GEORGETOWN SCIENTIFIC RESEARCH JOURNAL
Volume Three
Edition Two
Spring 2023

Analysis of the Relationship between PARP1 and BRCA1 Suggests PARP1 Gene Has a Role in Breast Cancer

Kush Modi, Tony Joseph

Analysis of the Relationship between PARP1 and BRCA1 Suggests PARP1 Gene Has a Role in Breast Cancer

Kush Modi[1], Tony Joseph[2]

[1]Department of Biology, Georgetown University, Washington, D.C., United States of America
[2]Department of Biology, CUNY Brooklyn College, Brooklyn, NY, United States of America
E-mail: kmm488@georgetown.edu
https://doi.org/10.48091/gsr.v3i2.50

Abstract

Poly [ADP-ribose] polymerase 1 (PARP1), one of the genes in the PARP family, is mainly involved in the detection and repair of DNA damage in cells, and its upregulation has been associated with tumorigenesis. PARP1 is essential to all cells in the body as it ensures that DNA is replicated correctly. The PARP1 protein addresses repair of single-stranded breaks (SSBs) in DNA by initially binding near the point of break in the DNA. While it is bound to the region of the SSB, PARP1 transfers ADP ribosyl moiety from NAD+ to acceptor proteins. This leads to the recruitment of DNA repair proteins to the region of DNA breaks. The PARP1 protein also aids the double-stranded break (DSB) repair of DNA by recruiting the homologous recombination (HR) pathway proteins. Due to this role of PARP1 in DNA repair, it has been associated with cancer growth. Using databases, including UniProt, Xena Browser, and CBioPortal, this article explores the relationship between PARP1 mutations and BRCA1-mutated breast cancer. BRCA1 is a tumor suppressor gene, which is involved in DNA repair through the HR pathway. Therefore, in BRCA1-mutated cells, the lack of tumor suppressor factors leads to cancer growth. However, in a cell that has both BRCA1 mutations and PARP1 inhibition, DNA damage cannot be repaired, leading to apoptosis. Hence, PARP1 inhibitors have become essential in BRCA1-mutated breast cancers. There are several PARP1 inhibitors that are currently being used to treat breast cancer, which work using several mechanisms of action, including PARP1 trapping, which prevents the repair, transcription, and replication of DNA. This article also focuses on the clinical trials of three specific drugs, Olaparib, Iniparib, and Veliparib, which are used to treat breast cancer. However, due to the lack of understanding surrounding PARP1 inhibition mechanisms and potential drug combinations, more research needs to be done to understand potential biomarker targets and PARP1 inhibitor resistance.

Keywords: PARP1, BRCA1, breast cancer, DNA repair, gene expression

1. Introduction

Poly [ADP-ribose] polymerase 1 (PARP1) serves as a first responder enzyme, detecting DNA damage and assisting in the selection of a repair pathway. The enzyme works by interacting with and conformationally altering ADP-ribose units on various DNA repair factors, such as RAD51 and 53BP1, and by performing ADP-ribosylation of histones, which leads to decompaction of chromatin structure. Additionally, it is involved in the regulation of nucleotide excision repair, non-homologous end joining, microhomology-mediated end joining, homologous recombinational repair, and DNA mismatch repair, among other DNA repair pathways (Figure 1).[1,2] The PARP1 enzyme is also involved in single-stranded DNA (ssDNA) repair in cells

(Figure 1). As a result of this function, the repair of ssDNA breaks in cells is slowed when PARP1 levels in the cell are low or when PARP1 activity is inhibited by small molecules. When ssDNA breaks occur during DNA replication in the absence of PARP1, the replication fork pauses, resulting in the accumulation of single-strand DNA (ssDNA) breaks.[3] Homologous recombination (HR) repair, a potentially error-free repair mechanism, is used to mend these ssDNA breaks (SSBs). As a result, PARP1-deficient cells exhibit a hyper-recombinogenic phenotype, or an increased frequency of HR.[3]

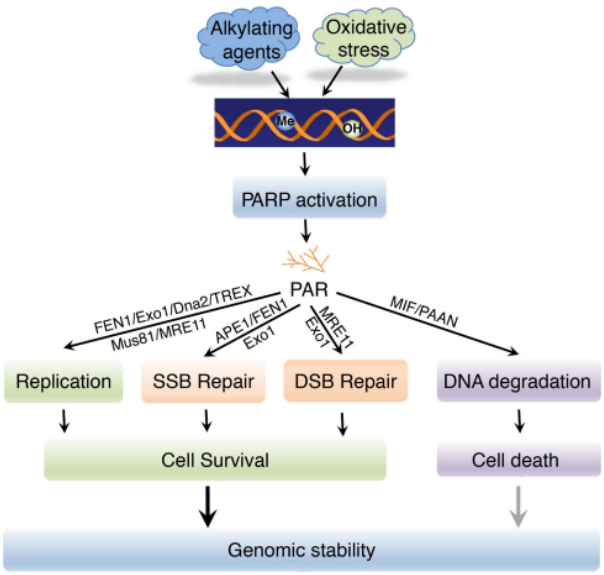

Figure 1. In the presence of DNA damage, PARP1 is activated which leads to ADP-ribosylation. This process will either lead to replication, SSB repair, DSB repair, or will lead to cell death.[2]

