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Editorial

Science in Focus: Combining Radiotherapy with Inhibitors of the DNA Damage Response

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Radiotherapy kills cells by damaging DNA and the immediate outcome after radiotherapy (does the cell die or survive?) is determined in large part by the ability of the cell to repair the DNA damage inflicted by radiation. The fact that radiotherapy is a useful treatment for cancer indicates that, in general, the cells of the normal tissues are better equipped to repair DNA damage than their malignant counterparts. In line with this general observation, there is increasing evidence that abnormalities in the DNA damage response (DDR) are a fundamental characteristic of cancer. This evidence base is now sufficiently robust for 'genome instability and mutation' to feature as one of the two 'enabling characteristics' of cancer that were included in Hanahan and Weinberg's 'Hallmarks of cancer: the next generation' in 2011 [1]. As well as contributing to carcinogenesis and malignant progression, DDR defects in cancer represent a promising therapeutic target, most famously illustrated by the sensitivity of BRCA-deficient breast and ovarian cancers to drugs that inhibit poly(ADP-ribose) polymerase (PARP) [2].

The cellular response to DNA damage comprises two main elements: cell cycle checkpoints and DNA repair (Figure 1). Physical and biochemical repair of radiation-induced DNA damage is executed by three main pathways: non-homologous end-joining (NHEJ) and homologous recombination, which repair double-stranded DNA breaks (DSB); and base excision repair, which repairs single-stranded DNA breaks (SSB) (reviewed in [3]). In the context of conventional external beam radiotherapy, DSB are generated in far fewer numbers than SSB, but are highly mutagenic and are cytotoxic if unrepaired. By contrast, the more numerous SSB are less cytotoxic, less mutagenic and more easily repaired. However, unrepaired SSB can be converted to DSB in the context of DNA replication and can interfere with important cellular processes such as gene transcription. Both pathways play important roles in the day-to-day maintenance of genomic integrity as well as the cellular response to genotoxic cancer treatments [4].

Cell cycle checkpoints have evolved to protect cells from the potentially catastrophic consequences of either replicating damaged DNA or attempting to undergo mitosis while carrying unrepaired DNA breaks. Inappropriate DNA replication is prevented by activation of the G1/S checkpoint, governed primarily by the ATM/p53/p21 signalling pathway, whereas entry into mitosis is guarded by the G2/M checkpoint under the control of ATM/ATR/Chk1/Chk2/Wee1 signalling. Additional cell cycle regulation is provided by intra-S phase and mitotic spindle checkpoints (reviewed in [5]).

In the context of cancer, defects in DNA repair result in the acquisition and accumulation of mutations that can drive carcinogenesis and malignant transformation, whereas dysfunctional cell cycle checkpoints are associated with an increase in the frequency and severity of chromosomal aberrations. Loss of cell cycle checkpoint integrity is a critical event in malignant progression: oncogenic stress in low grade tumours is associated with constitutive activation of cell cycle checkpoint proteins, including ATM, Chk2 and p53, which are significantly reduced in corresponding high grade tumours [6]. This somewhat counterintuitive observation led to the hypothesis that activated cell cycle checkpoints function as a 'brake' on malignant progression of low grade tumours. Consistent with this theory, acquisition of 'loss of function' mutations in these checkpoint proteins, most commonly p53, is associated with malignant progression. Although not a universal phenomenon, the concept of the DDR as an 'anti-cancer barrier' is a plausible explanation for the high prevalence of DDR dysfunction in malignant disease, and identifies a family of attractive therapeutic targets (reviewed in [7]).

