[Frontiers In Bioscience, Scholar, 9, 343-356, June 1, 2017]

Poly(ADP-Ribose) polymerase 1: a therapeutic hope in gynecologic cancers

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1. ABSTRACT

The Poly(ADP-ribose) polymerase-1 (PARP1) is a multifunctional nuclear protein involved in a variety of cellular functions. Recently, its role in the onset, progression and therapy resistance of cancers in general and reproductive cancers in particular has been recognised. The PARP associated signaling is perceived to play a key role in the development, sustenance and relapse of reproductive cancers. This has led to the preclinical and clinical assessment of PARP inhibitors as targeted therapeutic agents in reproductive cancers. In the first part of this review, we have summarized the current status of PARP in the onset, progression and therapy resistance of reproductive cancers. In the second part of the review, we have discussed the translational applications of PARP inhibitors, underscoring the perceived therapeutic opportunities, bottlenecks and the utility of the ongoing clinical trials.

2. INTRODUCTION

The increase in the incidence of reproductive cancers in recent times is associated with the changes in lifestyle, diet and environment. Reproductive cancers start in the male and female reproductive organs and often acquire aggressive and metastatic attributes. Besides lower quality of life and mortality, infertility is also a major issue associated with reproductive cancers. Among the female reproductive cancers breast, ovarian, cervical and endometrial are more common while the vaginal, fallopian and choriocarcinomas are rare but have registered increased incidence in the last decade. Breast cancer is the leading cause of cancer deaths while cervical cancer is the third most common reproductive cancer among females. The mortality: incidence ratio for cervical cancer is 52 percent whereas it reaches 26 percent for endometrial and 62 percent for ovarian cancer (1). Prostate cancer has

second highest incidence and ranks fifth in mortality rate worldwide, while it is third major cancer causing death in developed countries. Incidence of testicular cancer is relatively lower and is commonly diagnosed in patients of 20–35 years of age. In reproductive cancers the clinical and pathological features are distinct in germline and sporadic types as the gene specific mutations are varied. Although early diagnosis and therapeutic options have vastly improved, the prognosis of majority of these cancers remains poor. According to an International Agency for Research on Cancer survey, the annual increase in new cancers cases in the last decade was 14.1 million with 8.2 million deaths. The expected increment in these cases by 2030 is projected at a staggering 21.7 and 13.0 million respectively. Thus it is imperative to understand the mechanisms of cancer onset, progression and relapse and identify critical regulators of oncogenesis for devising improved therapeutic strategies.

3. ETIOLOGY AND GENETICS OF REPRODUCTIVE CANCERS

3.1. Breast cancer

In majority of cases inheritance of mutations in two vulnerable genes is responsible for breast cancer progression. Around 10 percent of all reported cases of breast cancer are due to germline mutations in the BRCA1/2 genes. Among diverse subtypes, invasive ductal carcinoma represents 80 percent of all invasive breast cancers, which is further sub-classified into three categories based on the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal receptor 2 (HER2). Another subtype known for high chemoresistance is the triple negative breast cancers (TNBCs), lacking expression of all the three hormonal receptors. Sporadic, BRCA1/BRCA2 deficient tumors display different gene expression profiles and hormone receptors compared to that of the BRCA1 deficient tumors which are primarily hormone receptor negative tumors. Mutations in the BRCA1 gene leads to the activation of stress related genes like MSH2 (involved in DNA repair) and PDCD5 (involved in apoptosis). For BRCA2 negative patients, increased expression of cyclin D1 was observed compared to that of the BRCA1 mutations. Thus, such differential expression of certain set of genes is used to identify subtype of tumor in patients for further diagnosis and treatment (2).

3.2. Endometrial cancer

Endometrial cancer is the fourth most common cancer of the female reproductive tract. The major types of endometrial cancers based on pathological and molecular profiling include estrogen dependent, low grade type 1 tumors found in almost 80 percent of the cases. Type 2 cancers have serous papillary or clear cell histology with poor prognosis (3).

