

IN THE SPOTLIGHT

Androgen Receptor Signaling Fuels DNA Repair and Radioresistance in Prostate Cancer

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Summary: Successful treatment by genotoxic modalities including radiotherapy is commonly hampered by treatment resistance in advanced cancers. Two new studies now reveal that androgen receptor signaling transcriptionally upregulates a large subset of DNA repair genes, thereby enhancing the repair capacity and promoting radioresistance of prostate cancer. These results provide a mechanistic rationale for a combined treatment by ionizing radiation and androgen deprivation therapy. *Cancer Discov*; 3(11); 1222-4. ©2013 AACR.

See related article by Polkinghorn et al., p. 1245 (2).

See related article by Goodwin et al., p. 1254 (1).

A combination of androgen deprivation therapy (ADT) with radiotherapy currently represents a standard-of-care approach for treatment of prostate cancer, particularly for patients with high-risk disease. In numerous clinical trials, such combined treatment showed improved disease-free and overall patient survival, for both high- and intermediate-risk prostate cancer, when compared with radiotherapy alone. Although the clinical benefits of combining radiotherapy with androgen deprivation seem indisputable, this contrasts sharply with our lack of validated mechanistic understanding of the cellular and molecular basis for such synergistic therapeutic effects. This unsatisfactory situation may now be finally improving, thanks to exciting findings reported in two articles, published in this issue of *Cancer Discovery*, by Goodwin and colleagues (1) and Polkinghorn and colleagues (2). Both studies identified a close interplay between androgen receptor (AR) signaling and the cellular DNA damage response (DDR) machinery. More specifically, the authors report that upon exposure to ionizing radiation, AR becomes activated and transcriptionally upregulates a large subset of DNA repair genes, thereby enhancing the DNA repair capacity and hence promoting radioresistance of human prostate cancer cells. This emerging concept offers not only a plausible rationale for the clinically observed synergy between ionizing radiation and ADT treatments (3), but also raises additional important issues about ADT itself and provides motivation for considering future treatment strategies incorporating drugs that target the DNA repair pathways.

From a broader perspective, an intimate link between DDR and cancer is hardly surprising, given that DDR defects may either predispose to (through unrepaired DNA lesions causing mutations), or facilitate progression of, various types of

cancer (4). Furthermore, as most currently used nonsurgical treatment regimens rely on genotoxic effects of chemotherapy and/or radiation, the status of the DDR machinery of the patient as well as the tumor itself impact the treatment outcome. DNA damage inflicted by such treatment modalities also causes negative side effects such as those in the gastrointestinal tract or bone marrow, and the enhanced resistance to genotoxic treatments in tumors often reflects aberrantly elevated DNA repair (4, 5). Finally, the DDR machinery provides an intrinsic biologic barrier against endogenous DNA damage caused by cancer-associated replication stress, and may slow down or block early stages of tumorigenesis by triggering cellular senescence or cell death (6). In prostate cancer, DNA repair and AR have also been jointly implicated in mediating disease-specific chromosomal translocations (7). Overall, such intriguing links between DDR and cancer, and the clinical experience with combined ADT and radiotherapy, inspired the two teams to examine the potential role of AR signaling in the ionizing radiation response of human prostate cancer.

In one of the two new studies, Polkinghorn and colleagues (2) first assessed changes in the gene expression profiles of a human castration-resistant prostate cancer (CRPC) model treated with the second-generation antiandrogen drug ARN-509, followed by examination of a series of primary castration-sensitive prostate cancers. Combined, these analyses identified a robust set of 144 DDR-related genes, the “AR-associated DNA repair gene signature,” as a prominent part of the canonical AR transcriptional output. They further validated this gene signature as being upregulated by androgen in a suitable human prostate cancer cell line and, importantly, pinpointed a subset of 32 of the DNA repair genes as containing AR binding sites, mainly in their enhancer sequences, thereby confirming these genes as genuine direct AR targets (2). As the logical next step, Polkinghorn and colleagues (2) tested, and indeed confirmed, their prediction that androgen deprivation would lead to enhanced DNA damage and slow repair of ionizing radiation-induced DNA double-strand breaks (DSB), arguably the most toxic type of damage among the ionizing radiation-induced DNA lesions. Using clonogenic assays in a scenario that mimicked combined ADT and radiotherapy treatment, the authors also

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confirmed that androgen deprivation resulted in enhanced cell death of ionizing radiation-treated human prostate cancer cells. Finally, to validate the involvement of DNA repair pathways identified as AR targets, Polkinghorn and colleagues (2) used functional reporter assays to show that the major positive effect of AR signaling on the ionizing radiation-induced DSB repair was attributable to classical nonhomologous end-joining (NHEJ) repair, despite some genes whose products contribute to the other major DSB-repair pathway of homologous recombination also being identified as AR targets.

