DNA Repair Dysfunction in Pancreatic Cancer: A Clinically Relevant Subtype for Drug Development

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, with a 5-year survival rate of $\leq 7\%$ across all stages. The limited success of conventional therapies for PDAC is at least partially attributable to its genetic heterogeneity. Precision targeting of known PDAC subtypes may positively affect the outcome of this disease. An important actionable subtype in this cancer is associated with DNA repair dysfunction, including cases with germline *BRCA* mutations. This subtype can be targeted by inhibitors of poly(ADP-ribose) polymerase (PARP). *BRCA* mutation-associated PDAC may be the first biomarker-driven subtype in this disease that can be successfully targeted. However, DNA repair defects can extend beyond the narrow spectrum of *BRCA1/2* mutations in PDAC and are present in a large proportion of patients with familial PDAC. This review describes the subgroup of patients with PDAC with aberrant DNA repair and discusses diagnostic and therapeutic options.

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Pancreatic ductal adenocarcinoma (PDAC) is a life-threatening disease and is the fourth-leading cause of cancer death in the Western world. In 2016, an estimated 53,070 patients were diagnosed with PDAC and 41,780 people died of the disease in the United States.¹ Most patients are diagnosed with advanced disease and median overall survival (OS) is < 6 months, a figure that has not changed in the past 2 decades.² Patients with PDAC with a good performance status experience a median OS of 9 to 11 months with combination therapies (gemcitabine/nab-paclitaxel or FOLFIRINOX).^{3,4} Despite numerous phase II/III studies of PDAC in the past decade, treatment options remain limited.⁵

Advances in other solid tumors have been possible due to biomarker selection of specific patient populations. Successful examples include *ALK*-positive lung cancer and *HER2*/neu-positive breast cancer.^{6,7} This review describes the subgroup of patients with DNA re-

pair mechanism aberrations, their identification, and therapeutic options.

Historical Perspective

A biological repair process follows chemical and environmental damage to DNA. The first link to defective DNA damage repair (DDR) and cancer arose from 2 clinical observations. Cleaver⁸ noted that patients with the autosomal recessive disorder xeroderma pigmentosum, who are at an increased risk of developing skin cancer, have difficulty in repairing UV light-related DNA damage. It was later demonstrated that the specific defect in this case resulted from mutations in the nucleotide excision repair system. The second observation in the 1990s was Lynch syndrome, a hereditary nonpolyposis colorectal cancer resulting from microsatellite instability (MSI), resulting from DNA mismatch repair impairment (MMR).⁹ Additionally, in 1991, King et al¹⁰ discovered that the *BRCA1*

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gene on chromosome 17 is involved in homologous recombination repair. Mutations in *BRCA1/2* predispose women to familial breast and ovarian cancers, men to prostate cancer, and both sexes to upper gastrointestinal malignancies, including PDAC. Other cancers associated with defective DNA repair include Bloom syndrome, Werner syndrome, and Fanconi anemia. It has been hypothesized that cancers with a hereditary predisposition may frequently harbor mutations in DNA repair genes.¹¹

Germline DNA Repair Defects and PDAC

The genetic basis of PDAC has been explored in several recent studies, and increased PDAC risk was found to be associated with inherited syndromes, of which the most intensely investigated group is with *BRCA1/2* germline mutations. The prevalence of germline *BRCA* mutations was initially thought to be approximately 4% to 5% in PDAC.¹² However, more recent and larger prescreening efforts for the POLO study (discussed later) demonstrated a higher prevalence, and has a prescreening selection for *BRCA* germline mutations. To date, >1,000 patients with metastatic PDAC who received platinum-based therapy have been screened, with an incidence rate of 6% to 7% detected in this unselected patient population.¹³ In high-risk populations, including the Ashkenazi Jewish population, the prevalence can be up to 20%.^{14,15} Other inherited PDAC syndromes have mutations in *MMR* genes, *CDKN2A*, and the hereditary pancreatitis genes.^{16,17}

Next-generation sequencing studies have further noted *PALB2* and *ATM* germline mutations in PDAC kindreds. In the PACGENE Consortium study, 10% of patients with PDAC and a positive family history (kindred with ≥ 2 first-degree relatives with PDAC) had germline mutations in one of the genes mentioned.¹⁸ The Ontario Cancer Registry used a more variable definition of family history and noted a lower incidence (3.8%) of germline mutations in these genes using a 13-gene panel.¹⁹ Wider gene panels that incorporate additional DNA repair genes may be incremental in this regard. A recent 25-gene panel investigated 303 patients with familial PDAC and noted germline mutations in 10 genes (*ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *PALB2*, *PMS2*, *BARD1*, *CHEK2*, *MUTYH*, and *NBN*), most of which are involved in DNA repair, in 12% of the cases.²⁰ Also

of interest in this group were the Fanconi anemia (*FANCC* and *FANCG*) genes that are mutated (somatic or germline) in a fraction of young patients with PDAC.²¹ Uncommon pancreatic types, such as acinar carcinoma, have a higher prevalence of *BRCA* germline mutations.²² The role of several of these DNA repair genes has only recently been explored in PDAC.