3.3. Cervical cancer

In cervical cancers around 80 percent of all cases are reported from the developing countries (4). Infection with one of the 15 genotypes of carcinogenic human papillomavirus (HPV) results in the onset of almost all cases of cervical cancer. Most of the squamous cervical cancers are identified by the presence of HPV DNA. The E6 and E7 transcriptional units encode proteins required for viral replication. E6 binds and inactivates p53 by subjecting it to proteasomal degradation leading to disruption of cell cycle check point whereas, the E7 oncoprotein binds to and inactivates products of the retinoblastoma gene, pRb, leading to unchecked cell cycle progression (5–7). Cervical cancer is triggered via the infection of the cervical epithelium at the transformation zone, persistence of the viral infection, progression of infected epithelium to cervical pre-cancer and invasion through the epithelial basement membrane. Infection is quite common in young women in their first decade of sexual activity. Patients receiving immunosuppressive agents, multiple sexual partners, history of genital warts and HIV coinfection are at high risk of developing cervical cancer (4).

3.4. Ovarian cancer

Ovarian cancers are the most lethal and alone accounts for over 50 percent of gynecologic cancer deaths, attributed to diagnosis at later stage. The invasive mucinous ovarian cancers metastasize to the gastrointestinal tract, including the colon and stomach. Endometrioid and clear cell ovarian cancers are associated with regressive menstruation from the endometrium. High grade serous ovarian cancers arise from the surface of the ovary and the distal fallopian tube (8). Disease is diagnosed at advanced stages and only treatment regimen is surgery along with carboplatin and paclitaxel chemotherapy. The malignancy is prone to platinum derived drugs with response rates of 70 to 90 percent in previously untreated patients, but only 30 percent are eventually treated through surgical intervention and chemotherapy (9). Most ovarian cancer patients suffer from therapy resistance, disease relapse and poor prognostic outcomes (10,11). As the first line of treatment, maintenance chemotherapy has only limited therapeutic value, it is imperative to look for targeted therapeutics (12,13).

4. PARP1 ASSOCIATED SIGNALING IN REGULATION OF REPRODUCTIVE CANCERS

The Poly(ADP-ribose) polymerase (PARP1) utilizes NAD as a substrate and transfers its product ADP-ribose units to target nuclear proteins for post-translational modification (14). Being a multifunctional regulator, it is involved in DNA repair, transcriptional and post-transcriptional modulation of gene

Table 1. Comparative role of PARP1 in various cancer and PARP inhibitors in combination with other drugs in clinical trials

Cancer types	Subtypes	PARP levels	PARP inhibitors in clinical trial	References
Breast cancer	Infiltrating ductal carcinoma (ER^-/PR^-/ $HER2^-$/TNBC	Very High	Olaparib, Olaparib in combination with PI3K inhibitor or AXL inhibitor	43,45
Ovarian cancer	Adenocarcinoma, papillary serous type	High	Olaparib, Veliparib in combination with doxorubicin or topotecan	50
Prostate cancer	Adenocarcinoma	Low compared to ovarian & breast cancer	Rucaparib in case of radiosensitized prostate cancer cells deficient in PTEN	59
Endometrial cancer	Uterine adenocarcinoma	High	Olaparib in PTEN deficient cancers	57
Cervical cancer	Squamous epithelial carcinoma	High	Olaparib in combination with carboplatin, Veliparib in combination with topotecan, Veliparib in combination with paclitaxel	56

expression, angiogenesis, inflammation, differentiation and the regulation of cell death (15). The PARP family constitutes of seventeen members but PARP1 accounts for 90 percent of the total enzymatic activity (16). PARP1 and PARP2 sense DNA damage and recruit repair proteins thus linking the DNA single strand breaks with repair pathways. Understanding the function of PARP1 in BRCA1/2 associated and non-associated reproductive cancers is critical as PARP1 is involved in DNA repair pathways and plays a crucial role in cancer progression. Following section describes the PARP1 expression and its role in regulating different reproductive cancers. An overview of role of PARP1 in reproductive cancers is depicted in Figure 1.

