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Poly (ADP-Ribose) Polymerase (PARP), an Emerging Target for Controlling Metastatic Prostate Cancer under BRCAness

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Abstract

PARP1 is identified as an enzyme for addition of poly (ADP-ribose) to target protein(s) and is also important for DNA repair at the site of DNA single strand break (SSB). However, under PARP-inactivated states, unrepaired SSB is converted to double strand break (DSB) in S-phase, and then homologous recombination (HR) system participates in repair of DSB-injured DNA. In this process, BRCA1/2 and their binding effectors, such as RAD51 and PALB1, are recruited to the injured site for initiating HR-based DNA repair. If HR-associated molecules, such as BRCA1/2, are deficient via a dysfunctional mutation or down-regulated (so called, BRCAness), cancer cells undergo further DSBs and eventually result in apoptotic cell death. In response to HR-deficiency, PARP1 is activated to repress SSB, a source of DSB before DNA replication, hence suggesting a new target of PARP1 for inducing synthetic lethality under BRCAness. Indeed, PARP1 inhibitor (PARPi) is found to be useful for delaying the progression of BRCA1/2-mutated ovarian cancers in phase-II clinical trials. Metastatic prostate cancer (PCa) is now the second leading cause of cancer deaths among males in the Western countries. Radiation and androgen receptor inhibition (ARi) (i.e., pharmaceutical castration) are the standard therapy to delay PCa progression, but these conventional treatments result in a malignant selection of castration-resistant PCa clones. Previous studies described the potential use of PARPi for sensitizing radiotherapy or chemotherapy to castration-sensitive PCa in a rodent model. The recent highlighted finding is that ARi treatment down-regulates BRCA1, Rad51, Rad54 and RMI2, all are necessary for HR post-DNA DSB damage, thus indicating the acquisition of BRCAness-like phenotypes by ARi. In this review, we will describe the recent information on significance of PARPi in advanced PCa. Clinical effects are now being evaluated in patients with metastatic PCa, and some are promising. PARP1 inhibition may become a principle-based strategy for arresting metastatic PCa, if patient selection is carefully performed, on the basis of genomic (or phenotypic) detection of BRCAness.

Keywords: BRCAness; DNA damage; Homologous recombination; Irradiation; PARP inhibitor; Prostate cancer

Introduction

Cellular DNA damage occurs continuously, in exposure to intrinsic and extrinsic stresses, such as chemotherapy, irradiation, smoking and reactive oxygen species. PARP1 acts as a DNA damage sensor and binds to the site of single strand break (SSB) [1]. PARP1-DNA binding results in the recruitment and addition of poly(ADP)-ribose (i.e., PARylation) of DNA repair proteins, such as XRCC1, DNA ligase III and DNA polymerase-β to restore the SSB site via base excision repair (BER). If this process is impaired, SSBs can be converted to double strand break (DSB), due to collapse of DNA replication fork during S-phase of the cell cycle [1,2].

Under such an inducible DSB damage, BRCA-based sequential process is critical for DSB repair process via homologous recombination (HR) [1,3]. The serial steps include: (i) detection of DSBs by MER11A-NBS1-Rad50 complex, allowing for recruitment of DNA checkpoint kinase ATM; (ii) BRCA1-dependent resection of 5' DNA side; (iii) loading of Rad51 onto DNA by BRCA2 bound for PALB1/2; (iv) Rad51 activation on DNA for incorporating homologous double helix; and (v) DNA synthesis using homologous DNA as a template, resulting in 2nd end DNA capture, DNA ligation and its structure resolution, as reviewed [3,4]. In other words, BRCA1/2 loss-of-function (or loss-of-production) causes an HR-deficient condition.

There is now growing evidence to show that PARP1 is critical for DNA repair and cell death/survival balance [1,2]. Defective or insufficient DNA repair are frequently encountered in a variety of human cancer cells, and PARP1-mediated DNA repair is thought to be an alternative cascade, especially under the defective condition of HR. For instance, PARP1 activation level is elevated in solid tumor cells, along with germline or somatic mutations of HR-related genes, such as BRCA1/2 and Rad51 [3]. Two landmark studies demonstrated in 2005 that HR-related molecule-deficient cancer cells become vulnerable to PARP1 inhibitors (PARPi) [5,6]. This result is also reproducible in other types of "sporadic" cancers, such as pancreatic cancer and colon cancer, with a decrease in HR-related molecules [1-4,7], indicating an extensive role of PARP1 for maintenance of cancer cell malignancy.

Targeting of PARP1 in HR-dysfunctional cancer cells confers a proof-of-concept for synthetic lethality-based oncotherapy. PARPi may also be useful for killing cancer cells, beyond BRCA1/2 mutation, via induction of DNA damage response, especially after irradiation. This review describes biology and recent clinical outcomes of PARPi-based therapy, with a focus of metastatic prostate cancers.

