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# Translation of Targeted Radiation Sensitizers into Clinical Trials

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**Over the past century, technologic advances have promoted the evolution of radiation therapy into a precise treatment modality allowing for the maximal administration of dose to tumors while sparing normal tissues. Coinciding with this technological maturation, systemic therapies have been combined with radiation in an effort to improve tumor control. Conventional cytotoxic agents have improved survival in several tumor types but cause increased toxicity due to effects on normal tissues. An increased understanding of tumor biology and the radiation response has led to the nomination of several pathways whose targeted inhibition has the potential to radiosensitize tumor cells with lesser effects on normal tissues. These pathways include those regulating the cell cycle, DNA damage repair, and mitogenic signaling. Few drugs targeting these pathways are in clinical practice, although many are in clinical trials. This review will describe the rationale for combining agents targeting these pathways with radiation, provide an overview of the current landscape in the clinical pipeline and attempt to outline the future steps.**

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## Background

The technological leaps in radiation delivery over the last 30 years have dramatically increased tumor delivered doses while sparing adjacent normal tissues and thereby lowering toxicity. Despite this, outcomes for many locally advanced solid malignancies remain poor. As described by other articles within this issue, the integration of classical chemotherapeutic agents with radiation has been met with both successes and failures but is the standard of care for the majority of locally advanced malignancies. More recently, our increased understanding of the biological differences between tumor and normal cells as well as the differential responses of tumor and normal cells to radiation has prompted the investigation of molecularly targeted agents as radiosensitizers (Fig.). Despite intense work in this area, only 2 targeted drug classes are considered standard therapy with radiation: epidermal growth factor receptor (EGFR) inhibition with cetuximab in head and neck cancer, and androgen receptor targeting with testosterone deprivation in intermediate and high-risk prostate cancer.[1,2] There are many worthy approaches being investigated for tumor radiosensitization such as nanoparticles or agents that modify tumor metabolism or the hypoxic microenvironment. However, in this review we will focus on agents under clinical investigation with radiation that modify the DNA damage response (including the cell cycle and DNA repair), prosurvival signaling pathways and the host immune response (Table).

## Cell Cycle and DNA Repair

Radiation induces damage to DNA in the form of both DNA single-strand breaks (SSB) and double-strand breaks (DSB). DSBs are the predominant mediator of radiation-induced cell death; however, SSBs are also relevant given their potential for conversion to complex DSBs in replicating cells. The ability of cells to repair radiation-induced DNA damage influences their inherent radiation sensitivity. SSBs are repaired by the SSB repair pathway, which is also used for repair of SSB intermediates formed during base excision repair (BER). In contrast,

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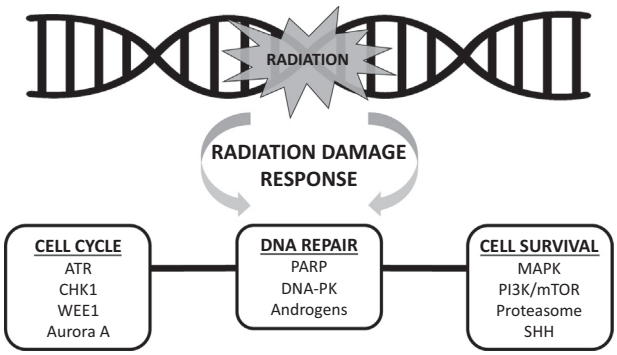


**Figure** The cellular radiation response entails initiation of DNA repair and activation of proteins to coordinate the cell cycle and cell survival. Many proteins within the cell cycle and survival pathways often have overlapping functions involved with DNA repair as described in the text. Inhibition of these intertwined processes is being explored as a strategy for radiosensitization and targetable pathways are illustrated.