4.1. PARP1 in breast cancer

Differential expression of PARP1 was reported in different histological subtypes of breast cancer commonly in infiltrating ductal (IDC) and lobular carcinomas. Furthermore, PARP1 expression has been reported to be 30 percent higher in IDC breast tumors negative for ER, PR, and /or HER2, including TNBCs compared to that of the receptor positive subtypes (17). A recent study has highlighted the interesting relationship of BRCA1, PARP1 and NAD where BRCA1 regulates PARP1 expression in ER dependent manner (18). Majority of the BRCA1 associated breast cancers have high nuclear PARP1 expression except for sporadic invasive breast cancers, although few BRCA1 associated patients do have very low PARP1 expression. PARP1 association with DNA repair proteins varies according to tumor subtypes and genotypes. Studying PARP1 correlation with DNA repair marker proteins and tumor types could help in identifying the target genes as predictive markers for PARP inhibitor therapy (19). Recent studies have established that the elevated levels of PARP1 and phospho-p65 in Her2 positive breast cancer patients make cells sensitive to PARP inhibitors via modulating NFkB activity (20). Differential PARP activity in various cancers could increase the sensitivity of PARP inhibitors to chemotherapy. One of the possible reasons for increase in the PARP activity is its interaction with chromatin remodelling complex component NuA4 thus influencing the downstream pathways (21). Expression of Heterochromatin Protein (HP1) family members varies in certain cancers and also with different grades. It regulates BRCA1 and thus is involved in homologous recombination (HR) repair. HP1 expression also affects PARP inhibitor therapy response and thus could be one of the potential prognostic markers for breast cancer (22).

Recent studies have indicated that mutations in several genes involved in DNA repair could also result in the increased PARP activity[23]. Enhanced PARP activity was observed in the vicinity of the replication fork, where PARP1 mediates Mre11 dependent replication restart and stalled replication fork can further enhance activation of PARP1 (23). Further, BRCA2 also has a major role in the repair of stalled replication fork by binding with Rad51 and thus protecting the degradation of the replication fork. Mutations in BRCA2 or Rad51 or Mre11 blocks the stalled replication fork and could probably increase the activity of PARP1 (23–25).

4.2. PARP1 in endometrial cancer

The mechanisms leading to the progression of endometrial cancer and its regulation by PARP associated signaling are yet to be fully understood. A recent study has reported the role of PARP1 in non-neoplastic and neoplastic endometrial cancers in human. The study reported that PARP1 expression varies according to the phase of menstrual cycle and there is a gradual increase in the expression of PARP1 from endometrial hyperplasia to grade I endometrial carcinomas (ECs) with a sharp decrease in the advanced stages of Ecs (26). Interestingly, change in the expression is proportional to the expression level of progesterone receptor since PARP1 is known to regulate

