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Clinical Significance of PARP-1 Inhibitors in Cancer Chemotherapy

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ABSTRACT

Poly (ADPribose) polymerase 1 (PARP-1) protein plays an important role in the repair of single strand breaks (SSBs) in the DNA. This is mediated by base excision repair (BER) of SSBs. PARP-1 inhibition allows accumulation of SSBs and consequently double strand breaks (DSBs). PARP inhibitors disrupt the BER and causes cell damage and death, especially in breast cancer susceptibility proteins 1 (BRCA 1) or BRCA2mutated cell in which homologous recombination (HR) pathway is defective. PARP-1 is effective as a single agent in BRCA-1 and BRCA-2 mutated ovarian and breast cancer. In addition, a number of studies have shown beneficial effects with PARP-1 inhibitors in combination with cytotoxic agents that target SSBs, especially in case of triple negative breast cancers (TNBC). Here we have reviewed potential clinical applications of PARP-1 inhibitors and issues associated with it for successful cancer chemotherapy.

Keywords: *BRCA, DNA repair, PARP inhibitors, breast cancer, ovarian cancer*

Introduction

The American Cancer Society (ACS) recently estimated that over 600,000 of Americans are projected to die, whereas 1600,000 new cancer cases would be diagnosed in 2013. Recent discoveries of novel-targeted therapies have revolutionized the oncology treatment in the last decade. Traditional anticancer agents were limited due to their non-selectivity towards cancer cells, drug resistance and that they had a very narrow therapeutic window, which limited their use due to unfavorable toxicities to normal cells. Therefore, novel-targeted agents have proved beneficial and have significantly improved the patient survival. This has also been possible due to our better understanding of drug-drug interactions and considerably improved efficacy of clinical anticancer agents when used in combination chemotherapy. The objective has been to multi-target the cancer cells to limit development of resistance, while designing compounds that possess maximum activity with the least or no cross-resistance, and that in conjunction the two agents will demonstrate synergy, or improved effectiveness than when they were used as monotherapies. Combining Poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors with cytotoxic agents such as chemotherapy or radiation therapy is synergistic in many preclinical models. With novel and selective mechanisms of action, PARP-1 inhibitors have moved from the laboratory to the clinic in just the last few years.

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PARP exist in 17 isoforms, and have been characterized based on sequence homology within the catalytic domain[1] and amongst them, PARP-1 is the first to be characterized and perhaps best known member of the PARP family. PARP-1 accounts for more than 90% of cellular PARP activity. PARP-1 is a chromatin-bound nuclear enzyme involved in the detection and damaged-DNA repair pathway, importantly the base excision repair (BER) of single strand breaks (SSBs).[2] PARP constitute a