Somatic Mutations Associated With Aberrant DNA Repair

With increased understanding of cancer genetics, the mechanisms of DNA repair have been increasingly understood over the past decade. It has been proposed that DDR defects also occur in sporadically occurring tumors, such as somatic *BRCA1/2*, *ATM*, *RAD51*, *FANCC*, and *PALB2* mutations (Figure 1). The clinical implications of these mutations and response to DNA repair inhibitors are under investigation.

DDR Dysfunction in Cancer

Cancer cells typically have reduced or aberrant DNA repair and damage signaling response, and are reliant on alternative pathways that may be susceptible to DNA-damaging agents. Double-strand break repair (DSBR) pathways include nonhomologous end joining and homologous recombination repair, whereas single-strand breaks are repaired by base excision repair, MMR, and nucleotide excision repair.²³ DDR is a well-defined process, and its components are classified into sensors, transducers, mediators, and effectors (Figure 2). *ATM*, *ATR*, and DNA-PK (DNA-dependent serine/threonine protein kinase catalytic subunit) kinases are important components of this mechanism.²⁴ Genetic sequencing has highlighted the importance of these pathways in PDAC.

Recent large-scale whole-genome sequencing (WGS) of PDAC has subtyped these cases based on molecular profiles (Table 1). These studies identified a well-defined subgroup of patients (12%–17%) harboring DDR-deficient tumors. Bailey et al²⁵ defined these patients as having an aberrant *BRCA* pathway. From a cohort of 456 tumors, 32 oncogenic genes were identified, which aggregated into 10 molecular mechanisms. The *BRCA* pathway included *BRCA1/2*, *ATM*, and *PALB2*, with a prevalence of 5% in germline and 12% in somatic PDACs. Waddell et al²⁶ performed WGS studies of PDAC and classified this

DNA Repair Dysfunction in PDAC

Figure 1. Types of DNA repair.

Abbreviations: BER, base excision repair; DSB, double-strand break; HR, homologous recombination repair; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining.

disease into 4 subtypes based on the patterns of structural variation: stable, locally rearranged, scattered, and unstable. Unstable genomes have >200 structural variations and are enriched with aberrant DNA repair genes, including *BRCA1/2* and *PALB2*. Other genetic mutations detected in the unstable subtype include *ATM*, *FANCM*, *XRCC4*, and *XRCC6* and a previously described *BRCA* mutational-signature.²⁷ Connor et al²⁸ classified 255 PDACs based on mutation signatures and identified 4 major subtypes, including a DSB group attributed to deficiencies in homologous recombination and DSB that occurred in 11% of tumors.

Mutations in these genes, however, account for only half of the patients with unstable genomes or the DDR mutational signature. Additional mechanisms involved in aberrant DNA repair may include hypermethylation, which can silence the *BRCA* or *PALB* genes. Thus, the spectrum of DDR in PDAC is vast and still being understood. These studies also correlate well with clinical observations, in which there may be a clinical DDR phenotype (family history of *BRCA*-associated malignancies and responsiveness to platinum-based therapies without any known genomic DDR aberrations).²⁹

DDR Therapeutics

Therapeutic strategies to target DNA repair pathways have been used in anticancer treatments for decades.

The best recognized among these are the chemotherapeutic DNA-damaging agents (platinum, topo II/I inhibitors, antimetabolites, alkylating agents, and radiation; Table 2). Novel DDR inhibitors can be categorized into 3 groups based on their mechanism of action: (1) agents targeting DDR sensor proteins, which include poly(ADP-ribose) polymerase (PARP) inhibitors; (2) agents targeting DDR-signaling proteins (DNA-PK, ATM, ATR); and (3) agents causing transient cell cycle delays, such as checkpoint inhibitors and WEE-1 inhibitors (Table 2). These agents are being investigated alone or in combination with DNA-damaging chemotherapy or radiotherapy.^{30,31}

Foremost among the targeted DNA repair inhibitors in clinical development today are the PARP inhibitors. PARP has a role in DNA base excision repair and repair of DNA single-strand breaks. In patients with germline *BRCA1/2* mutations, cancer cells depend on PARP-1 for their survival. In these cases, synthetic lethality induced by PARP-1 inhibitors has resulted in clinical benefit.³² The PARP-1 inhibitor olaparib demonstrated durable antitumor responses in *BRCA1/2*-mutated ovarian, breast, and prostate cancers.^{33–35} Olaparib and, more recently, rucaparib have been FDA-approved for *BRCA1/2*-mutated ovarian cancer. Ongoing studies are investigating the role of PARP-1 inhibitors in PDAC with *BRCA* mutations and other DNA repair defects.