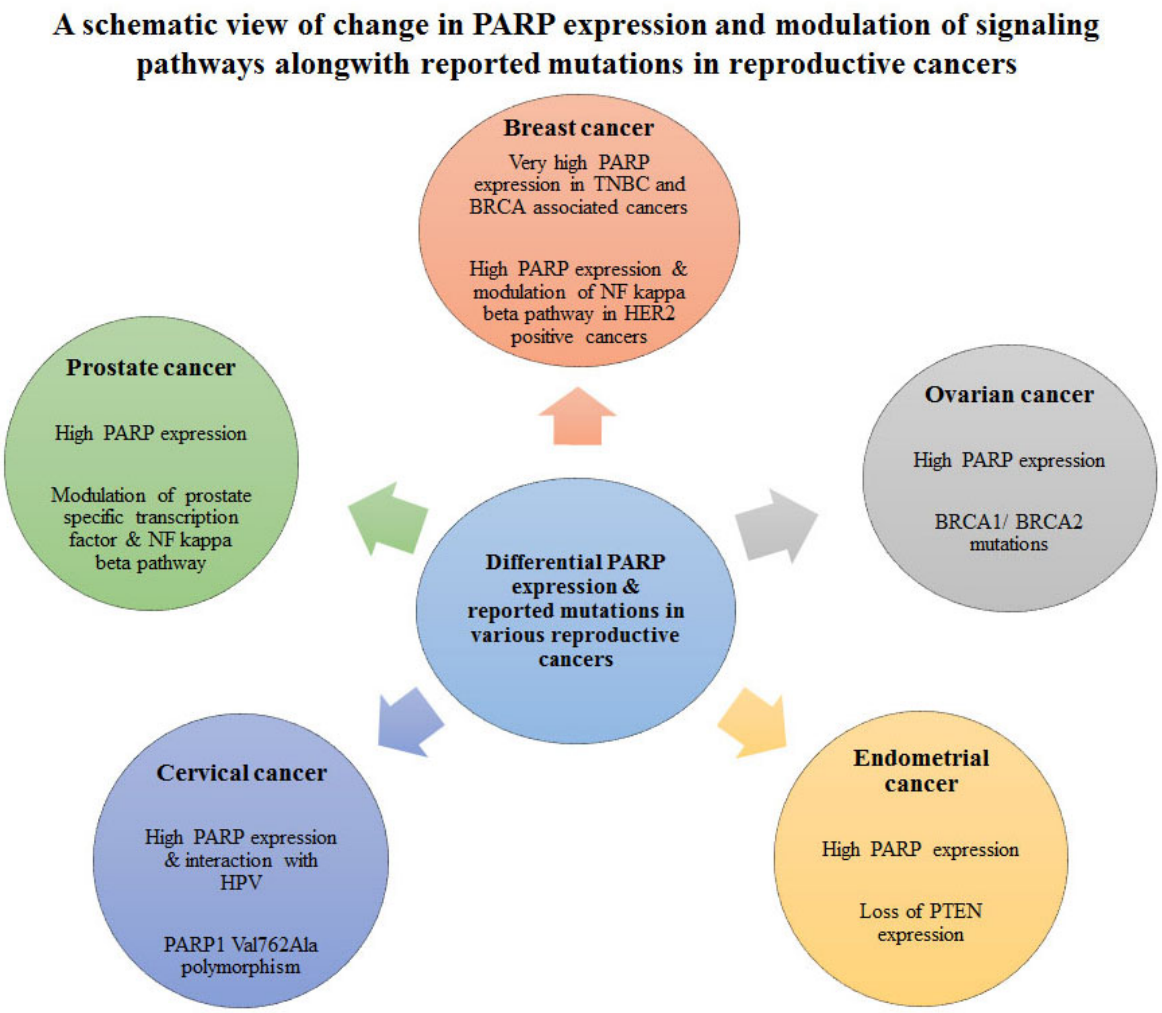

Figure 1. A Schematic view of change in PARP1 expression and reported mutations in reproductive cancers.

the progesterone receptor expression. In epithelial endometrial carcinoma, loss of PTEN (phosphatase and tensin homolog) function is the most prevalent molecular aberration. It is involved in the HR pathway of DNA repair through the transcriptional regulation of RAD51 (27). It has been reported that PTEN deficiency in endometrial cancer regulates sensitivity towards PARP inhibitor (28). Loss of PTEN function results in the defect in homologous recombination pathway of DNA repair thus making cells sensitive to PARP inhibitors and thus PARP inhibitors could be a good therapeutic option for a subset of endometrial cancers. The precise role of PARP associated signaling regulating progesterone and progesterone receptor in endometrial cancer progression through antagonizing the estrogen driven endometrial proliferation is yet to be elucidated (29).

4.3. PARP1 in cervical cancer

In a study to find any rationale between HPV (human papilloma virus) infection and PARP1 expression during cervical cancer progression, a recent investigation analyzed the expression level of PARP1 in low as well as high grade intraepithelial bruises as well as in invasive squamous cell carcinomas of the cervix and verified its interaction with HPV infection. The study reported a significant association between PARP1 expression and HPV positivity in thehigh grade squamous intraepithelial lesions (HSILs) group suggesting that PARP1 could be useful to differentiate HSIL HPV-related and squamous cell carcinomas (SCCs) (30). Statistical analysis of cervical cancer patients for the occurrence of PARP1 Val762Ala polymorphism suggested it to be a genetic risk factor for the occurrence of cervical cancer (31).

4.4. PARP1 in ovarian cancer

Out of all ovarian cancer patients, 10 percent cases carry a BRCA1 or BRCA2 mutations, leading to a high susceptibility of acquiring ovarian cancer. Patients with stage III and stage IV of