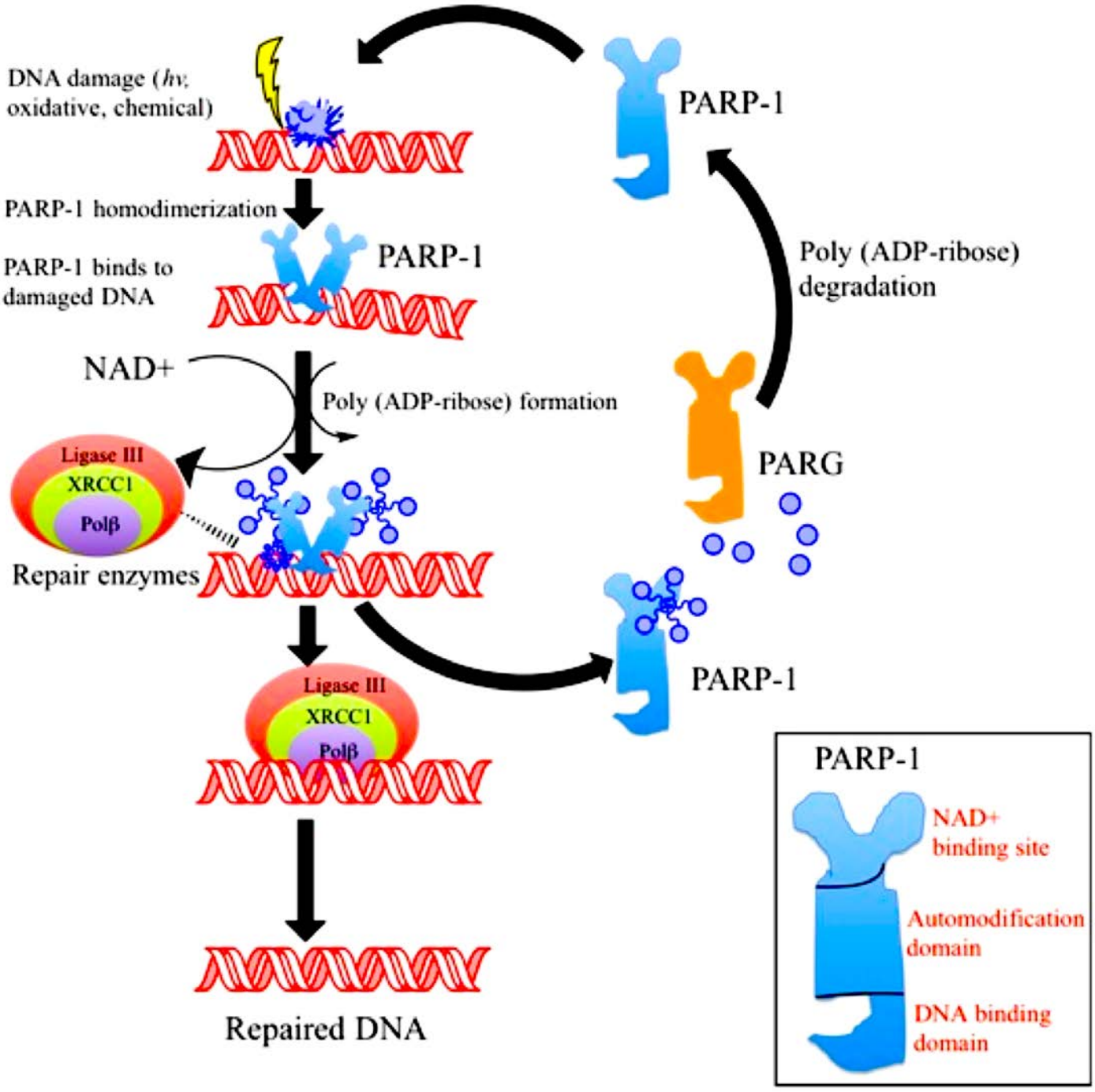


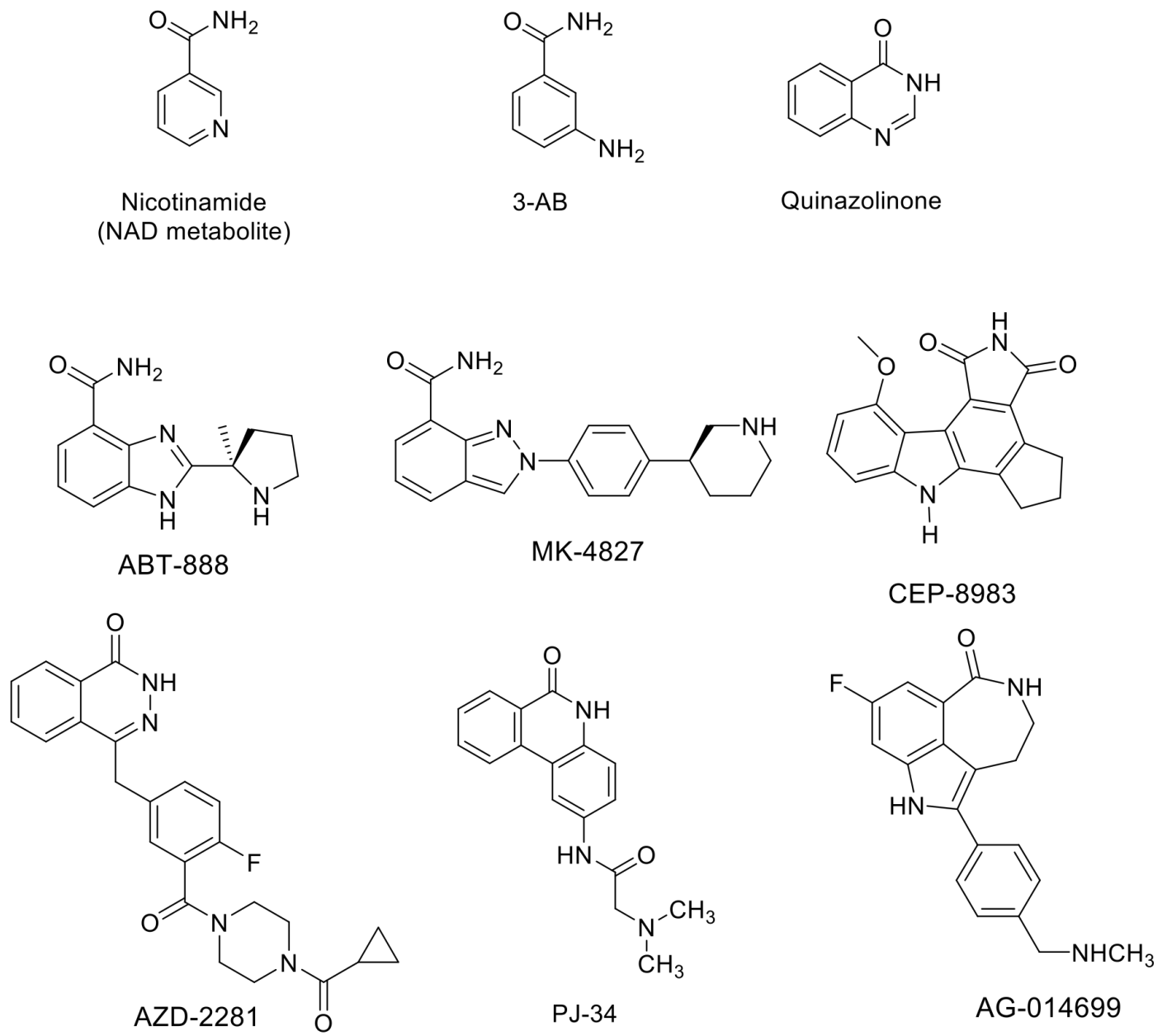
Figure 1. Role of PARP1 in DNA repair: DNA damage activates PARP1 enzyme resulting in homodimerization of the enzyme. Then the DNA binding domain of PARP-1 binds to the damaged DNA and consumes Nicotinamide Adenine Dinucleotide (NAD^+) as a substrate to produce linear and branched polymers of ADP-ribose units covalently bound to substrate proteins. Poly (ADP) ribosylation (PARylation) either occurs on PARP-1 itself (automodification) or on an array of nuclear target proteins. These PARylated nuclear proteins amplify the repair process through chromatin decondensation and dynamic nucleosome remodeling increasing the accessibility of base excision repair (BER) proteins such as X-ray repair cross-complementing protein 1 (XRCC1), DNA ligase III and DNA polymerase β (pol β) to the damaged DNA.

family of cell signaling enzymes which catalyzes the poly(ADP-ribosyl)ation of DNA-binding proteins and have emerged as critical regulatory components of the immediate cellular response to DNA damage (Figure 1).

This protein plays a key role in maintaining genome integrity through modulation of multiple cellular responses (including base excision repair, necrosis and apoptosis) in the face of genotoxic stress [3,4]. ADP-ribosylation reactions are involved in many physiological and pathophysiological processes, including inter- and intracellular signaling, transcription, DNA repair pathways, cell cycle regulation, and mitosis, as well as necrosis and apoptosis [5].

PARP-1, the founding member of the PARP family, is a molecular sensor of DNA breaks, playing a key role in the spatial and temporal organization of break repair through the local synthesis of poly (ADP-ribose) (PAR) at damaged sites, and were expressed at high levels throughout the embryo. Only Parp-1 and Parp-2 have been shown to be activated by DNA strand breaks [6]. PARP-9 [B-aggressive lymphoma-1 (BAL-1), macro PARP] has recently been discovered in patients with certain types of diffuse large B-cell lymphomas (DLBCL) and described as a new nuclear protein encoded by the BAL gene, which is expressed in the thymus and specific regions (neuroepithelium) of the brain and gut [7]. PARP-14 is weakly expressed, mainly in the thymus during development and in adulthood, it is essentially co-expressed with PARP-9.