Single-agent PARP inhibitor therapy has demonstrated clinical responses in *BRCA*-associated

Figure 2. DNA repair pathway and drugs in development. Abbreviations: DSB, double-strand break; SSB, single-strand break.

PDAC, and additional clinical trials evaluating PARP inhibitors in combination with platinum-based chemotherapy are ongoing. Two single-arm phase II studies of single-agent PARP inhibitors have been conducted in patients with germline *BRCA*-mutated malignancies. In one study,³⁴ 23 patients with germline *BRCA* mutation–associated PDAC were treated with olaparib after gemcitabine therapy; all patients had received prior gemcitabine and >50% received a prior platinum-containing regimen. The objective response rate was 22%, disease control rate was 57%, progression-free survival

was 4.6 months, and OS was 9.8 months. Another study³⁶ investigated the role of rucaparib in 19 patients with PDAC who received 1 to 3 prior chemotherapy regimens for locally advanced or metastatic PDAC. Rucaparib demonstrated clinical benefit in 6 (32%) of the 19 patients; 1 had a complete response and 2 had partial responses, whereas 4 had stable disease. The objective response rate, the primary end point for the study, was 16%. No response was seen in platinum-refractory cases.

Emerging data from germline *BRCA* mutation–associated PDACs suggest that patients with platinum resistance may also be PARP inhibitor–resistant. This cross-resistance was also observed previously in ovarian cancer.³⁷ Therefore, it is suggested that although it is important to treat patients with DDR initially with platinum-based treatments for tumor burden reduction, there may be benefit to introducing PARP inhibitors into the therapeutic plan before platinum resistance develops. This strategy forms the background for the POLO study. In this international trial, patients with germline *BRCA*-mutant PDAC are randomly assigned after platinum-based induction therapy to maintenance

Table 1. DDR Subgroups in Pancreatic Ductal Adenocarcinoma		
DDR Classification	Prevalence	Reference
Oncogenic alterations in <i>BRCA</i> pathway genes	Total: 17% 5% germline 12% somatic	Bailey et al ²⁵
Unstable genome	14%	Waddell et al ²⁶
<i>BRCA</i> mutation signature	NA	Alexandrov et al ²⁷
Double-strand break deficiency	Total: 10.8% 4.4% germline 1.6% somatic 4.8% <i>BRCA</i> ness	Connor et al ²⁸

Abbreviations: DDR, DNA damage repair; NA, not available.

Table 2. DDR Therapeutics

Mechanism	Target Inhibition	Compounds
DDR sensors	PARP	Niraparib, talazoparib, olaparib, veliparib
DDR transducers/signaling pathway	DNA-PK	MSC2490484A, VX-984, CC-115
	ATM	AZD0156
	ATR	AZD6738, VX-970
DDR effectors	CHK1	MK8776, LY2603618, CCT245737, GDC0575
	CHK1/2	LY2606368
	WEE-1	AZD1775
Binds base excision repair sites	Topo II inhibitors	TRC102

Abbreviations: DDR, DNA damage repair.

therapy with olaparib or to placebo (ClinicalTrials.gov identifier: NCT02184195).

Germline DDR Dysfunction: Prognostic or Predictive

PDACs with germline *BRCA* mutations are the most extensively investigated subgroup of the DDR dysfunction subgroup; these patients are identified through germline *BRCA1/2* testing. Retrospective analyses indicated that these patients experience improved survival with platinum-based chemotherapy compared with non-platinum-based treatments or historic controls.³⁸ The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma currently recommend treating these patients with platinum-based treatments, specifically gemcitabine/cisplatin.³⁹ These observations have led to the hypothesis that “*BRCA*-positivity” may be a predictive biomarker for platinum/PARP inhibitors. The prognostic role of *BRCA* mutations is less proven. In a retrospective case-control analysis of patients with surgically resected PDAC (stage I/II), no significant difference was demonstrated in median OS (37.06 vs 38.77 months; $P=.838$) or disease-free survival (14.3 vs 12.0 months; $P=.303$) between *BRCA* mutation-positive cases and controls.⁴⁰ The prognosis of patients with surgically resectable *BRCA*-associated PDAC thus appears to be no different from that of patients with sporadic PDAC. The role of platinum-based adjuvant therapy in this setting is still unclear.

Aberrant DNA Repair: Identification of Patients

WGS studies were described earlier. The current clinical assays for DDR are limited to sequencing a panel of genes that are associated with an inherited risk of PDAC and other cancers. Given the large spectrum of DDR deficiency, functional assays will be the next frontier of research in this field.