In the other highly complementary study, Goodwin and colleagues (1) first documented that ADT potentiates the tumor-suppressive impact of ionizing radiation in AR-proficient, but not in AR-negative human prostate cancer cell lines, grown either *in vitro* or as xenografts *in vivo*. Notably, a particularly dramatic synergistic effect of ADT and ionizing radiation was observed in CRPC models mimicking the clinically most relevant advanced, castration-resistant stage of the disease. In support of AR involvement, supplementation of androgen-depleted cells by a synthetic androgen rescued the ionizing radiation-induced growth suppression, indicating a survival benefit of AR signaling in response to genotoxic insult. Analogous to the study by Polkinghorn and

colleagues (2), Goodwin and colleagues (1) observed a robustly enhanced growth-suppressive effect of a next-generation AR antagonistic drug (here MDV3100) when combined with ionizing radiation, in contrast to either treatment alone. Also consistent with the other study, AR was found to directly bind and stimulate expression of several DNA DSB-repair genes, particularly *PRKDC* that encodes the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), and to promote resolution of DNA damage. In addition, these authors also reported activation of AR upon irradiation, an intriguing effect attributable to reactive oxygen species evoked by radiation (1) and to a positive feedback role of DNA-PKcs that (apart from its canonical role in DSB repair by NHEJ) serves as a cofactor in AR-mediated transcription (1, 8).

Taken together, these two studies suggest the following mechanistic model in which AR and the DNA repair machinery tightly cooperate to promote genome integrity, and hence survival of prostate cancer cells (Fig. 1). AR transcriptionally stimulates expression of a wide range of DNA repair genes, many of them through direct interaction of AR with AR binding sites in gene enhancer regions. Prominent among the AR-regulated DDR genes were those encoding components of the NHEJ repair pathway, particularly DNA-PKcs and Ku70 (1, 2, 9). Other repair pathways affected by AR signaling

