# DNA repair as treatment target

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The extensive links between DNA damage and cancer are well documented [1]. DNA damage underlie many of the mutations or genetic rearrangements that are observed in cancer and indeed, we know that agents that cause DNA damage in many cases also cause cancer [2]. More recent data suggest the existence of cancer-specific DNA damage, caused for instance by oncogenes or tumour microenvironment [3]. This high level of DNA damage together with defects in DNA repair, often found in cancer, will synergise to cause a high level of genetic instability in cancer.

Several anti-cancer drugs used in the clinic today induce DNA damage as their mode of action, resulting in cell death either directly or following DNA replication [1]. The underlying DNA repair status will be important for the efficiency of the therapy and developing resistance to anti-cancer therapies can often be explained by increased capability of resistant cancer cells to repair the cytotoxic lesions.

## Multiple DNA repair pathways contribute to genome stability

Many different DNA lesions are formed in cells, the most common being small base lesions and DNA single-strand breaks (SSBs) and the most toxic lesions being interstrand crosslinks and DNA double-strand breaks (DSBs) [4]. Most DNA lesions are formed during normal metabolism and are likely to be highly important contributors to the generation of cancer-causing mutations. To withstand the high load of DNA damage, several DNA repair pathways have evolved [5]. Base excision repair has evolved for repairing numerous different forms of base damage. There is a large variety of DNA glycosylases that recognise different DNA base lesions and remove the damaged base. The resulting apurinic or apyrimidic (AP) site is then recognised by an AP endonuclease (APE1), which creates a nick that, after processing by PNKP, can be re-ligated by Ligase 1 or 3 in a process controlled by additional proteins (see Caldecott [6] for details). Similar proteins are also involved in the repair of SSBs, although they are not recognised by glycolsylases and do not need APE1-mediated DNA incision. Instead, Poly ADP-ribose polymerase (PARP1) mediates the recognition of free SSBs and then recruits the other factors required for SSB end-processing and ligation [6]. Since a SSB is present as an intermediate step during base excision repair, it has been suggested that PARP1 is involved in this process. However, PARP1 does not influence base excision repair *in vitro* [7] or in cells [8]. On the other hand PARP inhibitors trap PARP1 onto the SSB intermediate [8], making PARP inhibitors ideal for inhibiting base excision repair.

Mismatch repair is important to remove misincorporated DNA bases during replication, which might otherwise give rise to mutations.

Nucleotide excision repair is important to repair large DNA lesions, such as those produced following UV damage or poly-aromatic hydrocarbons [5]. There is also a significant overlap between the nucleotide excision repair pathway and the interstrand crosslink repair pathway, which is highly relevant, as many anti-cancer drugs are crosslinkers. In particular, the ERCC1 protein is recognised as an important prognostic marker in the treatment of gastric adenocarcinomas with 5FU and cisplatin [9], which is likely related to its activity in crosslink repair. Although the interstrand crosslink repair is highly relevant for the response to many anti-cancer drugs, molecular understanding of the pathway is still largely lacking.

The repair pathways after DSBs have been more intensively investigated and are executed by non-homologous end-joining (NHEJ) or homologous recombination (HR) [10]. While NHEJ ligates the two ends together directly, the HR pathway requires a DNA template, which is present after replication. Furthermore, HR is important for repair during replication and also to mediate a restart of stalled replication forks [11]. The HR pathway is a particularly important factor, determining the responses to many anti-cancer agents and hence, identifying inhibitors to

HR would be important in combating resistance to many anti-cancer drugs [12].

## Synthetic lethality in DNA repair pathways, a new path for novel anti-cancer therapy

Complete loss of DNA repair is not compatible with life as too many spontaneous DNA lesions would accumulate, obstructing faithful replication and transcription. However, loss of an individual repair pathway can often be compensated for by the functions of another pathway. The other pathway(s) would 'buffer' the consequences of the loss of the first DNA repair pathway. However, these other repair pathways are unlikely to repair the DNA as effectively or accurately as the first choice of pathway and hence mutations might arise. Loss of a DNA repair pathway is sometimes associated with cancer, e.g. loss of the mismatch repair machinery in hereditary non-polyposis colorectal cancer, or loss of the *BRCA1* or *BRCA2* genes in hereditary breast or ovarian cancers. In such a scenario, the cancers may rely more heavily on a buffering pathway in order to maintain cancer cell survival. We and others discovered earlier that the *BRCA* defective cells and tumours are intrinsically sensitive to PARP inhibitors, owing to the defect in HR in the absence of BRCA function [13,14]. Hence, the *BRCA* defective cancers need PARP for survival and this relationship is described as synthetic lethality. Synthetic lethality arises when a mutation in either of the two genes is compatible with survival, while mutations in both genes result in cell death.

The PARP inhibitors have proceeded into clinical trials with very successful results, demonstrating that the synthetic lethal approach to killing cancer is working [15].

Many more synthetic lethal interactions within the DNA repair area are likely to be present and much effort has been used to identify these. However, this has not been easy and we will likely have to wait another few years before we have a similar synthetic lethal concept entering clinical trials.

## Augmenting DNA damage selectively in cancers is a means to clinical success

In principal, radiotherapy, chemotherapy or the use of PARP inhibitors in the synthetic lethal approach all work by increasing the amount of DNA damage in the cancer cells to unsustainable levels. The difference with the synthetic lethal strategy and in a sense also with radiotherapy is that DNA damage can be introduced selectively in the cancer cells only, minimising the side effects to normal cells. It is well established that some cancers respond very poorly to treatment, for instance, pancreatic cancers. A problem with pancreatic cancer is that the tumours are very dense and show a high degree of hypoxia [16], which prevents drugs from entering into the tumours as well as causing resistance to radiotherapy. Recently, it has been demonstrated that oncogene inhibitors increase vascularisation [17] and in combination therapy radically improve treatment of pancreatic cancers [18], likely by allowing drugs and radiotherapy to induce DNA damage. Hence, the ability to augment the level of DNA damage in cancers, by any means, is a credible strategy for improving cancer treatment.

## Conflict of interest statement

The author is named inventor on two patents filed from the University of Sheffield on the use of PARP inhibitors to kill recombination defective cancers.

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