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Review

Opportunities for translation: Targeting DNA repair pathways in pancreatic cancer

Elaina N. Maginn *[,1], Camila H. de Sousa [1], Harpreet S. Wasan, Euan A. Stronach

Molecular Therapy Laboratory, Department of Cancer and Surgery, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0NN, United Kingdom

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) remains one of the poorest prognosis neoplasms. It is typified by high levels of genomic aberrations and copy-number variation, intra-tumoural heterogeneity and resistance to conventional chemotherapy. Improved therapeutic options, ideally targeted against cancer-specific biological mechanisms, are urgently needed. Although induction of DNA damage and/or modulation of DNA damage response pathways are associated with the activity of a number of conventional PDAC chemotherapies, the effectiveness of this approach in the treatment of PDAC has not been comprehensively reviewed. Here, we review chemotherapeutic agents that have shown anti-cancer activity in PDAC and whose mechanisms of action involve modulation of DNA repair pathways. In addition, we highlight novel potential targets within these pathways based on the emerging understanding of PDAC biology and their exploitation as targets in other cancers.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the poorest prognosis cancers with a very high mortality, accounting for ~2% of cancer cases worldwide [1]. The common symptoms of PDAC include abdominal or back pain, obstructive jaundice, and weight loss. However, these usually appear towards the later stages of the disease and the vast majority of patients thus present with advanced inoperable, metastatic disease with a median survival of 4–11 months [2,3]. For patients who present with operable disease (<15% of cases) tumour resection (Whipple procedure) is the treatment of choice, and optimal surgery can result in a cure, although the median overall survival (OS) remains low at 15-19 months. Even in operable cases of PDAC the overall 5-year survival rate is only 11% without adjuvant chemotherapy, and 21% with [1,2]. The use of adjuvant chemotherapy has consistently demonstrated OS benefits above resection alone and may delay disease recurrence; thus it is recommended for all patients [4]. However, as PDAC is more prevalent amongst the elderly, with a median age of diagnosis of 72 years, additional medical conditions may contraindicate surgical procedures [5,6].

Abbreviations: ATR, ATM-Rad3-related; BER, base excision repair; Chk1, checkpoint kinase 1; DDR, DNA damage response and repair; DNA-PKcs, DNA-PK catalytic subunit; DOT1L, DOT1-like; DSB, double strand break; FOLFIRINOX, folinic acid, 5-FU, irinotecan, oxaliplatin; 5-FU, 5-fluorouracil; HR, homologous recombination; Mdm2, murine double minute 2; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; NSCLC, non-small cell lung cancer; OS, overall survival; PARP, poly-ADP-ribose-polymerase; PARPBP, PARP1 binding protein; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; SSB, single-strand break; TDP, tyrosyl-DNA-phosphodiesterase; TIM, timeless; VCP, vasolin containing protein

* Corresponding author. Tel.: +44 20 759 42121.
E-mail address: e.maginn@imperial.ac.uk (E.N. Maginn).
[1] Authors contributed equally.

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PDAC originates in the pancreatic ductal epithelium and evolves in a step-wise manner from pre-malignant lesions to fully invasive cancer [7]. PDAC development has been linked to a number of environmental factors such as tobacco smoking, which increases risk by ~2-fold [8]. In addition, advanced age and chronic medical conditions such as diabetes and pancreatitis are associated with increased risk [9,10]. Familial PDAC accounts for ~10% of cases and is associated with germline mutations in a number of genes including *BRCA2* and *PALB2* [11]. A characteristic set of molecular aberrations for PDAC development has been identified, with the genetic aberrations and associated cellular events underlying disease progression (e.g. cell growth and proliferation, apoptosis, migration) defined as early (*KRAS*, *ERBB2*), intermediate (*CDKN2A*) or late (*TP53*, *SMAD4*, *BRCA2*) occurrences during the process [12]. Extensive heterogeneity in the genetic aberrations detected both between PDAC patients [13,14] and within multiple clonal populations of individual tumours [15] have been documented. As such, a common specific molecular initiator of PDAC, if one exists, has yet to be defined. However, PDAC-associated genomic aberrations can be classified into core signalling pathways – including *KRAS* signalling, cell invasion and adhesion, DNA damage control, apoptosis [13,14,16] – thereby identifying key processes with the potential for therapeutic targeting.

For over 15 years, gemcitabine, either as single agent or in combination with other cytotoxic drugs, has been the standard chemotherapeutic agent for PDAC. However, while combining gemcitabine with other cytotoxic agents has improved progression-free survival (PFS) in some trials, a significant increase in OS, compared with gemcitabine monotherapy, has not been convincingly demonstrated in the majority [17–19]. Recently the gemicitabine-free FOLFIRINOX protocol (5-fluorouracil (5-FU), folinic acid, irinotecan, oxaliplatin) has demonstrated an increased overall survival to 11.1 months, from 6.8 months for gemcitabine alone [20]. However, toxicity and safety issues limit the routine administration of this regime to less than half of the advanced cases [20,21]. A more tolerable chemotherapy recently developed is the combination of gemcitabine with albumin-bound paclitaxel (*nab*-paclitaxel, Abraxane®) [22] which has demonstrated efficacy in patients with advanced PDAC [23–25], with a phase 3 clinical trial showing an improvement in median OS to 8.5 months, compared with 6.7 months for gemcitabine alone [23].

