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REVIEW

DNA damage response and prostate cancer: defects, regulation and therapeutic implications

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DNA damage response (DDR) includes the activation of numerous cellular activities that prevent duplication of DNA lesions and maintain genomic integrity, which is critical for the survival of normal and cancer cells. Specific genes involved in the DDR such as *BRCA1/2* and *P53* are mutated during prostate cancer progression, while various oncogenic signaling such as Akt and c-Myc are activated, enhancing the replication stress and increasing the genomic instability of cancer cells. These events may render prostate cancer cells particularly sensitive to inhibition of specific DDR pathways, such as PARP in homologous recombination DNA repair and Chk1 in cell cycle checkpoint and DNA repair, creating opportunities for synthetic lethality or synergistic cytotoxicity. Recent reports highlight the critical role of androgen receptor (AR) as a regulator of DDR genes, providing a rationale for combining DNA-damaging agents or targeted DDR inhibitors with hormonal manipulation or AR inhibition as treatment for aggressive disease. The aims of this review are to discuss specific DDR defects in prostate cancer that occur during disease progression, to summarize recent advances in understanding the regulation of DDR in prostate cancer, and to present potential therapeutic opportunities through combinational targeting of the intact components of DDR signaling pathways.

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INTRODUCTION

Prostate cancer remains the second most common cancer type in western societies. Despite recent therapeutic advances, metastatic castration-resistant prostate cancer (mCRPC) is incurable, and novel treatment approaches are needed. Abiraterone, a selective CYP17 inhibitor that decreases androgen biosynthesis within the tumor microenvironment, prolongs overall survival before and after chemotherapy in patients with mCRPC, but the duration of benefit is modest when compared with placebo (~5 months and ~4 months, respectively).[1,2] Similarly, enzalutamide, a potent androgen receptor (AR) inhibitor that impairs the nuclear translocation of AR, prolongs overall survival before and after chemotherapy in patients with mCRPC—but again only modestly, by ~2 months and ~5 months, respectively, when compared with placebo.[3,4] Thus, novel therapeutic strategies are needed.

Multiple lines of evidence link AR signaling to the DNA damage response (DDR) in prostate cancer cells. Clinically, radiation therapy (which promotes apoptosis via DNA damage) is more effective when combined with androgen-deprivation therapy (ADT) in treating patients with high-risk localized disease.[5] Apart from additive apoptotic effects of AR inhibition and radiation therapy, recent preclinical studies have elucidated a novel mechanism to explain this observation, whereby AR signaling regulates multiple genetic activities and pathways that influence the DDR.[6,7] These results suggest that the exploration of these complex associations may provide novel therapeutic opportunities for patients with mCRPC.

DNA is continually exposed to various insults causing a range of lesions such as single strand breaks (SSBs), double strand breaks (DSBs), bulky adducts, base mismatches, insertions and deletions and base alkylation.[8] Genomic instability refers to a high frequency of alterations within the genome of a cellular lineage. As genomic instability is deleterious to the organism, normal mammalian cells possess exquisite response mechanisms to avoid accumulation of DNA damage and maintain genomic integrity.[9] These mechanisms are known collectively as the DDR and include detection of DNA damage, accumulation of DNA repair factors and physical repair of the lesion.[8] This critical response program has two very well-coordinated functions: (i) to prevent duplication and partitioning of the lesion into daughter cells and (ii) to repair the lesion. The cellular actions that manifest as cell cycle arrest following DNA damage are known as 'checkpoint' functions and are considered as a critical part of the DDR.[10] Depending on the severity of the lesion and the capacity of the DDR system to repair it, cells will resume proliferation, become senescent (a state of irreversible cell cycle arrest) or undergo programmed cell death (apoptosis) to remove damaged DNA from the cellular population.[10,11]

SSBs and DSBs are detected by specialized complexes that recruit ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad3 related (ATR) to the site of the lesion, leading to increased phosphorylation of H2AX. ATM recruitment, which is mainly related to DSBs leads to Chk2 activation and subsequent stabilization of p53, promoting G1/S cell cycle arrest through p21, and providing cells with time to repair the damage avoiding the replication of the damaged DNA.[12] ATR on the other hand which is mainly recruited to the site of SSBs phosphorylates and activates Chk1 which in turn phosphorylates Cdc25 and Wee1, leading to S and G2/M arrest and initiation of DNA repair.[12–15]