Table 2. PARP inhibitors in clinical trials

Drug combination	Cancer type	Mode of administration	Clinical status	References
Iniparib (BSI-201) + Carboplatin, gemcitabine	Triple-negative breast cancer	IV	Phase 2	76
Iniparib + Carboplatin, gemcitabine	Ovarian cancer	IV	Phase 2	77
Olaparib (200 mg bid) + weekly paclitaxel	Triple-negative breast cancer	Oral	Phase 3	78
Veliparib (ABT-888) + cyclophosphamide	breast cancer, ovarian cancer	Oral	Phase 1 Ongoing	79
Veliparib + TMZ	Metastatic breast cancer	Oral	Phase 2	80

ovarian cancer cases have a greater degree of therapeutic resistance and relapse and mortality even though ovarian cancers with BRCA mutations have better response towards chemotherapy and increased survival rates than those having sporadic cancers. Till date, information regarding the BRCA mutation status has not brought any significant success in selection of particular therapy for ovarian cancer (32). Mice models having compromised ability for repair of double strand DNA breaks by the HR pathway are sensitive towards inhibition of ssDNA (single stranded) breaks by PARP inhibitors thus giving a basis for synthetic lethal approach to treat various cancers. Occurrence of strong and lethal synergy between two otherwise non-lethal events forms the basis of synthetic lethality. As a result, PARP inhibition in such lethal condition causes lesions in DNA that gets even more severe in combination with tumour restricted loss of gene function for DNA repair pathways. PARP inhibition is quite effective against cells having biallelic loss for BRCA1 or BRCA2, hence making PARP inhibitors effective for tumours having BRCA mutations. As a result, the toxic effects in untransformed healthy cell would be minimized and thus maintaining the normal homologous recombination process (32).

4.5. PARP1 in other reproductive cancer

The PARP1 expression in prostate cancer is relatively low compared to the ovarian and breast cancers (17). Expression levels do not change significantly in prostate cancer but there are evident changes observed in the PARP protein in the nuclear matrix and matrix attachment regions (MAR) in the prostate tissue samples. Barboro *et al.* reported that PARP1 expression in the nuclear matrix increases with tumor aggressiveness. PARP inhibition in such cells reduces the MAR loop size, cell migration, invasion and histone acetylation, thus involved in cancer progression through chromatin modulation and gene transcription (33). Certain nuclear hormone receptors are transcriptionally regulated by PARP1 and hence PARP1 could be involved in androgen receptor target genes expression. A recent study has shown a decrease in the AR recruitment to promoters of its target genes in presence of PARP inhibitors (34). PARP1 and DNA–PKcs interaction with prostate specific transcription factor ERG activates transcription of EZH2, a highly expressed gene in metastatic prostate cancer (35). One of the many reasons for the onset and progression of prostate cancer is the constitutive activation of the NFkB signaling pathway and this activation of NFkB is regulated by PARP1 by either directly interacting with the p300/CBP proteins or PARylation of the inhibitory subunits of NFkB (36,37).

5. CURRENT STATUS OF PARP INHIBITORS FOR TREATMENT OF BRCA ASSOCIATED AND NON-ASSOCIATED REPRODUCTIVE CANCERS

In spite of the improved chemo-radiotherapy and targeted therapeutic strategies, there is little improvement in the overall survival of reproductive cancer patients. Besides these treatment modalities there exist long term consequences on reproductive health of patients leading to subfertility or infertility and other associated disorders in both males and females. Therefore, there is an ever growing need for targeted therapeutics with lesser side effects. In this context, based on the recent studies, PARP inhibitors are perceived as promising therapeutic agents for cancers in general and hereditary cancers in particular. As discussed above, PARP inhibitors are competitive inhibitors which compete with NAD for binding to PARP1 and thus inhibit PARP activation. Besides the competitive inhibitory mechanism, some PARP inhibitors also exhibit synthetic lethality by trapping PARP1/2 on to DNA and the potency of trapping is inhibitor specific. PARP-DNA complex trapping is most efficiently done by BMN673 followed by olaparib and then veliparib. The PARP-DNA complex is more cytotoxic than the single stranded breaks produced by the catalytic inhibition of PARP (38,39). Moreover, differential response is also observed with the chemotherapeutic drugs in combination with the PARP inhibitors. PARP inhibitors induced PARP trapping sensitizes cells to temozolomide while catalytic inhibitors are effective for combinations with camptothecin.

PARP1 is reported to be involved in tumor transformation to metastasis and thus PARP inhibitors target the metastatic cascade (40). As

evident from the recent studies, PARP inhibitors have potent effect as single agent, in combination and as adjuvant in the metastatic setting. Seven PARP inhibitors are in various stages of clinical trials for treatment of different cancers. In the following section we have summarized the use of PARP inhibitors in the treatment of BRCA associated and non-associated reproductive cancers and their advancement in clinical trials.