Functional Assays

Focusing entirely on genomic alterations will not be sufficient due to hypermethylation and other epigenetic alterations of the DNA repair genes. Functional assays of DDR deficiency need to be explored in parallel. To obtain a comprehensive molecular understanding of homologous recombination repair process, rather than taking a single gene approach to analyze homologous recombination repair in cells, Peng et al⁴¹ used a genome-wide gene expression profiling approach to measure the cellular transcriptome reprogramming in homologous recombination-deficient (HRD) cells. They identified 230 genes that were differentially expressed between HRD cell lines (with *BRCA1*, *RAD51*, or *BRIT1* loss) and controls ($P<.001$), and designated this set the HRD gene signature. The HRD signature genes were involved in cell cycle regulation, DNA replication, and DNA repair pathways. The investigators showed responsiveness of this signature to PARP-1 inhibition. Additional assays include *RAD51* foci at DNA damage sites in biopsies after neoadjuvant chemotherapy in breast cancer. Failure to generate *RAD51* foci in cells was predicative of a pathologic complete response ($P=.011$).⁴² Recently, deleterious *ATM* mutations have been recognized in the germline of families with familial PDAC, suggesting that *ATM* is a susceptibility gene in hereditary PDAC.¹⁸ Somatic *ATM* loss, as shown by immunohistochemistry (IHC), was observed in 50 (12.8%) of 396 PDAC.⁴³ Impaired *ATM* signaling may be identified by protein loss (IHC) and serve as a biomarker for the identification of the DDR signature in PDAC. PARP inhibition in combination with paclitaxel was recently evaluated in patients with gastric cancer harboring *ATM* loss; however, phase III results were negative.⁴⁴

To summarize, the DDR phenotype has been identified in PDAC; however, the full spectrum is not well-defined. To further define the DDR pheno-

type, we have initiated a clinical trial of PARP inhibition with olaparib in DDR-deficient PDAC. The patient population includes individuals with *ATM* loss, genetic aberrations known to lead to DDR dysfunction (other than *BRCA* mutations), and a history of ≥ 2 breast, ovarian, or pancreatic cancers in ≥ 2 first-degree relatives. All patients are being investigated for DDR signature, and the results will be correlated with radiologic response rate (ClinicalTrials.gov identifiers: NCT02677038 and NCT02511223).

Immune Therapy and DNA Repair Deficiency

In non-small cell lung cancer associated with high nonsynonymous mutation burden and DNA repair pathway mutations, improved rates of radiologic response and progression-free survival were demonstrated when treated with checkpoint inhibitors.⁴⁵ *BRCA1/2* mutated high-grade serous ovarian carcinoma is associated with a higher mutation burden compared with non-*BRCA1/2*-mutated tumors, higher predicted neoantigens, and higher expression of “immune” genes that are associated with cytotoxicity.⁴⁶ IHC studies demonstrated that *BRCA1/2*-mutated tumors exhibited significantly increased CD3-positive and CD8-positive tumor-infiltrating lymphocytes (TILs), as well as elevated expression of PD-1 and PD-L1 in tumor-associated immune cells compared with homologous recombination-proficient tumors. Preclinical efficacy was demonstrated in the combination of PARP inhibition with cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors in a *BRCA1*-deficient murine ovarian cancer model.

With this combination therapy, effector T cells were increased in the peritoneal cavity.⁴⁷ Another DNA repair alteration associated with responsiveness to checkpoint blockage is defective MMR that results in MSI. Pembrolizumab is FDA-approved for MSI-high cancers, including PDAC.⁴⁸ MMR deficiency in PDAC, however, is rare.

In PDAC, concordance of PD-L1 expression with *BRCA2* and *BRCA1* mutations was demonstrated in 50% and 13% of cases, respectively. Compared with the general PDAC population, *BRCA1*-mutated cases have a higher incidence of PD-1 TILs, whereas *BRCA2*-mutated cases had a higher incidence of overexpressed PD-L1.⁴⁹ WGS and transcriptome analysis identified 12% DDR cases in PDAC, and these were also associated with antitumor immune activation.²⁸ DSBR and MMR subtypes were associated with increased expression of antitumor immunity, including activation of CD8-positive T lymphocytes and overexpression of regulatory molecules (CTLA-4, PD-1, and indolamine 2,3-dioxygenase 1), corresponding to a higher frequency of somatic mutations and tumor-specific neoantigens.²⁸ Thus, considerable evidence currently exists to explore immune therapy approaches in DDR-deficient patients.

Conclusions

The DDR-deficient subtype of PDAC constitutes an important, clinically relevant, and actionable subset that extends beyond *BRCA* deficiency, and this subset has many targeted therapeutic possibilities. However, identification of this subset beyond the spectrum of *BRCA1/2* deficiency remains a challenge.

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