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# DNA Damage Repair and the Emerging Role of Poly(ADP-ribose) Polymerase Inhibition in Cancer Therapeutics

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## ABSTRACT

**Purpose:** As a result of improved understanding of DNA repair mechanisms, poly(ADP-ribose) polymerase inhibitors (PARPi) are increasingly recognized to play an important therapeutic role in the treatment of cancer. The aim of this article is to provide a review of PARPi function in DNA damage repair and synthetic lethality and to demonstrate how these mechanisms can be exploited to provide new PARPi-based therapies to patients with solid tumors.

**Methods:** Literature from a range of sources, including PubMed and MEDLINE, were searched to identify recent reports regarding DNA damage repair and PARPi.

**Findings:** DNA damage repair is central to cellular viability. The family of poly(ADP-ribose) polymerase proteins play multiple intracellular roles in DNA repair, but function primarily in the resolution of repair of single-strand DNA breaks. Insights through the discovery of germline *BRCA1/2* mutations led to the understanding of synthetic lethality and the potential therapeutic role of PARPi in the treatment of cancer. Further understanding of DNA damage repair and the concept of *BRCA*-like tumors have catalyzed PARPi clinical investigation in multiple oncologic settings.

**Implications:** PARPi hold great promise in the treatment of solid tumors, both as monotherapy and in combination with other cancer therapeutics. Multiple PARPi clinical trials are currently underway. Further understanding of aberrant DNA repair mechanisms in the germline and in the tumor genome will allow clinicians and researchers to apply PARPi most strategically in the era of personalized medicine. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮) 

**Key words:** DNA damage, DNA repair, neoplasms, poly(ADP-ribose) polymerase inhibitors.

## INTRODUCTION

Maintenance of genetic integrity is central to cellular viability. Disrupting genomic stability through the introduction of DNA damage compromises genetic accuracy with resultant mutations leading to cell death or pathology. Cellular mechanisms exist to protect DNA integrity, specifically through a DNA damage response (DDR) system that provides surveillance for and repair of DNA damage to decrease mutation burden.

The hallmark of cancer cells is genomic instability introduced by various insults that lead to DNA damage. Investigating the predisposition of patients with heritable breast cancer led to the identification of *BRCA1/2*, genes encoding tumor suppressor genes involved in DDR with the goal to maintain genomic instability. Since that landmark discovery, increased understanding of *BRCA*-mediated carcinogenesis and DDR mechanisms has led in turn to a growing arsenal of anticancer therapies. Cancer therapeutics used to induce DNA damage, such as radiation therapy and chemotherapy, now includes targeted therapies to DDR proteins, in the form of poly(ADP-ribose) polymerase inhibitors (PARPi). Fully understanding the caretaker role of poly(ADP-ribose) polymerase (PARP) in development of both inherited and sporadic cancer development will allow clinicians to fully exploit this class of anticancer agent either as monotherapy or synergistically with additional targeted agents or traditional chemotherapeutics.

Our aim is to provide a review of PARP function in DNA damage repair and synthetic lethality, and demonstrate how these mechanisms can be exploited

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to provide new PARPi-based therapies to patients with solid tumors.

## METHODS

Literature from a range of sources, including PubMed and MEDLINE, were searched to identify recent reports regarding DNA damage repair and PARPi.

## RESULTS

### DNA Damage Repair

The DNA damage response (DDR) system evolved to detect and repair the tens of thousands of potentially mutagenic endogenously and exogenously acquired DNA lesions that typically accrue each day.[1,2] This system encompasses multiple redundant DNA repair pathways that repair lesions with the aim to mitigate DNA damage and preserve genomic stability. These include repair of more commonly encountered single-stranded breaks (SSBs), small DNA lesions or modifications affecting single base pairs, and more lethal double-stranded breaks (DSBs).

SSBs most commonly occur as direct consequence of daily cellular operations, such as oxidation by reactive oxygen species. Repair of lesions induced by ultraviolet radiation and alkylating agents generate SSBs with repair of isolated nucleotide defects, such as with endonuclease removal of DNA lesions detected by mismatched repair DNA surveillance systems or by removal of photodimer lesions or chemotherapy-induced crosslinks. Ultimately, these lesions may also prevent actively replicating polymerases from traversing the lesion. These SSBs are detected and repaired by pathways that include base-excision repair, which is the major pathway of SSB repair (BER). The SSB pathway is composed of several proteins that systematically repair DNA by removal of lesions, regeneration of sequence by polymerases, and sealing the break with ligases with several regulator proteins. Specifically, this includes removal of lesions with damage-specific DNA glycosylases (for example UNG, NEIL, and MYH) and endonucleases (APE1 and FEN1), which creates an SSB. This break is then stabilized by PARP1, which binds the SSB, and then recruits the DNA-repair scaffolding protein XRCC1. XRCC1 interacts with DNA polymerase β and DNA ligase to replicate the DNA and repair the SSB.[3,4] Additional mechanisms to repair specific DNA lesions include nucleotide excision repair, mismatch repair, and direct repair mechanisms that correct erroneous methylation or alkylation by use of enzymes (eg, $O^6$-methylguanine DNA methyltransferase).

Whereas the BER pathway repairs the most common DNA lesions, DSBs are the most deleterious and lethal lesions. DSBs can result from stalled and subsequent collapsed replication forks, such as inter- and intrastrand crosslinking, ionizing radiation, or chemotherapy (topoisomerase inhibitors and platinum agents). Additionally, DSBs may accumulate with persistence of unrepaired SSBs or defective repair pathways. Four major pathways repair DSBs. Each pathway is interconnected with signaling molecules capable of activating downstream cellular events affecting cell fate, such as cell cycle arrest, cell death, or tumorigenesis. These pathways include classical nonhomologous end joining (c-NHEJ), alternate- EJ (alt-EJ), single-strand annealing (SSA), and homologous recombination (HR).[5,6]

DSBs repaired by the first pathway, c-NHEJ, rely upon rapid blunt-ended enzymatic ligation, whereas the alternate pathways generate overhangs for repair involving polymerases. The benefit of c-NHEJ is its rapid kinetics that may be useful in suppressing chromosomal translocations. However, the repair process does not involve sequence homology with replication and is highly error-prone. Alternatively, the end clipping that generates staggered overhangs can be repaired by the alt-EJ, SSA, or HR pathway. However, despite some homology-dependent repair, both alt-EJ and SSA result in loss of genetic information, and are also notoriously error-prone. For example, SSA repair results in deletion of DNA between areas of repeats, or microhomologous regions, whereas alt-EJ, a pathway using PARP1 and XRCC/DNA ligase III, has demonstrated its tendency to join DSBs on separate chromosomes resulting in translocations. The advantage of the fourth major DSB repair pathway, HR, is its dependence on a sister chromatid template for high-fidelity repair. It is considered error-free repair. The cell cycle phase dictates the predominant DSB repair pathway with end resection and HR predominating in the S phase and G2 phase when sister chromatid templates are available. Cyclin-dependent kinase-mediated phosphorylation of multiple proteins mediates these pathways and includes ataxia telangiectasia mutated (ATM) kinase-dependent phosphorylation, which promotes end-resection and HR.[5,6]