Broaden Terminology of BRCAness

Ashworth et al. first defined the original term "BRCAness" as "loss-of-function" mutations of BRCA1 or BRCA2 gene in gynecological cancers [3]. HR-based DNA repair system does not function under BRCAness, since BRCA1/2 is essential in this process. More importantly, breast and ovary cancers with a genotype(s) of BRCAness are highly vulnerable to PARPi [3-6], suggesting a synthetically lethal effect by PARPi. This discovery provided a conceptual model for personalized medicine, based on individual genomic data of cancers. The terminology of "BRCAness" is now expanded to phenotypic dysfunction of BRCA1/2-drived HR. For instance, lowered protein expression of HR components, such as BRCA1/2 and Rad51 leads to "acquired" deficiency of HR with PARPi sensitization (i.e., acquired BRCAness) in sporadic cancers, even if HR-involved molecules are wild-type. DNA-damaging drugs, such as cisplatin, or irradiation enhances DNA damage in cancer cells. Of note, BRCAness-like phenotypes are introduced, after chemo- or irradiation-induced DSB, thus rendering cancer cells sensitive to PARPi during these conventional therapies [7,8]. PARPi is also useful for killing tumor cells that are deficient in ATM [9], a key master gene for functional HR. According to the expanded term of BRCAness, application of PARPi is now extensive in chemotherapy and radiotherapy in animal models, convincing a role of PARPi in anti-tumor therapy beyond BRCAness. This preclinical data encouraged pharmaceutical researchers to develop PARPi, as described below.

Development of PARP Inhibitor (PARPi)

As described above, PARP1/2 is an abundant nuclear enzyme to poly-(ADP-ribose) ylate target proteins by use of nicotinamide adenine dinucleotide (NAD^+) as a co-factor [1]. Different compounds are now developed to compete with binding of NAD^+ (a natural ligand of the enzyme) to PARP1/2, resulting in enzymatic inactivation. Indeed, almost all PARPi have a "nicotinamide pharmacophore" that results in competitive inhibition with NAD^+ by masking the catalytic domain of PARP1/2. Thus, these compounds are commonly known as PARPi.

There are now three types of commercially available PARPi in the United State [10]. Olaparib (AstraZeneca) was the first drug to be approved by FDA in 2014 for the treatment of BRCA1/2-germline mutated ovarian carcinoma. FDA approval of rucaparib (Pfizer/Clovis) was then announced on December 2016, according to the clinical results of ovarian cancer with genotypic BRCAness. In addition, Niraparib (Merk/Tesano) was also approved on March 2017 by FDA for maintenance therapy of recurrent platinum-sensitive ovarian cancer, regardless of BRCAness status. Other two candidates, veliparib (ABT-888, Abott) and talozaparib (BMN673, BioMarin) have now entered phase-II/III trials in different tumor types. The major adverse effects of PARPi (grade 3-4) include anemia, fatigue, vomiting and thrombocytopenia [10,11].

It is important to discuss how PARPi produces anti-tumor effects beyond BRCAness. There are two cascades leading to cancer death. One is called "synthetic lethality" effect, especially during BRCAness with HR-deficiency. In this process, PARPi acts as an inducer for SSBs (e.g., G1-phase) and a resultant over-accumulation of DSBs (i.e., S-phase), rendering cancer cells apoptotic during the cell cycle [1]. Another mechanism is mediated via "PARP trapping". Murai et al. [12] reported that PARPi-mediated trapping of PARP1/2 on the damaged DNA leads to cytotoxic effect, in part, through inhibiting DNA replication. Such a direct poison effect may explain the BRCAness-independent cytotoxicity, produced by niraparib. Indeed, PARP-DNA trapping is stronger in niraparib than in other types of PARPi [12]. Thus, we predict that not only "synthetic lethality" but also "PARP trapping effect" provides the reason why PARPi is effective under (or beyond) BRCAness. Based on this concept, we will describe the potential use of PARPi for controlling prostate cancers, as followed.

PARPi as a Radio-Sensitizer for PCa Inhibition

Metastatic PCa is still incurable and is now ranked as the 2nd cancer death among men in the United States. BRCA germline or somatic mutations account for only 12 to 20% of CRPC [13]. X-ray irradiation induces SSB and often DSB, being dependent on its dose. Considering that PARPi acts like SSB/DSB-inducer (or PARP-DNA trapper), it is reasonable to assume that PARPi synergizes with radiation to increase cytotoxicity in PCa cells. Pre-clinical data have shown that PARPi may increase the efficacy of radiotherapy in PCa. Veriparib (ABT-888) was found to enhance the anti-tumor effect by ionizing radiation (6 Gy) in a xenograft model of human PCa-derived PC-3 cells [14]. However, it is uncertain whether PARPi leads to clonogenic kill when combined with radiotherapy. Gani et al. found that AZD-2281 inhibited cellular PARP activity under both oxic and hypoxic conditions [15]. The addition of AZD-2281 radiosensitized human PCa-derived 22Rv1 cells under oxia, acute hypoxia and chronic hypoxia *in vitro*. The combination of AZD-2281 with fractionated radiotherapy resulted in a significant growth delay and clonogenic kill in a murine model. Gut toxicity was not enhanced under the combined regimen of PARPi plus radiotherapy regimen. This is the first preclinical study to demonstrate direct clonogenic kill *in vivo* by the addition of AZD-2281 to radiotherapy. The use of PARPi in the context of PCa radiotherapy warrants further investigation in clinical trials. Genomic analysis suggests the loss-of-PTEN, or gain-of-ETS gene fusion (i.e., TMPRSS2-ERG fusion) as a causative factor for PARPi to enhance radio-sensitization [16].