PARP1 transfers the ADP-ribosyl moiety from NAD+ to acceptor proteins after binding to SSBs, resulting in lengthy chains of polyADP-ribosylated (PARylated) polymers. This permits DNA repair proteins like DNA polymerase, DNA ligase III, and scaffolding proteins like XRCC1 to be recruited to SSB sites. PARP1 has been demonstrated to interact with the DNA dependent protein kinase complex involved in non-homologous end-joining and may also facilitate homologous recombination by recruiting components like ATM, Mre11, and Nbs1 to regions of double-stranded DNA damage.[4]

As mentioned before, PARP1 is required for single-strand break repair. PARP1 is also considered to be essential for base excision repair (BER), as various investigations have suggested, because single-strand breaks are also formed as an intermediary of BER.[5] However, evidence demonstrating the sensitivity of PARP1-defective or PARP1-inhibited cells to drugs that cause base damage is conflicting. Another study discovered that while PARP1 was not necessary to repair base damage, it was essential to repair single-strand breaks caused by hydrogen peroxide. There is also evidence that PARP1-dependent and PARP1-independent SSBR pathways exist, with one study finding that PARP1 is essential for SSBR in the G1 but not the S phase of the cell cycle.[1] PARP1i, on the other hand, inhibits SSBR at all stages of the cell cycle.[3] DNA repair pathways are promoted by PARP1, including the HR pathway. However, the inhibition of PARP1 can lead to cancer suppression, namely in breast cancers associated with BRCA1 mutations.

This paper aims to provide a meta-analysis on the existing literature as well as genomic data from databases regarding PARP1 to find a possible correlation between the expression of the PARP1 gene and BRCA1 mutations, specifically in breast cancer.

Multiple tools and databases, specifically UniProt database, CBioPortal, and Xena Browser, were used to determine such relationships. These are open-access databases, making them accessible for public research. Specifically, these databases hold genomic data, mutation profiles, and clinical data. UniProt database was used to investigate the mechanism by which PARP1 repairs the breaks in DNA strands and how PARP1 inhibitors can be used to inhibit this function of the PARP1 protein. CbioPortal was used to investigate the alteration frequencies of the PARP1 gene in different types of cancers, which helps to understand the relationship between the PARP1 gene and breast cancers. The database was also used to investigate

which tissues had the highest expression levels of the PARP1 gene. Xena Browser was used to find the extent of the role of PARP1 in the prognosis of patients with breast cancer. Using the information and results obtained from these databases, the paper further details the role of the PARP1 gene in breast cancer and establishes a relationship between BRCA1 mutations and PARP1 inhibition.

An overview of the PARP1 gene and protein was split into six parts for this study: the catalytic domain, mutation profile, copy number, gene expression in tissues, its relevance to breast cancer, and PARP1 inhibition.

2. Catalytic Domain

The UniProt database shows the catalytic domain of PARP1 (Figure 2), which is crucial because of its role during the process of PAR synthesis that is involved in DNA repair.[6] The catalytic domain is involved in the creation of the ribose-ribose glycosidic bond and of a ribose-ribose bond that allows for elongation and branching in DNA repair.

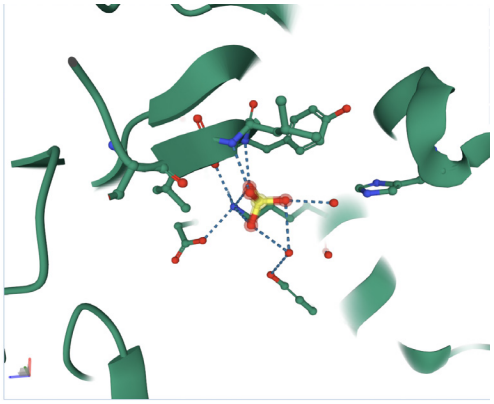

Figure 2. The catalytic domain of PARP1 protein is where the catalysis of three chemically different enzymatic reactions during PAR synthesis occurs. Retrieved from UniProt Database.[6]

When the PARP1 gene is stimulated by DNA damage, the C- terminal domain starts to synthesize, through the catalysis of NAD+, chains of polyADP-ribose (PAR) fanned chains (Figure 2). Numerous inhibitors can tie PARP1 in a direction looking like that of its substrate NAD+ and lock the catalytic site. The C-terminal region, otherwise known as the active site, contains the area that allows PARP1 to restrict NAD+ and competitive inhibitors. For example, nicotinamide, 3-amino benzamide, and 3-methoxy benzamide manipulate the PARP1gene in certain targeted therapies.

3. Mutation Profile

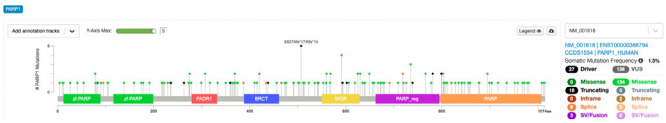

Figure 3. Diagram of all mutations that occur within the PARP1 gene. A majority of the mutations were missense mutations with a frequency of 134. Mutations are evenly spread through all parts of the PARP1 genome. In total, 163 individual data points were used to compile the diagram. Retrieved from CBioPortal Database.[7]

An analysis of the CBioPortal Database showed the mutation profile in Figure 3, which suggests that a majority of mutations in the PARP1 gene are missense mutations, as seen by the green lines.[7] However, the mutations are dispersed throughout, and there is no single, major peak seen that is significant enough to show that a specific region on the gene is more susceptible to mutations. In addition, it is seen that most of the mutations are characterized as a Variant of Uncertain Significance (VUS). This means that there is an alteration in the PARP1 gene, but researchers have not yet found out whether the change is harmless or increases the risk of developing cancer. There are 27 mutations that are categorized as driver mutations that bolster the development of cancer.[7] However, since a relatively large number of mutations are VUS, more research needs to be done in order to determine whether the mutations in the PARP1 gene are directly linked to the development of cancer.