5.1. PARP inhibitors in breast cancer treatment

PARP inhibitors are promising anti-cancer agents for the treatment of BRCA1/2 mutated tumors due to synthetic lethality in HR defective cells with similar efficacy in certain sporadic TNBCs harboring BRCAness phenotype due to epigenetic silencing of the BRCA gene. Various studies with different PARP inhibitors have assessed the safety, efficacy and maximum tolerated doses for BRCA1/2 mutated tumors. A study by Tutt and colleagues has shown that Olaparib at two different dose regimes exhibit favorable therapeutic index in patients carrying BRCA1/2 mutations (41).

PARP inhibitors have also been studied in combination with conventional drugs and targeted inhibitors. A study performed by Cruz *et al.* reported that breast cancer cells proficient in BRCA/FA (fanconi anemia) can be sensitized to PARP inhibitor therapy by inhibiting the p21 activated kinase (PAK1) (42). Similarly, inhibition of AXL, a receptor tyrosine kinase sensitizes TNBC cells to PARP inhibition by targeting the DNA repair pathway. AXL is overexpressed in certain cancer cells including breast cancer and is known to play a critical role in the metastatic progression and is thus correlated to the markers of epithelial-mesenchymal transition (43). AXL and PARP inhibition exerts synergistic effect on TNBC cells. TNBCs characterized by the aberrant PI3K signaling and defective HR repair capability show enhanced vulnerability to PARP inhibition (44). Juvekar and colleagues have reported synergistic effects of PI3K and PARP inhibitor combination in BRCA deficient cells via mechanisms mediated through the DNA protein kinase (45).

5.2. PARP inhibitors for ovarian cancer treatment

Clinical studies with PARP inhibitors in ovarian cancer therapy have evolved from *in vitro* studies assessing functional activity of these inhibitors as a single agents in BRCA-deficient cancer cells to that of multiple phase III clinical trials. Olaparib (AZD2281) is a PARP1 and PARP2 inhibitor that has undergone the most extensive clinical trials in ovarian cancer. It has been tested in phase I and II studies; as a single agent, showing anti-cancer activity in BRCA mutated ovarian cancer in addition to sporadic high grade serous carcinomas without known germline BRCA mutations (32,46,47). A recent study reported that patients with platinum-sensitive chronic serous ovarian cancer having BRCA mutations are most likely to be benefited from single agent olaparib treatment (48).

Another PARP inhibitor veliparib (ABT888) has undergone extensive testing in combination with various chemotherpeutic agents and is recently being studied in phase II clinical trial as a single drug in recurrent BRCA associated ovarian cancer (49). Combinations of veliparib with doxorubicin, topotecan or cyclophosphamide has been tested in phase I trials (50).

Rucaparib is another PARP1 and PARP2 inhibitor being tested in a clinical trial for the treatment of recurrent ovarian cancers and has shown anti-ovarian cancer activity both *in vitro* and *in vivo*. It has shown potent anti-cancer responses in ovarian cancers exhibiting platinum resistance and recurrence (51–53).

Similarly, BMN 673 is another PARP inhibitor that has undergone phase I clinical trial in an open label study of once daily, oral administration in patients harbouring advanced or recurrent solid tumors. Currently, there is a phase III study testing BMN673 in patients with metastatic breast cancers, however, no phase III clinical trial for ovarian cancer have been initiated (54).

Niraparib (MK4827) is a selective PARP inhibitor being tested in phase I trial in both patients with chronic BRCA mutated and sporadic BRCA-proficient ovarian cancers. Recently, NOVA, a phase III study using niraparib versus placebo has been initiated for assessing its efficacy as a maintenance therapy in ovarian cancers (55).

5.3. PARP inhibitors for cervical and endometrial cancer treatment

A phase I pharmacokinetic/pharmacodynamic study with a combination of PARP inhibitor olaparib and carboplatin is being tested in refractory or recurrent endometrial cancers. A phase II clinical trial using veliparib in combination with topotecan is being carried out currently for treating persistent or recurrent cervical squamous and non-squamous carcinomas. Furthermore, a phase I/II limited access trial of veliparib in combination with paclitaxel is also in pipeline for the treatment of advanced persistent carcinoma of the cervix (56). PTEN inactivation has frequently been seen in majority of endometrial cancers and phosphatase independent roles of PTEN is crucial for homologous recombination pathways of DNA repair. Recently the anti-tumor activity of olaparib, and its sensitivity with PTEN status in endometrial cancer cell lines has been assessed. The results of this study indicated PARP

inhibitors as a promising tools for treatment of PTEN deficient endometrial cancers (57).