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Homologous recombination (HR) and nonhomologous end joining (NHEJ) are the main mechanisms implicated in the repair of DSBs.[16,17] HR takes place during late S phase to G2 phase of the cell cycle and promotes removal of a part of the DNA (including the DSB) by using the homologous sister chromatid to mediate synthesis of new DNA. BRCA1, BRCA2, RAD51 and PALB2 are components of the enzymatic machinery involved in this process. NHEJ promotes DSB repair by joining the ends of the lesion together throughout the cell cycle through the function of DNA-PK complex, which consists of the Ku-70–Ku-80 heterodimer and the DNA-PK catalytic subunit (DNA-PKcs).[8,18] Interestingly, recent data suggest that AR regulates NHEJ and subsequently impacts DDR in prostate cancer cells.[7] It should be noted that both HR and NHEJ can be mutagenic but particularly NHEJ can cause deletion or mutation of DNA sequences at or around the DSB site.[8]

In contrast to normal cells, a universal characteristic of cancer cells is genomic instability due to defects in the mechanisms involved in repair of DNA damage. It is notable that genomic instability was found to be associated with worse prognosis in patients with prostate cancer.[19] Familial forms of breast and ovarian cancer are associated with mutations in HR-related genes, such as *BRCA1* and *BRCA2*[20], while carriers of *BRCA1* and *BRCA2* mutations have an increased risk of prostate cancer.[21,22] Moreover, disruption of the ATM pathway, though loss of ATM itself or of downstream effector protein p53, has been observed in as many as 70% of tumors.[23,24] According to a recent study, *P53* and *ATM* were found to be mutated in 40% and 8%, respectively, of the CRPC cases examined by sequence analysis.[25] It is believed that dysfunctional DDR leads to accumulation of DNA lesions and promotes development of a precancerous phenotype,[26] while inactivation of critical DDR mediators such as ATM and p53 leads to development of malignancy.[26,27]

Importantly, recent data suggest that defects in one component of DDR (for example, *BRCA1* and *BRCA2* mutations affecting HR, implicated in the repair of DSBs) render cancer cells specifically susceptible to inhibition of a second DDR defect (for example, PARP1 inhibition affecting base excision repair, implicated in the repair of SSBs), a concept referred to as 'synthetic lethality'.[28,29] Synthetic lethality is defined as a type of genetic interaction, whereby the co-occurrence of two genetic events results in cellular death, while the presence of either event alone has no effect on cell viability. These events are detected only in cancer cells, so normal cells are spared, reducing the toxicity of therapy. In this context, DDR is critical for cancer cell survival but represents an opportunity that can be exploited for therapy using agents that target a second event.

The pro-survival activities of DDR are realigned and misappropriated during cancer progression by activation of oncogenes such as Ras, Akt and Myc, which enhances replication stress.[8,30–32] Replication stress is defined as the harmful effect of DNA that is only partially replicated because of slow progression (or 'stall') of the replication forks, which can be caused by oncogene-induced hyper-replication that activates multiple origins of replication per S phase, by nucleotide pool imbalance or by DNA damage.[33] This leads to increased DNA damage, which eventually increases genomic instability to a level that is incompatible with cell survival. However, induction of replication stress by hyperactive growth factor and oncogene signaling in established cancer can lead to compensatory upregulation of DNA repair pathways, promoting resistance to cancer therapy.[33]

Given the role of genomic instability in prostate cancer progression, recent evidence that agents targeting DDR may be effective in a subset of patients with prostate cancer, and reports that AR signaling regulates multiple genetic activities and pathways that influence DDR, the aim of this review was defined to describe DDR involvement in development and progression of prostate cancer, crosstalk between AR and DDR signaling pathways and therapeutic opportunities that result from targeting DDR especially at the lethal stage of this disease.

DNA DAMAGE RESPONSE AND PROSTATE CANCER

DNA damage response and prostate carcinogenesis

Inflammation is an important factor in prostate carcinogenesis. Regardless of etiology, inflammation produces cellular and genomic damage, induces secretion of cytokines and growth factors promoting cellular proliferation and angiogenesis and becomes more extensive over the lifetime of the individual.[34–36] Inflammatory lesions generate free radicals (for example, nitric oxides and single oxygen species released from phagocytic inflammatory cells) that cause severe oxidative DNA damage within prostate epithelial cells. These molecular changes result in increased risk of permanent mutations, as the damaged cells may proliferate.[37–40] According to the results of a recent study, which used an *in vitro* model of prostate cell inflammation, exposure of androgen-sensitive prostate cancer cells to inflammatory cytokines leads to loss of AR and downregulation of p53 signaling.[41] Interestingly, the administration of androgens restored p53/p21 function, inhibiting uncontrolled tumor growth related to DNA damage and genomic instability.[41]

Recent reports suggest a role for AR in the response to DNA damage during development of prostate cancer. In particular, Ide *et al.*[42] showed that AR activation by testosterone promotes ATM activation and Chk2 phosphorylation in response to H_2O_2-induced DNA damage. The authors suggested that testosterone suppresses prostate cancer initiation through activation of the DDR. These results are consistent with previous reports demonstrating that low testosterone levels are associated with advanced tumor stage, positive surgical margins and shorter overall survival.[43,44] Alternatively, other reports have associated high levels of free testosterone with high-grade prostate cancer,[45] highlighting the complexity of the relationship between AR and DDR with regard to prostate carcinogenesis.