4. Copy Number

As shown through the CBioPortal Database, PARP1 has more instances of amplification instead of deep deletion and shallow deletion (Figure 4).[7] Deep deletions refer to possible homozygous deletions, while shallow deletions refer to possible heterozygous deletions. Increase in PARP1 transcript and protein expression are characteristics of high-grade astrocytomas, particularly of Proneural and Classical Glioblastoma (GBM) subtypes.[8]

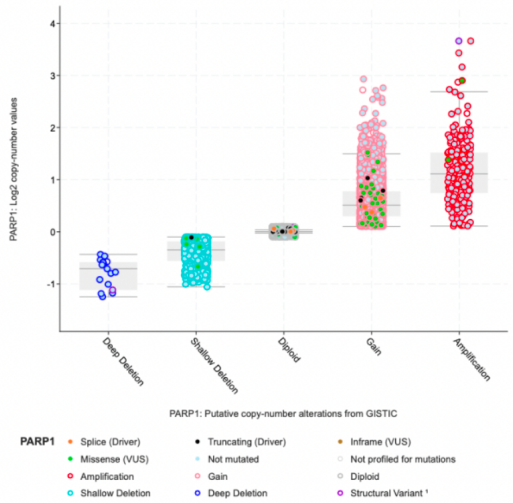

Figure 4. Diagram of all mutations that occur within the PARP1 gene, with a majority of mutations being missense mutations. Values compared are the type of copy number alterations and the frequency of each alteration. Amplification alterations showed the highest copy number value of the PARP1 gene. Deep deletion copy number alteration showed the lowest copy number value of the PARP1 gene. Retrieved from CBioPortal Database.[7]

5. Gene Expression in Normal versus Cancer Tissues

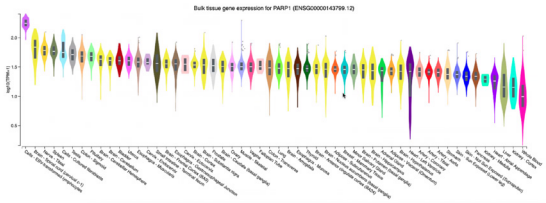

Figure 5. Violin plot of types of cells from different tissues and the frequency of PARP1 expression. Cells with EBV-transformed lymphocytes showed the highest bulk tissue gene expression for PARP1. However, most bulk tissues showed similar levels of gene expression. Retrieved from CBioPortal Database.[7]

Gene expression data in Figure 5 indicate that the PARP1 gene is normally expressed the most in EBV-transformed lymphocytes and in lymph nodes.[7] Epstein Barr Virus (EBV) is a double stranded DNA virus that is part of the herpes family. EBV has been linked to cancers such as nasopharyngeal cancer and fast-growing lymphomas due to its role in creating B-cell lymphoproliferations.[9] The high PARP1 expression levels in EBV-transformed lymphocytes, which are involved in cancers, corroborates PARP1's potential link to certain types of cancers.[10]

As shown in Figure 6, PARP1 mRNA expression is elevated in human primary cancers of the breast, endometrium, lung, ovary, and skin.[11]

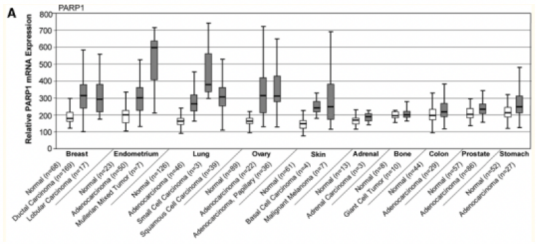

Figure 6. A boxplot analysis of Reads Per Kilobase of transcript per Million mapped reads (RPKM) of PARP1 in normal tissues compared to cancer tissues. The mRNA expressions of PARP1 are observed to be of similar levels in histologically normal tissues. Breast, endometrium, lung, ovary, and skin cancer all show elevated levels of PARP1 mRNA expression with high variability compared to their respective normal tissue mRNA expression. Retrieved from Valeria Ossovskaya and her research team.[11]

6. Relevance to Breast Cancer

BRCA1 is a tumor suppressor gene that produces proteins that help repair double-stranded DNA breaks and interstrand crosslinks through a homologous recombination pathway. BRCA1 also

plays a role in protein ubiquitination, chromatin remodeling, and transcriptional regulation.[12] It is well-known to be mutated in familial breast cancers and ovarian cancers.