5.4. PARP inhibitors in treatment of other reproductive cancer

Prostate cancers have a relatively lower percentage of BRCA deficient tumors and therefore PARP inhibition therapy is not perceived to be effective based on its synthetic lethal approach. However, with discovery of the novel functional roles of PARP1 in cell signaling, its importance in the treatment of BRCA non associated cancers is increasing. Besides its role in the DNA repair pathway, PARP1 plays a significant role in the transcriptional regulation seen in androgen receptor (AR) positive prostate cancer cells. PARP1 is shown to elicit premalignant phenotype by regulating the AR activity in prostate cancer cells (58). PARP inhibition sensitizes prostate cancer cells to DNA damaging agents or radiotherapy via the DNA repair pathway and through the inhibition of AR activity. Chatterjee and colleagues have reported that the PARP inhibitor rucaparib radio sensitized prostate cancer cells deficient in PTEN and overexpressing the ETS gene fusion protein TMPRSS2-ERG. This synergistic interaction induces senescence in cancer cells and reduces clonogenicity (59). PARP1 is shown to interact with the ETS fusion protein, ERG and regulate the ERG mediated signaling including cell invasion and progression. Targeting the ETS positive prostate cancers with PARP inhibitors inhibits ERG mediated invasion and potentiate DNA damage (60).

6. RESISTANCE TO PARP INHIBITORS IN REPRODUCTIVE CANCERS

PARP inhibitors as single agent or in combination with drugs targeting the DNA repair pathway have been exploited but there are reports of resistance being developed to these inhibitors (61,62). There are several potential mechanisms proposed for the PARP inhibitor resistance, including restoration of BRCA1 function in the BRCA1/2 mutated cancers, up-regulation of efflux pumps like pgp transporters, loss of 53BP1 upon restoration of homologous recombination and loss of functional PARP1 (63–65).There could be a possibility of unidentified factors responsible for resistance to PARP inhibitors. Chances of resistance increases upon progression and advanced stages of the disease. Therefore, it is imperative to devise strategies and identify agents that may overcome resistance to PARP inhibitors. A promising drug showing efficacy in the treatment of BRCA1 defective advanced tumors resistant to PARP inhibitors is ‘6-thioguanine’ (66). Another combinatorial approach using ABT-888 and vorinostat (a histone deacetylase inhibitor) has shown promising results in the preclinical setting. Vorinostat sensitizes PARP inhibitor resistant cell lines to 6-thioguanine and this effect was attributed to the increase in the phosphorylation status of eIF2alpha (67).

Another possible mechanism proposed for the resistance to PARP inhibitors is the presence of hypomorphic RAD51C mutants. Mutation in RAD51C increases error prone NHEJ pathway and less proficient HR pathway, thus targeting PARP1 will induce toxicity in cancer cells (25). During HR deficiency, double strand breaks (DSBs) are forced to be repaired by error prone NHEJ, which leads to chromosomal instability and apoptosis. Utilizing this principle for cancer therapy would assist in overcoming resistance developed due to continuous exposure to the PARP inhibitors. Inducing DSBs with low dose of ionizing radiations in combination with PARP inhibitors would drive tumors to cell death and hence synergistic toxicity approach would be effective therapy for HR deficient tumors.

Major proteins and kinases involved in the DNA repair pathways can be targeted to overcome the PARP inhibitor induced resistance. During replicative damage, cell cycle is regulated by one such kinase, ATR and recent report suggests that ATR inhibition can sensitize resistant cells to PARP inhibitors (68). The kinase, ataxia telangiectasia mutated (ATM) protein is also a DNA damage responsive protein and maintains genomic stability. Hence, ATM-deficient cells are sensitive to PARP inhibitors. Hong and colleagues have shown that 53BP1 depletion in ATM deficient cells provide resistance to PARP inhibitors (69). Thus gain- and loss-of function of various DNA damage responsive proteins need to be further studied to understand resistance mechanism and devise ways to overcome PARP inhibitor resistance.