Figure 2. Structure of PARP-1 inhibitors.

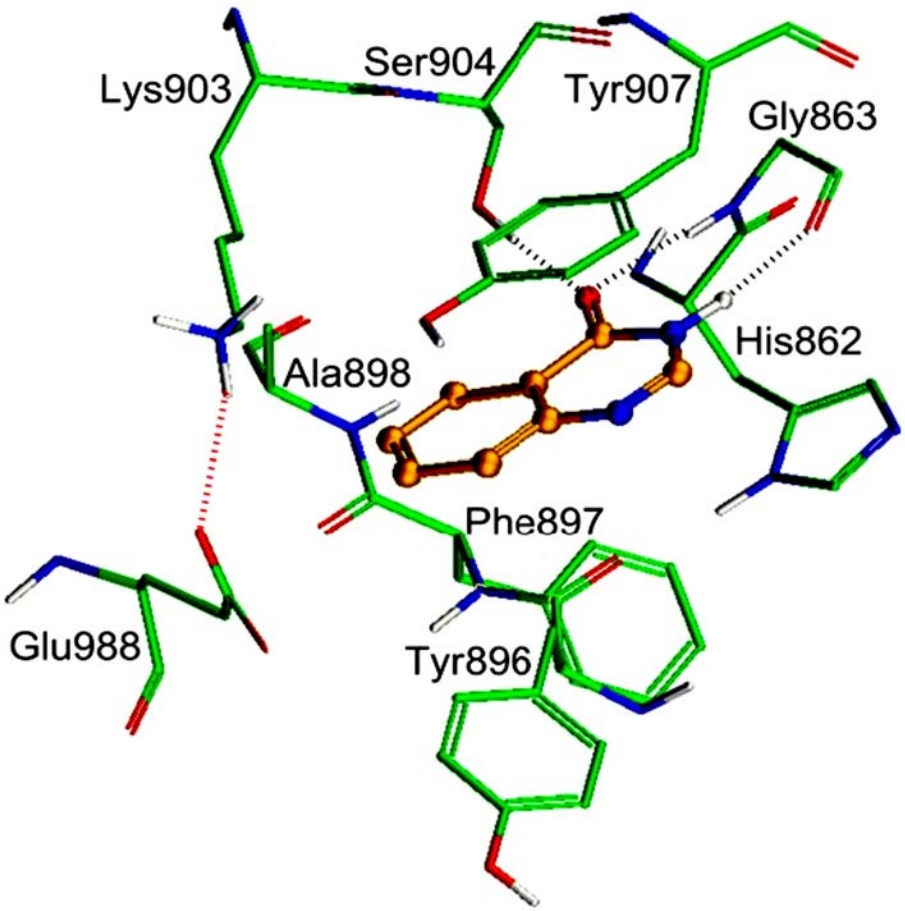


PARP-1 Inhibitors

During poly (ADP) ribosylation, PARP-1 utilizes NAD^+ to synthesize poly (ADP)-ribose units either on itself or on a variety of nuclear target proteins such as histones, topoisomerases, DNA polymerases and DNA ligases (Figure 1). This results in highly negative charged nuclear proteins, which in turn leads to the unwinding and repair of the damaged DNA through the base excision repair (BER) pathway. PARP inhibitors offer potential therapies for a wide variety of diseases such as inflammatory conditions, diabetes complications, neurological diseases, stroke and myocardial infarction [8-11]. However, presently, the most prominent clinical role for PARP inhibitors lies within the field of oncology especially the breast cancer susceptibility proteins (BRCA) resistant breast and ovarian cancers. Inhibition of PARP sensitizes tumor cells to cytotoxic drugs that induce DNA damage that would normally be repaired through the BER pathway. PARP-1 inhibitors have consistently demonstrated potentiating effects on the DNA-alkylating agent temozolomide (TMZ) in preclinical studies, including experimental models of solid tumors such as glioma, melanoma, colorectal, and breast cancer. PARP-1 inhibitors have been demonstrated to sensitize tumors to DNA-alkylating agents (TMZ and cyclophosphamide) as well as topoisomerase I poisons such as camptothecin and irinotecan (CPT-11) [4,12-15]. The PARP-1 counteracts camptothecin action by facilitating resealing of DNA strand breaks.[14,16] Hence, PARP-1 inhibition hampers topoisomerase-I activity favoring the toxic effects of the enzyme poisons. Indeed, preclinical *in vivo* studies have shown that the combination of the PARP-1 inhibitor CEP-6800 and CPT-11 significantly reduces tumor volume of HT-29 colon carcinoma subcutaneous xenografts compared to CPT-11 monotherapy [13]. TMZ is a second-generation DNA-alkylating agent and although TMZ was not effective in a phase II clinical trial against metastatic breast cancer as a monotherapy [17]. It is currently in phase II clinical trial in combination with the PARP-1 inhibitor AG014699 from Pfizer [18,19] and demonstrated promising results in a phase I trial [19].