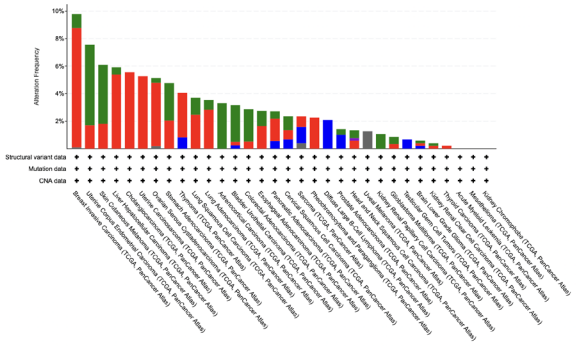

Figure 7. Diagram of the alteration frequencies of PARP1 gene in different types of carcinomas. Green represents mutations, purple represents a structural variant, red represents amplification, blue represents deep deletion, and grey represents multiple alterations. Breast invasive carcinoma showed the highest alteration frequency of the PARP1 genome at approximately 10%. A majority of the alterations across tissues was observed to be amplification. Retrieved from CBioPortal Database.[7]

Figure 7 shows that there is 9% amplification and 1% mutation in the PARP1 gene in breast invasive cancer.[7] The alteration frequency of the PARP1 gene is highest in breast-invasive carcinoma (Figure 7), which supports the significance of exploring the link between BRCA1 mutations and PARP1 in the development of breast cancer.

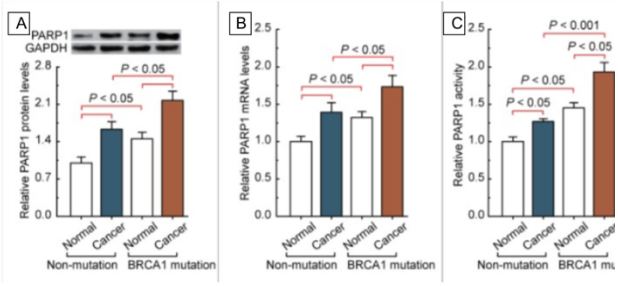

Figure 8. BRCA1-mutated breast cancer tissues showed significantly greater PARP1 levels and activity compared to the non-BRCA1-mutated breast cancer tissues and normal tissues. Blue bars represent non-BRCA1-mutated breast cancer tissues. Brown bars represent BRCA1-mutated breast cancer tissues. White bars represent normal tissues with or without BRCA1-mutations. 41 pairs of non-mutated and BRCA1-mutated cancer and normal tissues were used. The bar graphs show mean ± SD. A. Diagram of the relative PARP1 protein levels. B. Relative PARP1 mRNA levels. C. Relative PARP1 activity in normal and cancer tissues. Retrieved from Li and her research team.[13]

As seen in Figure 8.A, which compares relative PARP1 protein levels and the presence of BRCA1 mutations, PARP1 protein levels are higher in normal tissues with BRCA1 mutation compared to normal tissues without BRCA1 mutations.[13] More importantly, PARP1 protein levels are higher in cancer tissues with BRCA1 mutations than cancer tissues without BRCA1 mutations. Consistent with the data that was suggested in Figure 8.A, Figure 8.B demonstrates that relative PARP1 mRNA levels are greater in tissues with BRCA1 mutations than those without.[13] Figure 8.C, which shows relative PARP1 activity, suggests that PARP1 activity levels are significantly higher in BRCA-mutated tissues than in tissues without the BRCA1 mutations.[13]

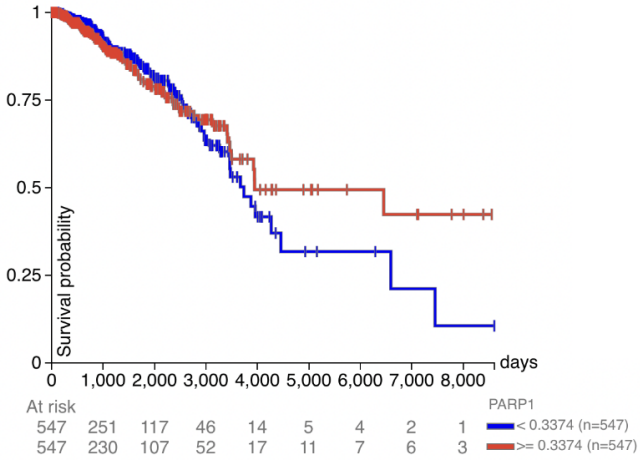

Figure 9. Diagram of the Kaplan Meier plot for breast cancer patients after the germline cells are removed. As shown in the diagram, the red line shows patients with copy numbers of PARP1 greater than or equal to 0.3374 and the blue line shows patients with copy numbers fewer than

0.3374. A total of 1094 patients were used in the study. Retrieved from Xena Browser Database.[14]

Figure 9 displays the difference in overall survival of patients with high copy numbers of PARP1 and low copy numbers of PARP1.[14] The difference in overall survival is not significant (p = 0.86).[14] This indicates that the PARP1 copy number does not affect the overall survival of breast cancer patients.

The results specifically highlight the positive relationship between the PARP1 gene and the BRCA1 mutations in cells, which further explains the onset of breast cancer.

BRCA1 performs DSB repair through the homologous recombination (HR) pathway. However, mutations in the BRCA1 gene, such as in breast and ovarian cancer, can cause a decrease in BRCA1 levels due to a disruption in the HR pathway. This results in an increase in intracellular NAD levels which, in turn, causes an increase in PARP expression and activity.[15] This increase helps to repair DNA damage with the help of PARPs. As NAD is consumed, its intracellular quantity falls, which further inhibits BRCA1 expression. This increases the reliance on PARP1 in cells to repair damaged DNA DSBs.[16] Thus, targeting PARP1 and inhibiting its activity can prevent cancer cells with BRCA1 mutations from repairing damaged DNA, resulting in cell apoptosis.