AR Inhibitor-Inducible BRCAness

The patients bearing PCa initially respond to anti-androgen therapy, but most eventually develop castration-resistant PCa (CRPC), with distal metastasis to systemic bones. Novel androgen receptor (AR) signaling inhibitors, such as abiraterone acetate and enzalutamide can extend the life of metastatic patients for 5 months, but these drugs are not curative. Li and Thompson recently reported that several types of CRCP cell lines (i.e., VCap, LNCaP, and CWR22Rv1 cells) acquired the higher expression of HR-associated genes, such as BRCA1, RAD51AP1, RMI2 [17]. Strikingly, a new AR-inhibitor (ARi), enzalutamide repressed these gene transcriptions, creating the HR-deficiency and pharmaceutically inducible BRCAness. When each HR-associated molecule, such as Rad51, Rad54 and RMI2, was depleted by siRNA knockdown methods, these cells became vulnerable, in response to olaparib. CRPC is resistant to enzalutamide, but becomes sensitive to the ARi in the presence of olaparib of culture of CRCP cell lines. In this process, enzalutamide plus olaparib enhanced the DSB damages, G1/S arrest and eventually apoptosis in cancer cells. Furthermore, this combination therapy was shown to be effective for arresting cancer growth in a xenograft model of mice. Pretreatment of ARi is necessary for olaparib to produce the maximal anti-tumor effects on CRPC, possibly via inducing acquired BRCAness (i.e., lead-in ENZ plus OLA therapy). ARi alone cannot kill CRCP, because of its resistance. However, this inhibitor may be promising as a BRCAness-

inducer, especially before the start of PARPi treatment, as described below.

Clinical Studies of PARPi in PCa Patients

Based on the previous experimental data, Mateo et al. [18] hypothesized that metastatic CRPC, possibly with DNA-repair defects would respond to PARP inhibition with olaparib. To test this hypothesis, they conducted a phase 2 trial (i.e., TOPARP-A trial) in which patients with metastatic CRPC were treated with olaparib tablets at a dose of 400 mg twice a day [18]. Overall, 50 patients were enrolled; all had received prior treatment with docetaxel, 49 (98%) had received ARi (such as abiraterone or enzalutamide). The next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes (including BRCA1/2, ATM, Fanconi's anemia genes, and CHK2) in 16 of 49 patients who could be evaluated (33%). Of these 16 patients, 14 (88%) had a positive response to olaparib, including all 7 patients with BRCA2 loss (4 with somatic loss, and 3 with germline mutations) and 4 of 5 with ATM aberrations. Of interest, these genomic aberrations were uncommon in non-responding patients. Anemia (20%) and fatigue (12%) were the most common adverse events (grade 3-4). Overall, it was shown that olaparib therapy in patients with mutants of DNA-repair genes led to a high response rate. Now, the second stage of this trial (i.e., TOPARP-B trial) is ongoing, where patients are being pre-selected based on detection of tumor genomic aberrations that is associated with PARPi sensitivity.

Summary and Future Perspective

In this article, we reviewed the biological function of PARPi, based on a principle of DNA repair system. PARPi acts as an inducer of DSB accumulation, as a result of increased SSBs, and cancer cells must be removed via apoptosis under HR-deficient or HR-decreased conditions. Thus, use of PARPi under HR-deficiency provides the first model of synthetic lethal therapy, especially under genotypic BRCAness. Based on the results of TOPARP-A trial, FDA awarded “breakthrough designation” to develop PARPi in treating a subset of metastatic PCa patients (January 2016). Li et al. found the significance of ARi(lead-in) and PARPi combination under ARi-inducible BRCAness in mice [17]. The effects of ARi plus PARPi on metastatic PCa are currently being evaluated in phase-II clinical trials (NCT01576172 for veliparib and NCT01972217 for olaparib) [10,11]. PARP1 is also critical for mRNA transcription through PARylation of transcriptional regulators [19]. Experimentally (and perhaps, clinically), a long-term use of PARPi causes PARPi resistance. Polo-like kinase-1 likely contributes to PARPi resistance in BRCA-mutant CRPC [20]. Basic research on PARPi resistance will shed more light on molecular mechanism for an alternative pathway of DNA repair. PARP1 can be a key modulator for replication of oncogenic virus genome, as reported in herpesvirus, such as EBV or KSHV [21,22]. PARP has a multiple effect via PARylation of target proteins that is involved in oncogenesis. How to practice prospective selection and analysis of DNA damage response genes, including HR- and BER-associated genes is an attractive theme for advances in cancer biology, therapeutics and personalized medicine as well.

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