A more recent report suggests that AR inactivation leads to telomere dysfunction, contributing to genomic instability and progression of prostate cancer.[46] Bowen *et al.*[47] found that the prostate cancer suppressor NKX3.1, which is a target of AR, activates ATM, enhancing the DDR and thus contributing to DNA integrity in prostate epithelial cells. Notably, ATM missense mutations and polymorphisms increase the risk of prostate cancer development.[48,49] According to these data, it is conceivable that impaired DDR may promote prostate carcinogenesis while AR may maintain genomic integrity in the earlier stages of the disease through DDR activation, mainly by activating the ATM-Chk2 pathway. Further, it is believed that reactive oxygen species-induced unrepaired DNA damage may be one of the main mechanisms related to initiation of this disease.[50] Finally, it has been suggested that mutational or epigenetic inactivation of DDR components is selected during neoplastic development, allowing malignant progression.[8]

DDR defects related to prostate cancer

In established prostate cancers, multiple defects in various DDR components have been described. p53 was found to be mutated in 3–20% of prostate cancers at diagnosis[51,52] and its dysfunction has been associated with high-grade disease,[53] cancer recurrence, castration resistance and metastasis.[54] Wild-type p53 is rapidly activated and stabilized in response to a range of genotoxic insults, including ionizing irradiation,[55] UV light[56] and ribonucleotide deletion.[57] This results in cell cycle arrest in G_1 and G_2 phases through induction of p21, 14-3-3σ and GADD45α and in apoptosis through upregulation of PUMA, BAX and BAK.[58] Inactivation of p53 renders cancer cells dependent on p53-independent mechanisms to promote cell cycle arrest for DNA damage repair,

specifically ATR-Chk1- and ATM-Chk2-dependent checkpoints.[59] Moreover, Chk2 mutations are more frequent in patients with prostate cancer than in the general population, according to an earlier report.[60] Finally, Beltran *et al.*[25] demonstrated that genomic alterations in HR DNA repair genes, including *ATM* (8%) and *BRCA2* (12%), were detected in CRPC. It should be mentioned that further studies are needed to establish the incidence of these mutations and explain their significance.

In general, the results of mechanism-based studies of DDR support the concept that aggressive cancers accumulating multiple defects in DDR due to deletions or mutations of DDR mediators and related defective cell cycle checkpoints may be particularly sensitive to DDR inhibition. In particular, loss of the ATM-Chk2-p53 component of the DDR creates a cancer with a DNA damage repair defect that can be exploited therapeutically with agents that lead to accumulation of DNA damage. For example, because defects in ATM-Chk2-p53 function render cancer cells more dependent on Chk1 to activate cell cycle checkpoints in the presence of DNA damage, inhibition of ATR and subsequent signaling mediated by Chk1 is a rational therapeutic strategy to push cancer cells to 'mitotic catastrophe'. In support of this hypothesis, ATR and Chk1 inhibitors are effective in these cancer cells. Selective Chk1 inhibitors have been found to promote aberrant mitosis and increase cell death in cells harboring *P53* and *ATM-Chk2* mutations.[61,62] Inhibition of Chk1 in p53-mutant prostate cancer is an example of synthetic lethality. What is more, Chk1 knockdown was found to increase the apoptotic effects of radiation in prostate cancer cells associated with decreased activation of Cdc25C and Cdc2. Chk1 knockdown also confers radiosensitization in prostate cancer stem cells.[63] Similarly, AZD7762, a Chk1 and Chk2 inhibitor, abrogates G2/M arrest and leads to mitotic catastrophe associated with increased apoptosis, which enhances the cytotoxic effects of bendamustine, melphalan and doxorubicin in p53-deficient multiple myeloma cells.[64]