The results seen in Figure 8 suggest that PARP1 presence in cells is, in general, higher in tissues with BRCA1 mutations and in cancer tissues. This provides significant evidence that PARP1 plays an important role in the onset of BRCA1-mutated breast cancers. This result collaborates with that of Figure 6, which shows that breast cancer has high PARP1 mRNA expression within its cells, establishing the relationship between BRCA1 and PARP1 genomes.

These results fit with our understanding of the function of PARP1 and BRCA1 genes as both are involved in DNA repair, a function that carcinogenic cells aim to manipulate.[11] As a result, it is common to see that both PARP1 and BRCA1 mutations lead to cancer.

More specifically, the PARP1 gene has a positive correlational relationship with BRCA1 in terms of invasive breast cancer development. Figure 7 suggests that amplification, which is an increase in the number of copies of a gene, plays a more significant role in the development of breast invasive cancer than PARP1 mutations. This amplification increases the activity of the PARP1 gene, thus increasing the repair of damaged DNA allowing the cancer cell to divide quickly. This prevents cell apoptosis and allows the tumor to proliferate and grow.

7. PARP1 Inhibition Mechanism

Due to the well-established role of the PARP1 gene in the development of cancer, researchers have attempted to inhibit the activity of the gene in certain cells, primarily BRCA1-mutated cells. One of the main targeted therapies that affect the role of PARP enzymes in DNA repair is the PARP inhibitor.[17] In general, these PARP inhibitors block off the PARP enzymes and restrict them from repairing the SSBs and DSBs in cancer cells.[17] This eventually leads to apoptosis of the cancer cells, as shown in Figure 10.[17]

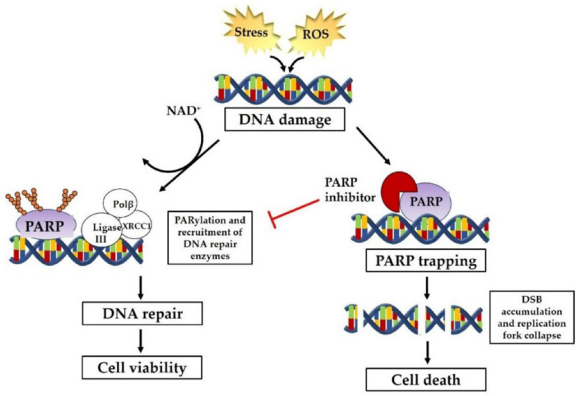

Figure 10. The mechanism of action by which the PARP inhibitor prevents DNA repair and induces cell death. Retrieved from Keung and his research team.[17]

The mechanism of action by which the PARP1 inhibitors work is yet to be fully

understood, and although several theories explaining the therapy's machinery have become known, there is yet to be a consensus reached. [17]

PARP1 inhibitors work by inducing synthetic lethality, which is a condition where two independent factors that would not usually cause cell death become lethal when they occur together.[1] In this case, synthetic lethality is caused by the presence of BRCA1 mutations and the action of PARP1 inhibitors. PARP1 inhibitors prevent the PARP1 enzymes from repairing the DNA, which causes the cells to rely on the HR pathway for addressing the defects in DNA.[18] However, in BRCA1 mutated cells, the HR pathway is defective, and hence the DNA cannot be repaired. This leads to cell apoptosis.[18] This specific mechanism of synthetic lethality allows the PARP1 inhibitors to target the tumor cells only. Normal cells would have the HR pathway to repair any DNA defects even if the PARP1 enzymes are inhibited by the PARP1 inhibitor, so they would survive. The PARP1 enzymes, as mentioned before, are known for their action in single-strand break repair (SSBR).[18] The inhibition of these enzymes by the PARP inhibitor can lead to an accumulation of DNA damage in the tumor cell and induce synthetic lethality.[18]

Another proposed mechanism of action of the PARP1 inhibitor is known as PARP1 trapping and explains why the cytotoxic effects of PARP1 inhibitors are evidently greater than not having any PARP1 protein in the cell. The binding of the PARP1 inhibitors to the active site keeps the PARP1 and PARP2 enzymes trapped on the DNA, preventing the utilization of NAD+ and the process of PARylation, a post-translational protein modification that recruits DNA repair factors, as seen in Figure 10.[17,19] PARP1 trapping results in DNA lesions, which leads to DSBs and stalling of replication forks, which can be lethal in HR deficient tumors, such as BRCA1 mutation tumors.[19]

In addition to the action of PARP1 in DNA repair, the enzyme is also involved in the transcription of certain proteins through chromatin structure regulation and histone PARylation.[20] PARP1 is specifically involved in the transcription of proteins involved in cancer development, such as P53 and NF-κB.[20] The inhibition of the transcription of certain oncogenes caused by PARP1 inhibitors can prevent cell proliferation and lead to cell apoptosis.