The majority of the inhibitors of PARP-1 contain either free or cyclic amide in their structures (Figure 2). Molecular insight between the PARP-1 and the inhibitors has been shown to bind with the catalytic domain of PARP-1 with "conserved" and "unconserved" interactions. Conserved interactions include two lone pair electrons of the carbonyl oxygen atom of amide forms two critical hydrogen bonds, one with the side chain hydroxyl of

Figure 3. Conserved interactions shown with PARP-1 and quinazolinone inhibitor [20].



Ser904 and the second with the backbone -NH of Gly863 (Figure 3). The -NH of the amide usually are involved in hydrogen bonding interaction with the backbone carbonyl oxygen atom of Gly863. Electron rich phenol side chain of Tyr907 is found to have critical role in the interactions with phenyl portion of the ligands in face-to-face, π-π interactions as shown in our previous published report [20]. Unconserved interactions include the other interactions present with the inhibitors based on their structures.

Thus there is sufficient preclinical and clinical evidence to support the notion that combined inhibition of PARP enzyme in conjunction with DNA-damage will significantly benefit tumor patients. Thus, development of PARP inhibitors could potentially be useful to gain disease control without potentiating side effects and is an interesting research area providing innovative cancer treatment opportunities.

Conclusion and Remarks

There is a great interest for the clinical development of PARP-1 inhibitors as a monotherapy against BRCA-associated ovarian or breast cancer or in combination therapy with other SSBs targeting chemotherapeutic agents in TNBC. However, a number of limitations need to be carefully addressed, before this can be successfully used in the clinics. It is important to realize that PARP on a continuous basis monitors DNA mutations; therefore PARP inhibition may lead to secondary malignancy similar to BRCA mutations, due to its inability to repair normal cellular processes. In addition, it is becoming clearer that PARP-1 inhibitors may require intact BER mechanisms and BRCA-mutations to produce synergistic response with specific DNA damaging agents. This is important to determine agents for combinatorial treatment. Previous clinical trials have shown differential toxicity profiles, pharmacokinetic profiles and resistance mechanisms of different PAPR-1 inhibitors, when used alone or in combinations with other chemotherapeutics, leading to not so favorable results in early clinical trials. Furthermore, the toxicity with long-term treatment with PARP-1 inhibitors is not tested yet and this may be a concern; especially myelosuppression, which was reported with continuous rather than intermittent treatment of PARP inhibitors.

A number of unanswered questions with PARP utility in clinics need to be addressed. For example, how are the PARP activated? What are the mechanisms for their cardio- and neuro-protection roles observed earlier? Does the PARP-1 sensitize cancer cells due to their effects on inflammatory pathways? The downstream signaling of PARP-1 mediated cascade i.e. range of signaling molecules recruited by PARP-1 is not clear. One may also need to identify clinical conditions and consider signaling pathways involved, in addition to pathogenetic and biochemical features that sensitizes the tumors to PARP inhibitors. For example, PARP-1 signaling has a wide scope and so abnormalities in PTEN, Rad51, ATM, Fanconi's anemia proteins, EMSY and TNKS should be considered in addition to BRCA1/2 mutations in patients with HR defects before treatment. Deeper understanding of DNA repair mechanisms, while refining the mechanisms of PARP-1 inhibition will improve clinical utility of PARP-1 inhibitors in the treatment of cancer.

Conflict of Interest

All the authors declared no potential conflict of interest.

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