Another example of synthetic lethality based on DDR defects is the effect of PARP inhibitors in BRCA1-mutated cancer cells. Apart from the above described disrupted ATM-Chk2-p53 signaling, another example of synthetic lethality in cancer cells related to DDR is defective HR. Specifically, it is known that defective HR secondary to *BRCA1* and *BRCA2* mutations may render cancer cells particularly sensitive to inhibition of SSB repair through PARP inhibitors.[65] Indeed, PARP inhibitors such as olaparib and niraparib present significant antitumor efficacy in ovarian and breast cancer and based on more recent data in prostate cancer with dysfunctional HR (for example, *BRCA1* and *BRCA2* mutations).[66] Two recent studies have demonstrated that male *BRCA1* mutation carriers younger than 65 years are more susceptible to prostate cancer compared with those who do not carry the mutation.[67] According to a recent report by Fong *et al.*,[66] olaparib showed antitumor activity only in patients carrying *BRCA1* or *BRCA2* mutations. Finally, Sandhu *et al.*[68] demonstrated that three of four patients with a *BRCA2* mutation and an *ERG* rearrangement showed significant response to olaparib (10–34 months on treatment), while the fourth patient exhibited primary resistance to PARP inhibitor MK-4827. Together, these results suggest that PARP inhibitors are mainly effective in tumors with HR deficiency, but more studies are needed to identify novel predictive biomarkers (in addition to BRCA1/2) to stratify patients that will be good candidates for this therapy.

The known defects of DDR related to prostate cancer initiation and progression and the related opportunities for development of strategies to induce synthetic lethality are summarized in Figure 1.

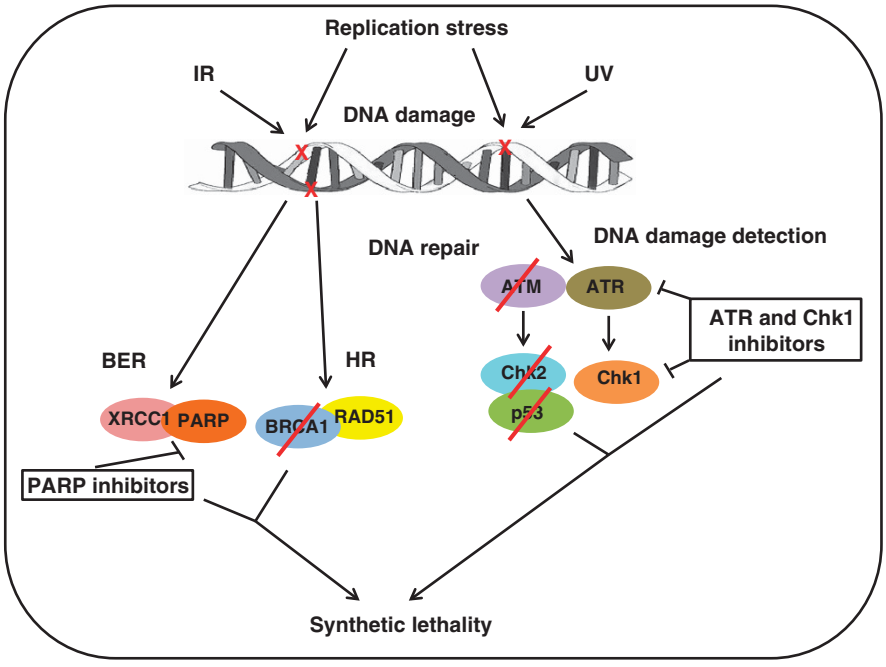

Figure 1. DDR defects implicated in initiation and progression of prostate cancer and opportunities for synthetic lethality. Replication stress, irradiation (IR) and ultraviolet light (UV) promote DSBs and SSBs, respectively, leading to activation of multiple pathways regulating DNA repair, including ATM-Chk2-p53, ATR-Chk1 and PARP signaling. These events promote repair of the damage providing survival benefit to cancer cells under stimuli inducing genomic instability. During prostate cancer progression, genetic abnormalities such as mutations or deletions of *p53*, *ATM*, *Chk2* and *BRCA1/2* (indicated by red bold slashes) have been reported; these abnormalities potentially compromise these pathways rendering other aspects of DDR critical for the cells' survival. Inhibition of alternative signaling (that is, Chk1 and PARP) with DDR-targeted agents (Chk1, ATR and PARP inhibitors) may provide opportunities for synthetic lethality in tumors with defective DDR. Clinically, the identification of particular defects in the DDR system may create opportunities for personalized treatment in patients with aggressive, hormone resistant prostate cancer. BER, base excision repair; HR, homologous recombination.