8. PARP1 Inhibitors and Synergy Compounds

The current generation of PARP1 inhibitors is the third one, and the drugs being developed are mainly those that restrict PARP1 enzymes. This generation of PARP1 inhibitors is considered to be more potent and more specific than those from previous generations. The first generation of PARP1 inhibitors were nicotinamide analogs, whose ability to inhibit PARP1 was discovered as early as 1971.[1] The third generation of these inhibitors, which is currently under development, have shown the greatest efficacy and fewest off-target effects to date. [1]

The PARP1 inhibitors that are present clinically today vary in their ability to trap the PARP enzymes. The ability of the PARP inhibitors to trap PARP from most to least able is Talazoparib, followed by Niraparib, followed by Olaparib and Rucaparib (which are roughly equal in ability), followed by Veliparib which is the least potent and is inactive even at 100 μM.[21] This difference in potency can be seen mainly due to the differences in structure with Veliparib being a simpler molecule with a molecular weight of 244 g/mol, while talazoparib is a much more rigid molecule with two racemic centers.[21]

Using PARP1 inhibitors in combination with other therapies is essential in lowering the dosage of the PARP1 inhibitors and increasing the effectiveness of the drugs. PARP1 inhibitors are often combined in treatment with alkylating agents (cytotoxic chemotherapies).[1] The alkylating agents work by joining an additional alkyl group to DNA, which results in DNA damage. This prevents the tumor cells from replicating, resulting in cell death.[1] However, these chemotherapies have adverse side effects and can result in acquired

mutations, causing chemoresistance.[1] This calls for a combination of PARP1 inhibitors and chemotherapies. In the Phase III VELIA trial, in which the PARP1 inhibitor, Veliparib, was used in combination with chemotherapy for the treatment of stage III or IV high-grade serous ovarian cancer, Veliparib showed positive results for Progression Free Survival (PFS).[22] Another study, the phase III BROCADE3 trial, showed that when Veliparib was combined with Carboplatin and Placitaxel (chemotherapy drugs) to treat HER2-negative and BRCA-mutated breast cancer, it resulted in 34% of patients not seeing tumor progression at 24 months compared to 20% of patients that took Carboplatin and Placitaxel only.[22] Another alkylating agent, Temozolomide, works by adding methyl groups to specific sites on the DNA molecule, which leads to single-strand breaks (SSBs).[23] These SSBs then require the PARP1 enzymes to repair the damage to the DNA, but PARP1 inhibitors would trap the PARP1 in its presence.[23] Preclinical studies have suggested that Talazoparib and Olaparib in combination with Temozolomide has a positive synergistic effect.[23]

PARP1 inhibitors and radiation therapies are also beginning to be used in combination to improve efficacy. Researchers believe that PARP1 inhibitors prevent single-strand breaks caused by radiation to be repaired.[1] This leads to replication fork collapse and double-strand breaks, which damages the DNA completely.[1] However, no clinical trials yet have proven the effectiveness of the PARP1 inhibitor in sensitizing tumor cells to radiation.

Phosphoinositide 3-kinases (PI3k) inhibitors, which inhibit a group of enzymes that are involved in tumor proliferation and growth, are also said to be more effective in combination with the PARP inhibitors.[1] The combination of the PI3k inhibitor, Buparlisib, and PARP inhibitor, Olaparib, to treat cellular ovarian cancer showed significant inhibition of tumor progression and disease proliferation.[24]

WEE1 kinase inhibitor, which inhibits WEE1 kinases that regulate the G2-M cell cycle checkpoint, is another potential drug to be used in combination with PARP inhibitors.[1] WEE1 kinase is an enzyme that, when inhibited, results in large magnitudes of genomic instability and eventual cell death.[1] Some studies have even shown that a combination of WEE1 inhibitor and PARP1 inhibitor reduces off-target toxicity and increases the tumor cell's sensitivity to radiation.[1]

However, there has also been some resistance recorded to PARP1 inhibitors. BRCA1 deficiency in tumor cells can be reversed through crossovers or mutations to form the wild-type BRCA proteins.[25] This means that the HR pathway is not defective anymore, and thus there is no synthetic lethality in the cancer cells in the presence of PARP1 inhibitors. Another mechanism of PARP1 resistance is the upregulation of p-glycoprotein efflux pump, which pumps foreign molecules out of the cell.[25] This reduces the concentration of PARP1 inhibitors present inside the cancer cell, thereby increasing resistance.

Iniparib or BSI 201 by Sanofi-Aventis is another drug that has gained some momentum from its clinical data. It is a drug that has a half-life of 4 minutes, after which it breaks down into an active metabolite.[26] In a Phase I trial, where BSI 201 was administered as a single agent to solid tumors, the 2.8 mg/kg dose showed approximately 50% PARP1 inhibition, and further doses increased the inhibition to around 80%.[26] In addition, there were no serious side effects observed and stable disease (SD) was seen in 6 out of 23 patients.[26] In another Phase I trial, where BSI 201 was combined with taxol and administered, positive results were seen.[26] One patient of ovarian cancer showed complete response (CR) for six months, and partial response (PR) was seen in five patients with renal cancer, uterine cancer, breast cancer, or sarcoma.[26] Another Phase II combination clinical trial was conducted where 116 patients with Triple Negative Breast Cancer (TNBC) were randomly placed into one of the two groups: Gemcitabine with Carboplatin or Gemcitabine with Carboplatin and Iniparib.[26] The median clinical benefit rate of 55.7% and median

progression free survival (PFS) of 5.9 months was observed with the Iniparib arm group compared to 33.9% and 3.6 months with the Carboplatin arm group.[26] These positive results pushed for a Phase III trial with Iniparib as a potential drug to treat TNBC.