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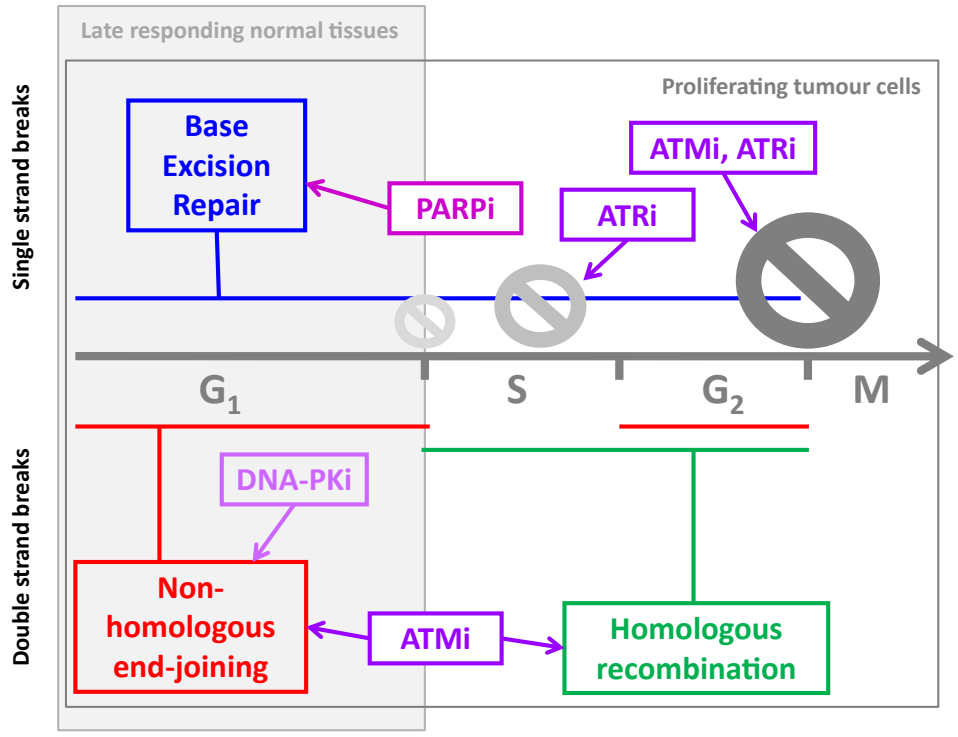

Fig 1. Highly simplified diagram showing key components of the DNA damage response (DDR), their relationships with the cell cycle and the sites of action of selected DDR inhibitors. The phases of the cell cycle are represented in grey along the central axis of the figure. G1/S, intra-S and G2/M cell cycle checkpoints are illustrated by grey symbols, with relative size and colour representing the extent to which tumour cells are dependent on their function. The major repair pathways for radiation-induced DNA breaks are shown, with single-strand break (SSB) repair pathways above and double-strand break (DSB) repair pathways below the cell cycle axis. The relevance of these cell cycle-dependent processes to effects of radiation–drug combinations on proliferating tumour cells and non-proliferating cells of late-responding normal tissues are indicated by the large grey boxes. Tumour specificity of the radiosensitising effects of poly(ADP-ribose) polymerase (PARP) inhibition is generated by the requirement for unrepaired SSBs to be converted to DSBs during DNA replication in S phase. Tumour specificity of inhibitors of ATM, ATR and Wee1 is predicted by the primary functions of their major targets taking place within S phase (ATR) and the G2/M checkpoint (ATM, ATR, Wee1).

Exploiting DNA Damage Response Dysfunction to Enhance Responses to Radiotherapy

When combining a novel agent with radiotherapy, a clinical benefit is only achieved if the therapeutic ratio is widened, so it is vital to consider effects on both tumours and normal tissues. In the context of radical radiotherapy, the radiation dose is limited primarily by the risk of causing irreversible damage to adjacent late-responding tissues, such as the lung, heart, kidney, bowel, spinal cord or brain. As described above, tumour cell DDRs differ from those of late-responding normal tissues in several ways and thus have potential as tumour-specific targets:

(1) rapid cellular proliferation, compared with minimal proliferation in late-responding tissues;
(2) elevated oxidative and replication stress;
(3) loss of function of the G1/S checkpoint and increased dependency on G2/M checkpoint integrity;
(4) defective DDR resulting from germline or somatic mutations in DDR genes and/or epigenetic or post-translational changes.

In parallel with the advances in cancer biology that revealed these potential targets, a range of potent and specific small molecule inhibitors of key DDR proteins have emerged, some of which have already entered the clinic. These dual developments make this an exciting and critical time in the evolution of individualised radiotherapy.

Poly(ADP-ribose) Polymerase Inhibitors

PARP is a base excision repair enzyme that, upon sensing and binding to SSB, catalyses the addition of long, branching chains of the poly(ADP-ribose) polymer (PAR) to a variety of nuclear proteins, including histones and other DDR proteins, thus facilitating SSB repair. Chemical inhibitors of PARP impede SSB repair and exert potent sensitising effects in combination with various cytotoxic drugs, including alkylating agents (temozolomide, cyclophosphamide), topoisomerase inhibitors (irinotecan, topotecan) and cisplatin. In combination with radiation they exert modest sensitising effects on tumour cells, but importantly this effect is only observed in actively replicating populations [8]. Radiopotentiating effects of PARP inhibitors (PARPi) have been shown *in vivo* in a broad

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