DSBs are repaired by one of 2 major DSB repair pathways including nonhomologous end-joining (NHEJ) and homologous recombination (HR). These repair pathways generally consist of damage recognition, coordination of repair machinery to the damaged site, and repair itself; all occurring within the time constraints of the cell cycle. Tightly coordinated with DNA repair processes, the cell cycle halts in response to DNA damage to prevent propagation of cells with a damaged DNA template. In response to DNA damage, cells transiently arrest proliferation at the G1, intra-S, or G2 cell cycle checkpoints. Given that many tumors have inherent defects in their cell cycle or DNA repair pathways, agents targeting compensatory or synthetically lethal pathways could potentially be used to exploit these repair deficits. Indeed, several classes of targeted agents that inhibit various steps of the DNA damage response pathway have been developed and are promising candidates for selectively increasing radiation efficacy.[3]

## Ataxia-Telangiectasia Mutated and RAD3-Related

Ataxia-telangiectasia mutated and RAD3-related (ATR) is an apical serine/threonine kinase in the DNA damage response pathway that is activated in response to a variety of insults including replication stress, replication associated DSBs, and damaged bases. The key substrate for ATR activation is likely single-stranded DNA that is subsequently bound by replication protein A, leading to ATR activation.[4] In turn, ATR activates downstream effector proteins that mediate cell cycle checkpoints, DNA replication, and DNA repair. ATR inhibitors such as AZD6738 are being developed both as monotherapy and as sensitizers to DNA damaging agents. AZD6738 has antitumor activity in ataxia-telangiectasia mutated (ATM) and P53-deficient tumor models as well as in combination with other agents such as cisplatin.[5-7] Although single agent phase 1 studies await publication, a dose-finding trial is underway to explore the use of AZD6738 with radiation. A similar compound, VX-970 (also known as VE-822), sensitizes pancreas cancer xenografts to gemcitabine or radiation and non–small cell lung cancer (NSCLC) xenografts to various chemotherapies.[8,9] Multiple trials combining this agent with cytotoxic therapies are ongoing, whereas its addition to cisplatin and radiation in locally advanced HPV-negative head and neck cancer or whole brain radiotherapy in NSCLC are due to open (NCT02589522 and NCT02567422). The tumor cell selectivity of ATR inhibition is not completely understood but may involve a greater reliance of tumor cells than normal cells on ATR activity because of oncogene-driven replication stress.[10] Further evidence for the existence of a therapeutic window for ATR inhibitors is provided by the observed tolerability of these agents alone and in combination with other systemic therapies.[5]

## Checkpoint Kinase 1

In response to DNA damage, checkpoint kinase 1 (CHK1) is activated in an ATR- or ATM-dependent manner. CHK1 phosphorylates and inhibits cell division cycle 25 A and C proteins resulting in inhibition of cyclin dependent kinase 1 and 2 (CDK1 and CDK2) and initiation of the intra-S and G2 checkpoints.[11] CHK1 also promotes HR and stabilizes stalled replication forks, which, like cell cycle checkpoints, contribute to cellular recovery from DNA damage and replication stress.[12-14] Based on these mechanisms, agents targeting CHK1 have been developed to sensitize tumor cells to chemotherapy or radiation.[3,12,15-18] Although development of this class of agents was slowed due to the cardiac toxicity and off target effects of the earlier agents (MK8776 and AZD7762), the CHK1 inhibitor prexasertib (LY2606368) is currently under active clinical investigation.[19,20] A phase 1 trial combining prexasertib and chemoradiation (cisplatin or cetuximab) in head and neck cancer has just opened.

## WEE1

WEE1, similar to CHK1, regulates the intra-S and G2 checkpoints but through direct inhibitory phosphorylation of CDK1 and CDK2, resulting in cell cycle arrest. WEE1 promotes HR and prevents aberrant origin firing during DNA replication.[21,22] In preclinical models, WEE1 inhibition synergizes with various chemotherapies, radiation, and chemoradiation.[23-25] AZD1775 (also known as MK1775) is being investigated in multiple phase 1 and 2 clinical trials as monotherapy and in combination with radiation, chemoradiation, or chemotherapy. As a radiosensitizer, AZD1775 is being tested alone in glioblastoma (GBM) and in combination with cisplatin (head and neck cancer, cervical cancer), temozolomide (GBM) or gemcitabine (pancreas cancer).

Consistent with other agents that abrogate the G2 checkpoint, WEE1 inhibition preferentially sensitizes *P53* mutant tumor cells to DNA damage given their absence of a P53-mediated G1 checkpoint.[26-28] This observation raises the possibility of using *P53* mutational status as a predictive biomarker to identify patients most likely to benefit from the combination of WEE1 inhibition and radiation. This strategy is

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