Olaparib is another PARP1 inhibitor that has been part of many clinical trials and is known to be effective in ovarian and breast cancers with BRCA mutations.

Olaparib binds to PARP1's catalytic domain and traps it on damaged DNA sites, preventing it from repairing the DNA molecule.[26] In a phase I trial, 50 ovarian cancer patients were given Olaparib as a single agent, out of which 20 patients had complete or partial response and 3 had stable disease (SD) for longer than 4 months.[26] There were also some mild side effects observed, including gastrointestinal upset and fatigue.[26]

However, Olaparib is less effective in cancers that do not have BRCA mutations. This was shown by a clinical trial where 55 patients with High Grade Serous Ovarian Cancer (HGSOC), regardless of BRCA status, were given 400 mg doses of Olaparib as a single agent.[26] Partial responses were seen in 14 patients.[26] 7 patients in the study had BRCA mutations and 3 of them had a response, putting the response rate at 43%.[26] Forty-six patients from the study did not have BRCA mutations, out of which 11 had a response, putting the response rate at 23.9%.[26] This indicates that, although Olaparib was effective regardless of BRCA integrity, it is more effective in tumors with BRCA mutations. Olaparib was also combined with Paclitaxel in a Phase I and II study on 19 TNBC patients.[26] 200mg of Olaparib was administered daily and 90 mg/m^2 of Paclitaxel was given for 3 out of 4 weeks.[26] 37% of the patients reported partial response, although there was neutropenia observed in patients.[26] More clinical studies have shown that the combination of Olaparib and chemotherapy drugs leads to myelosuppression, and more clinical research needs to be carried out to determine whether the lower dose of chemotherapy with PARP1 inhibitors is more advantageous than a higher dose of chemotherapy.

From the results, the relationship between PARP1 and BRCA1 mutations were depicted more clearly. It was shown that PARP1 presence was greater in cancer cells, more specifically breast cancer cells, than other cells. This suggests the role that PARP1 may play in the development of cancer. Another significant finding from this study was that PARP1 amplification plays a greater role in the development of breast invasive carcinoma than PARP1 mutations.

9. Conclusion

PARP1 plays a significant role in several cellular processes, including transcription and DNA repair. Research on their contribution to the development of tumors led to the discovery of PARP1 inhibitors, which have proven effective in treating certain types of cancers. Several clinical and preclinical trials have also suggested that these PARP1 inhibitors may be more effective in combination with specific types of drugs. The clinical relevance of PARP1 inhibitors remains clear. However, more research needs to be done in order to thoroughly understand the mechanism of action of both PARP1 inhibitors and therapy resistance. Furthermore, additional research has the potential to increase the benefit that PARP1 inhibitors provide to patients.

Acknowledgements

We thank Dr. Jagath Reddy Junutula, PhD and Dr. Meenakshi Vengarai, PhD for providing continued support and mentoring throughout this research. We also extend our gratitude to the Science Gurus team for providing us the opportunity to learn and perform this research under their guidance. Lastly, we would like to acknowledge the 2021 Cell Science Gurus interns.

References

1. Rose, M., Burgess, J. T., O'Byrne, K., Richard, D. J., & Bolderson, E. (2020). PARP inhibitors: Clinical relevance, mechanisms of action and tumor resistance. *Frontiers in Cell and*