7. GLARING GAPS IN KNOWLEDGE AND PERSPECTIVES

There are seventeen members in the PARP family and out of them a few are structurally and biochemically characterized till date. Still the structure and functional roles of many members have not been elucidated. Although PARP1 is a major protein and constitutes 90 percent of the total PARP activity, there is a possibility of other family members like PARP2 regulating critical cellular functions. Other PARP family members could be involved in signaling pathways involved in cancer progression, which could affect the therapeutic potential of PARP inhibitors. Recently identified function of PARP3 in epithelial-mesenchymal transition and stemness upon TGF beta (transforming growth factor) mediated ROS production also suggest that other PARP family members apart from PARP1 regulate cancer progression (70). Vyas and colleagues have reported four categories of PARPs based on domains and have identified diverse functions of PARPs. They are reported to be essential for cell

viability, cytoskeleton maintenance and focal adhesion (PARP14) (71). Thus other PARPs could be involved in regulating carcinogenesis. Further research of the other PARPs might help us find new drug targets.

PARP1 is reported to be involved in progression of several cancers by targeting different signaling pathways while in some cancer types it is tumor suppressive. Genetic disruption of *PARP1* in permutation with *p53* knockout increases the cancer incidence in mice, underscoring the role of PARP1 as a tumor suppressor (72). PARP1 inhibition could conceivably increase the risk of secondary malignancies, especially in combination with genotoxic drugs. Potential way to overcome this problem is through the combination of low dose of PARP inhibitors with the genotoxic drugs. Consequences of dual drug combination strategy and use of multiple drugs and their long term effects on healthy cells needs to be critically studied.

PARP inhibitors against ovarian and breast cancers in clinical studies seems to be promising. Besides other safety issues, level of PARP1 inhibition for clinical response and the adverse effects of long term treatment have to be addressed (73,74). PARP1 and PARP2 are inhibited by the current generation inhibitors, but their effects on other members of this family needs to be elucidated. Exploring the role of these inhibitors on other PARP family members might shed light on side effects of these inhibitors. Different PARP1 inhibitors have off shoot targets and might have different outcomes upon inhibition. The mechanism of each inhibitor has to be considered before use in cancer therapy. Involvement of PARP1 in other cellular functions raises concern that PARP inhibitors may have toxic effects. Also, the risk of secondary cancers arising from inhibition of DNA repair requires a careful consideration if these agents have to be used for longer periods.

PARylation plays a pivotal role during DNA damage response, whereby several proteins of repair pathway gets PARylated and PAR residues provide a platform for recruiting other DNA repair proteins. BRCT domains of repair proteins facilitates recognition of PAR moieties and further repair of damaged DNA (75). PAR residues are regulated by degrading enzyme poly ADP-ribose glycohydrolase (PARG) in a cell and thus PARG activity needs to be considered for effective therapeutic approach of PARP inhibitors, as PARG could have important role in developing resistance to PARP inhibitors.

Extensive studies finding the efficacy and safety of PARP inhibitors in combination with DNA damaging drugs, cytotoxic chemotherapy and as monotherapy are required. Further clinical trials will help elucidate the real potential of PARP inhibitors in cancer treatment chemotherapy and toxicity parameters associated with metabolic functions. There is an urgent need to identify biomarkers related to PARP1 for different cancers which will be useful in identifying and deciding the type of chemotherapy. Thus PARP inhibitors provide a promising avenue for the treatment of BRCA deficient and proficient reproductive cancers in the future.

8. ACKNOWLEDGEMENTS

JR acknowledge the support from Department of Biotechnology (DBT) for the DBT Bio-CARe fellowship. NS acknowledges the senior research fellowship from the Indian Council of Medical Research (ICMR). We wish to apologize to all colleagues whose work, because of lack of space, could not be cited. We thank all the members of the DP Mishra laboratory for helpful discussions. This work was supported by the grants from Department of Biotechnology (GAP0187) to DP Mishra. The CSIR-CDRI manuscript No is 9446.

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Abbreviations: PARP: Poly ADP-ribose polymerase-1, HR: homologous recombination, TNBC: Triple negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, HER: Human epidermal receptor, AR: Androgen receptor

Key Words: PARP, Reproductive cancers, PARP inhibitors, Drug Resistance, Clinical Trial, Review

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