: //doi.org/10.1093/emboj/cdg274
[11] Ceppi, I., Dello Stritto, M. R., Mütze, M., Richard, D.-J., Luke, B., & Ceccaldi, R. (2024). Mechanism of BRCA1–BARD1 function in DNA end resection and DNA protection. Nature, 634(7907), 492–500. https: //doi.org/10.1038/s41586-024-06385-1
[12] Farmer, H., McCabe, N., Lord, C. J., Tutt, A. N. J., Johnson, D. A., Richardson, T. B., Santarosa, M., Dillon, K. J., Hickson, I., & Knights, C. (2005). Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature, 434(7035), 917–921. https: //doi.org/10.1038/nature03445
[13] Wang, W. (2007). Emergence of a DNA damage response network involving Fanconi anemia and BRCA proteins. Nature Reviews Genetics, 8(10), 735–748. https: //doi.org/10.1038/nrg2159
[14] Zhang, X., & Li, R. (2018). BRCA1-dependent transcriptional regulation: implication in tissue-specific tumor suppression. Cancers, 10(12), 513. https: //doi.org/10.3390/cancers10120513
[15] Oliver, A. W., Swift, S., Lord, C. J., Ashworth, A., & Pearl, L. H. (2009). Structural basis for recruitment of BRCA2 by PALB2. Nature Structural & Molecular Biology, 16(12), 1231–1234. https: //doi.org/10.1038/nsmb.1688
[16] Rickman, K. A., Noonan, R. J., Lach, F. P., Sridhar, S., Wang, A. T., Abhyankar, A., Huang, A., Kelly, M., Auerbach, A. D., & Smogorzewska, A. (2020). Distinct roles of BRCA2 in replication fork protection in response to hydroxyurea and DNA interstrand cross-links. Genes & Development, 34(13–14), 832–846. https: //doi.org/10.1101/gad.336446.120
[17] Dedes, K. J., Wilkerson, P. M., Wetterskog, D., Ashworth, A., & Lord, C. J. (2011). Synthetic lethality of PARP inhibition in cancers lacking homologous-recombination repair. Cell Cycle, 10(8), 1192–1199. https: //doi.org/10.4161/cc.10.8.15273
[18] Bryant, H. E., Schultz, N., Thomas, H. D., Parker, K. M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N. J., & Helleday, T. (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature, 434(7035), 913–917. https: //doi.org/10.1038/nature03443
[19] Pettitt, S. J., Frankum, J. R., Punta, M., Lise, S., Alexander, J., Chen, Y., Yap, T. A., Haider, S., Tutt, A. N. J., & Lord, C. J. (2020). Clinical BRCA1/2 reversion analysis identifies hotspot mutations and predicted neoantigens associated with therapy resistance. Cancer Discovery, 10(11), 1475–1488. https: //doi.org/10.1158/2159-8290.CD-20-0366
[20] Weigelt, B., Comino-Méndez, I., de Bruijn, I., Tian, L., Meisel, J., Garcia-Murillas, I., Fribbens, C., Cutts, R., Cheang, M. C. U., & Glodzik, D. (2017). Diverse BRCA1 and BRCA2 reversion mutations in therapy-resistant BRCA-mutant cancers. Nature Communications, 8, 15588. https: //doi.org/10.1038/ncomms15588
[21] Bunting, S. F., Callen, E., Kozak, M. L., Kim, J. M., Wong, N., Maizels, N., McKinnon, P. J., Nussenzweig, A., & Nussenzweig, M. (2012). BRCA1 functions independently of homologous recombination in DNA interstrand crosslink repair. Molecular Cell, 46(2), 125–135. https: //doi.org/10.1016/j.molcel.2012.02.015