Developmental Biology, *8*. https://doi.org/10.3389/fcell.2020.564601
2. Wang, Y., Luo, W., & Wang, Y. (2019). PARP-1 and its associated nucleases in DNA damage response. *DNA Repair*, *81*, 102651. https://doi.org/10.1016/j.dnarep.2019.102651
3. Alemasova, E. E., & Lavrik, O. I. (2019). Poly(ADP-ribosyl)ation by parp1: Reaction mechanism and regulatory proteins. *Nucleic Acids Research*, *47*(8), 3811–3827. https://doi.org/10.1093/nar/gkz120
4. Rosado, M. M., Bennici, E., Novelli, F., & Pioli, C. (2013). Beyond DNA repair, the immunological role of PARP-1 and its siblings. *Immunology*, *139*(4), 428–437. https://doi.org/10.1111/imm.12099
5. Ko, H. L., & Ren, E. C. (2012). Functional aspects of PARP1 in DNA repair and transcription. *Biomolecules*, *2*(4), 524–548. https://doi.org/10.3390/biom2040524
6. UniProt Consortium European Bioinformatics Institute Protein Information Resource SIB Swiss Institute of Bioinformatics. (2022, May 25). *Poly [ADP-ribose] polymerase 1.* https://www.uniprot.org/uniprot/P09874
7. cBioPortal for Cancer Genomics. (n.d.). *TCGA PanCancer Atlas Studies.* https://www.cbioportal.org/results/mutations?case_set_id=all&gene_list=PARP1&cancer_study_list=5c8a7d55e4b046111fee2296
8. Murnyák, B., Kouhsari, M. C., Hershkovitch, R., Kálmán, B., Marko-Varga, G., Klekner, Á., & Hortobágyi, T. (2017). Parp1 expression and its correlation with survival is tumour molecular subtype dependent in glioblastoma. *Oncotarget*, *8*(28), 46348–46362. https://doi.org/10.18632/oncotarget.18013
9. Ayee, R., Ofori, M. E. O., Wright, E., & Quaye, O. (2020). Epstein Barr virus associated lymphomas and epithelia cancers in humans. *Journal of Cancer, 11*(7), 1737-1750. https://doi.org/10.7150/jca.37282
10. Rosado, M. M., Bennici, E., Novelli, F., & Pioli, C. (2013). Beyond DNA repair, the immunological role of PARP-1 and its siblings. *Immunology*, *139*(4), 428–437. https://doi.org/10.1111/imm.12099
11. Ossovskaya, V., Koo, I. C., Kaldjian, E. P., Alvares, C., & Sherman, B. M. (2010). Upregulation of poly (ADP-ribose) polymerase-1 (PARP1) in triple-negative breast cancer and other primary human tumor types. *Genes & Cancer*, *1*(8), 812–821. https://doi.org/10.1177/1947601910383418
12. Wu, J., Lu, L. Y., & Yu, X. (2010). The role of BRCA1 in DNA damage response. *Protein & Cell*, *1*(2), 117–123. https://doi.org/10.1007/s13238-010-0010-5
13. Li, D., Bi, F.-F., Chen, N.-N., Cao, J.-M., Sun, W.-P., Zhou, Y.-M., Li, C.-Y., & Yang, Q. (2014). A novel crosstalk between BRCA1 and poly (ADP-ribose) polymerase 1 in breast cancer. *Cell Cycle*, *13*(21), 3442–3449. https://doi.org/10.4161/15384101.2014.956507
14. UCSC, UCSC Genomics Institute, UCSC Computational Genomics Laboratory, & UCSC Xena. (n.d.). *Xena functional genomics explorer.* University of California Santa Cruz. https://xenabrowser.net/heatmap/
15. Hurtado-Bagès, S., Knobloch, G., Ladurner, A. G., & Buschbeck, M. (2020). The taming of PARP1 and its impact on NAD+ metabolism. *Molecular Metabolism*, *38*, 100950. https://doi.org/10.1016/j.molmet.2020.01.014
16. Zhang, D., Hu, X., Li, J., et al. (2019). DNA damage-induced PARP1 activation confers cardiomyocyte dysfunction through NAD+ depletion in experimental atrial fibrillation. *Nature Communications*, *10,* 1307. https://doi.org/10.1038/s41467-019-09014-2
17. Keung, M., Wu, Y., & Vadgama, J. (2019). PARP inhibitors as a therapeutic agent for homologous recombination deficiency in breast cancers. *Journal of Clinical Medicine*, *8*(4), 435. https://doi.org/10.3390/jcm8040435
18. Helleday T. (2011). The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Molecular Oncology, 5*(4), 387–393. https://doi.org/10.1016/j.molonc.2011.07.001
19. Shen, Y., Aoyagi-Scharber, M., & Wang, B. (2015). Trapping Poly(ADP-Ribose) Polymerase. *The Journal of Pharmacology and Experimental Therapeutics, 353*(3), 446–457. https://doi.org/10.1124/jpet.114.222448
20. Luo, X., & Kraus, W. L. (2012). On PAR with PARP: cellular stress signaling through poly(ADP-ribose) and PARP-1. *Genes &*

Development, 26(5), 417–432. https://doi.org/10.1101/gad.183509.111
21. Pommier, Y., O'Connor, M. J., & de Bono, J. (2016). Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. *Science Translational Medicine*, *8*(362), 362ps17. https://doi.org/10.1126/scitranslmed.aaf9246
22. Diéras, V., Han, H. S., Kaufman, B., Wildiers, H., Friedlander, M., Ayoub, J. P., Puhalla, S. L., Bondarenko, I., Campone, M., Jakobsen, E. H., Jalving, M., Oprean, C., Palácová, M., Park, Y. H., Shparyk, Y., Yañez, E., Khandelwal, N., Kundu, M. G., Dudley, M., Ratajczak, C. K., … Arun, B. K. (2020). Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet. Oncology*, *21*(10), 1269–1282. https://doi.org/10.1016/S1470-2045(20)30447-2
23. Zhang, J., Stevens, M. F., & Bradshaw, T. D. (2012). Temozolomide: mechanisms of action, repair and resistance. *Current Molecular Pharmacology, 5*(1), 102–114. https://doi.org/10.2174/1874467211205010102
24. Wang, D., Li, C., Zhang, Y., Wang, M., Jiang, N., Xiang, L., Li, T., Roberts, T. M., Zhao, J. J., Cheng, H., & Liu, P. (2016). Combined inhibition of PI3K and PARP is effective in the treatment of ovarian cancer cells with wild-type PIK3CA genes. *Gynecologic Oncology, 142*(3), 548–556. https://doi.org/10.1016/j.ygyno.2016.07.092
25. Mweempwa, A., & Wilson, M. K. (2019). Mechanisms of resistance to PARP inhibitors - an evolving challenge in oncology. *Cancer Drug Resistance (Alhambra, Calif.)*, *2*(3), 608–617. https://doi.org/10.20517/cdr.2019.50
26. Chen A. (2011). PARP inhibitors: Its role in treatment of cancer. *Chinese Journal of Cancer*, *30*(7), 463–471. https://doi.org/10.5732/cjc.011.1011

GSR Journal

Georgetown Scientific Research Journal