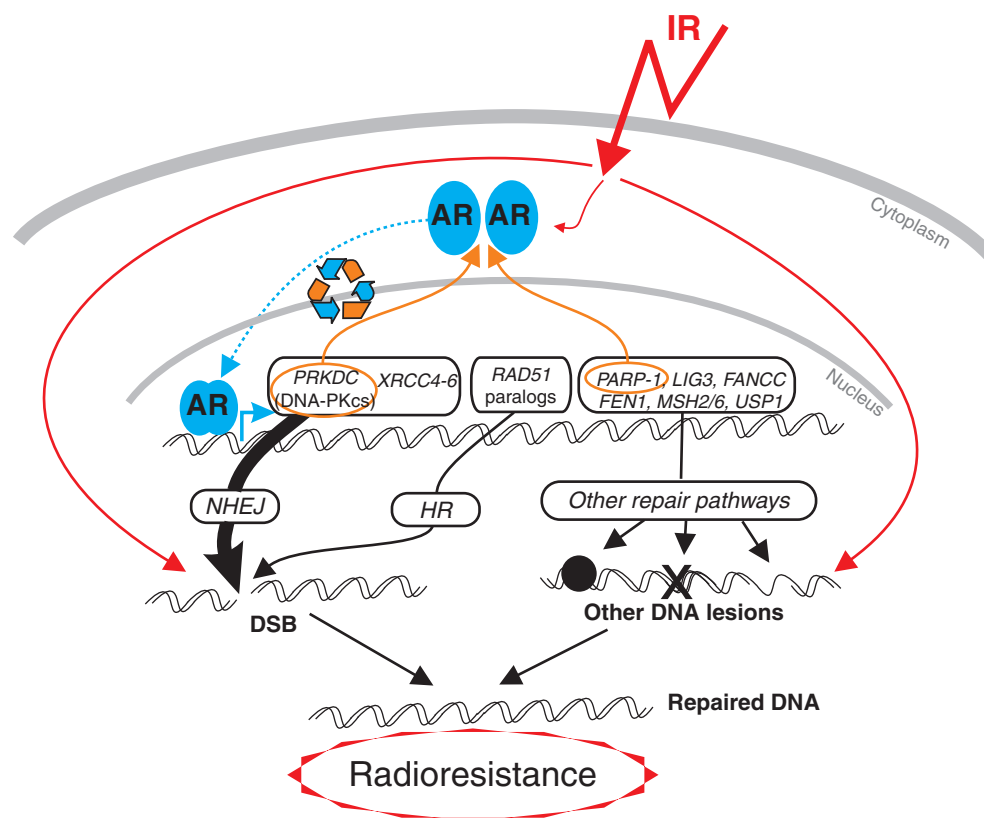


Figure 1. Schematic model of the functional interplay between AR and DNA repair machinery in prostate cancer cells exposed to ionizing radiation (IR). Upon irradiation, AR becomes activated through dimerization, relocates to promoters of numerous DNA repair genes, and activates their transcription (1, 2). Prominent among the AR targets is DNA-PKcs, a protein kinase critical for repair of DNA DSBs by NHEJ, which also feeds back (similar to PARP-1) to further stimulate AR, thereby creating a positive regulatory circuit. Enhanced expression of DNA repair factors promotes efficient repair of IR-induced DNA lesions, thereby enhancing the fitness of cancer cells and their radioresistance. HR, homologous recombination. See main text for details.

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include homologous recombination, mismatch repair, base excision repair, and the Fanconi anemia pathway, though functional stimulation by AR is clearly documented for the NHEJ-mediated DSB repair only (1, 2). An important feature of the emerging overall model (Fig. 1) is the activation of AR after irradiation, and the AR-stimulatory functions provided by DNA-PKcs and PARP-1 (1, 2, 8, 10), which both contribute to a regulatory circuit between the AR and DDR in response to a genotoxic insult. In biologic terms, and important for the outcome of prostate cancer treatment, this coordinated cellular response likely fuels more efficient repair of diverse types of DNA lesions, thereby supporting viability and enhanced resistance of the cancer cells to treatment by ionizing radiation.

The two reports provide valuable information about prostate cancer biology and response to treatment, at both mechanistic and conceptual levels. At the same time, these results also raise a host of burning questions. For example, we still do not know exactly how the ionizing radiation-evoked reactive oxygen species activate AR (1), and whether the AR-stimulated DNA repair genes, other than those in the NHEJ pathway (2), contribute to cancer cell survival and treatment resistance. Mechanistically, the AR cofactor roles of DNA-PKcs (1, 8) and PARP-1 (10) are important, yet we do not understand to what extent these are analogous to their canonical roles in the DDR achieved, respectively, through phosphorylation and parylation of diverse substrates (11), or whether these roles perhaps operate via some scaffold or other function. Last but not least, given the emerging bewildering heterogeneity between and within human tumors (12), it remains to be seen how diverse is the status of the discovered regulatory circuit of AR with DNA repair genes in subsets of cancer cells, including the candidate cancer-initiating/stem cells.

Arguably, the key contribution of the two studies is the rationale for the empirically observed synergy between androgen deprivation and radiotherapies. This important discovery now opens new avenues for personalized assessment of critical parameters of this mechanism when choosing treatment options, and suggests that additional drugs, such as small inhibitors of DNA-PKcs that are currently in clinical trials, may be exploited in the treatment of prostate cancer. An intriguing question is whether the commonly long-term ADT in the clinic, now shown to inhibit DNA repair (1, 2), might in fact contribute to the pronounced genomic instability seen in advanced prostate tumors. Furthermore, it is tempting to speculate that the discovered AR-DDR interplay, likely

beneficial during physiologic DNA repair of, for example, AR-transcription-associated DNA breaks, is “hijacked” by the cancer cells to increase their fitness and resistance to therapy. The exciting task ahead is to turn this new knowledge into smarter and more efficient therapies for prostate cancer, and possibly also for breast and ovarian cancers, provided a closely analogous scenario exists between the estrogen receptor and the DNA repair machinery.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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