Irrespective of the regimen used, low response rates and a lack of sustained therapeutic efficacy remain a fundamental problem and feature of PDAC. Uncertainty continues to exist about the optimal use of combination chemotherapy regimens and sequencing in the treatment of this malignancy. Recent advances in the molecular understanding of PDAC suggests that targeting the DNA repair capacity of PDAC, in combination with DNA damaging agents, may represent an effective therapeutic strategy. Consistent with this, a number of studies have demonstrated the therapeutic potential of chemotherapy regimens incorporating DNA damaging agents, in particular platinum-based compounds, in PDAC [17–19]. The induction of DNA damage and/or modulation of DNA damage response (DDR) pathways has also been associated with the activity of a number of other chemotherapeutic agents proposed for use in PDAC. This review aims to discuss translational research progress in this area and highlights potential targets and strategies for improving outcome in PDAC.

2. DNA damage response/repair (DDR) pathways as chemotherapeutic targets in PDAC

Damage to the DNA of a cell can occur spontaneously, for example due to replication errors, or may be induced by exogenous factors such as radiation and environmental chemicals. As such, accurate repair mechanisms are crucial in order to maintain genome integrity, and consequently all cells are equipped with a number of DDR pathways. If cells are unable to repair the damage, they may undergo apoptosis in order to prevent replication of abnormal cells. DDR pathways are therefore vital to cell survival, and the presence of multiple repair processes ensures that if one is lost, an alternative mechanism may compensate. The importance of understanding DDR pathways in the context of cancer biology is evident as the mechanism of action of a number of chemotherapeutic drugs is via induction of DNA damage. DNA lesions induced by chemotherapeutic drugs include bulky adduct formation, base damage or misincorporation, DNA crosslinks, and DNA breaks, either single strand (SSB) or double strand (DSB). The key pathways which repair these lesions are the nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) pathways. The principal processes and proteins involved in these pathways, as well as the common types of damage they recognise and repair, are listed in Table 1 (for detailed reviews of pathway mechanics see Jiricny [26]; Caldecott [27]; Leiber [28]; Cleaver et al. [29]; Moynahan and Jasin [30]).

Aberrant or dysregulated activation of DDR pathways are associated both with susceptibility to cancer, the tumourigenic process and resistance to chemo- and radio-therapy [31]. As such, disruption of these pathways has been identified as a strategic approach to increase therapeutic responses to DNA damaging agents in a number of cancer types (for excellent reviews see Al-Ejeh et al. [32]; Bouwman and Jonkers [33]; Lord and Ashworth [34]. The clinical relevance of targeting DDR pathways to enhance PDAC response to DNA damaging agents is highlighted by Jones et al., who identified DNA damage control as a core signalling pathway disrupted by PDAC-associated genetic aberrations. Additionally, polymorphisms within genes encoding DDR proteins have been associated with PDAC development and resistance to gemcitabine [35–38].

In addition to their application as enhancers of response to cytotoxic chemotherapy, the clinical development of DDR targeting drugs as anticancer agents has been designed around the concept of synthetic lethality, in which effectiveness is dependent on the genetic background of the cells with respect to competency in DDR pathways (Fig. 1). Poly-ADP-ribose-polymerase (PARP) inhibitors represent the most well known paradigm of synthetic lethality. PARPs are a family of nuclear enzymes, of which PARP-1, -2 and -3 are activated following binding to broken DNA ends. Subsequent to their activation, these proteins catalyse the formation of poly-ADP-ribose polymers which attract repair proteins, including XRCC1 and LIG3, to the sites of DNA damage. The best characterized member of this family is PARP-1, which is predominantly associated with BER-mediated repair of SSBs [39–42]. PARP-1 inhibition has been shown to be most effective in tumour cells with defective HR pathways, due to mutations in the *BRCA1* and/or *BRCA2* genes [43]. Conventionally, it has been understood that under these conditions PARP-1 inhibition prevents BER-mediated repair of SSBs, while DSB repair cannot occur due to inherent defects in HR pathways. The net result of this is accumulation of lethal levels of DNA damage [44,45]. *BRCA2* mutations have been associated with both sporadic and familial cases of PDAC [46–50]. Defects in other HR genes, namely *PALB2* (a BRCA protein binding protein) and *ATM* have been associated with PDAC [16,51]. The presence of such aberrations is likely to affect chemotherapy response, and as will be discussed later, should be a consideration when developing therapies incorporating DDR-targeting agents.

3. Gemcitabine and platinum compounds

Gemcitabine was established as the standard of care for PDAC following the pivotal phase III clinical trial in 1997 demonstrating its greater efficacy compared with 5-FU [52]. Conventionally, the mechanism of action of gemcitabine has been attributed to inhibition of DNA synthesis: as a nucleoside analogue, it is incorporated into replicating DNA in place of cytidine molecules. The position of the gemcitabine moiety as the penultimate nucleotide at the 3′ end of the nascent DNA strand is important in preventing its recognition and removal by DDR exonucleases, and its presence results in termination of the synthesis process. Additionally, gemcitabine actively inhibits DNA polymerase