Oncogenic signaling and DDR in prostate cancer

During development of prostate cancer, dysfunction of tumor suppressors such as PTEN[51] and activation of oncogenic signaling[69] contribute to progression of the disease and resistance to hormonal therapy. Recent reports based on preclinical models demonstrated that multiple oncogenic events contribute to disease progression, tumor growth and metastatic potential.[70–72] Interestingly, it is believed that prostate cancer progression is strongly associated with genomic instability and more particularly telomere dysfunction.[73,19] Of note, during prostate cancer progression oncogenic signaling related to replication stress such as Akt and c-Myc is frequently induced.[74] These observations and results are consistent with the general concept that activation of oncogenic signaling promotes DNA replication stress, leading to increased incidence of DSBs and subsequent genomic instability.[27]

Activation of Akt signaling, which is very common during prostate cancer progression,[51] is known to modify the cellular response to DSBs. In particular, Akt activation has been related to phosphorylation of Chk1, Topbp1 and Brca1,[75–77] while the same signaling modulates focal accumulation of critical mediators of DSB repair such as RAD51 and BRCA1.[78–80] Akt is known to physically associate with DKA-PKcs, while its inhibitors have been shown to reduce radiation-induced DNA-PKcs activation.[81,82] These results suggest that Akt activation enhances the activity of DNA-PKcs and subsequent NHEJ. On the other hand, excessive HR can be repressed in irradiated breast cancer cells with high Akt activity compared to cells with low Akt activity.[79] Moreover, Akt activation was found to be correlated with cytoplasmic retention of BRCA1 and RAD51 foci instead of nuclear accumulation in sporadic breast cancer biopsies.[79] These data suggest that Akt activation, which has been shown to contribute to the progression of prostate cancer, activates NHEJ. However, in astrocytoma Akt was shown to suppress HR.[83] As mentioned above, NHEJ can be mutagenic, which is consistent with the association of *PTEN* deletion with gene rearrangements such as the *ERG* fusion gene during prostate cancer development[84] and synthetic lethality from targeting PTEN-deleted cells with PARP inhibitors.[85]

c-Myc has been implicated in the development and progression of prostate cancer,[51] and its activation increases the aggressiveness of prostate cancer with *PTEN* deletions in transgenic mice.[86] Interestingly, recent reports have demonstrated a connection between c-Myc and ATM signaling. In particular, Liyanage *et al.*[87] showed that thymic lymphomas developed in ATM-knockdown mice are characterized by increased copies of the c-*MYC* gene. Moreover, c-Myc activation has been related to ATM inactivation in numerous malignancies, including B-cell lymphomas.[88] It is believed that the DDR and subsequent apoptosis resulting from c-Myc upregulation and c-Myc-induced replication stress are both reduced upon ATM loss, while tumorigenesis is significantly accelerated.[30] One hypothesis is that, upon c-Myc upregulation, ATM mediates the DDR to repair DNA damage and releases c-Myc-induced replication stress. The results reported by Pusapati *et al.*,[89] which were based on a mouse model of skin cancer, further supported the critical role of ATM in activating DDR upon c-Myc upregulation, leading to tumor growth inhibition.

Mechanistically, c-Myc upregulation induces cell proliferation and DNA damage accumulation, leading to induced ATM activity and increased phosphorylation of numerous subsequent targets such as Chk2 and p53, which prolongs the G_2 phase of the cell cycle, contributing to DDR.[30,90] Interestingly, induction of p53 in response to c-Myc overexpression requires ATM activity.[89] These results suggest that c-Myc activation induces replication stress and probably DNA damage as a result of reactive oxygen species accumulation, leading to DDR mediated by ATM-Chk2-p53 signaling. Overall, mutations or deletions of this pathway will promote carcinogenesis induced by c-Myc upregulation. However, during disease progression the same defects may render these cells susceptible to inhibition of ATM-independent nodes such as Chk1 and ATR. Abundant c-Myc sensitizes a variety of cells to drug inhibition of either Chk1 or ATR.[91,92] Similar results were observed for Ras-overexpressing tumors.[93] These results generally support the concept that aggressive cancers that accumulate deletions of tumor suppressors, DDR defects and oncogenic activation are particularly sensitive to ATR-Chk1 signaling inhibition.

The *TMPRSS2–ERG* chromosome fusion has been observed in 50–60% of prostate tumors[94,95] and has been associated with invasive activities and more aggressive forms of the disease.[96,97] This gene fusion results in androgen-regulated overexpression of oncogenes contributing to development of prostate cancer.[98] Brenner *et al.*[99] found that one of the top proteins interacting with *ERG* is DNA-PKcs, a molecule that plays a critical role in NHEJ as discussed above. In particular, the authors showed that PARP1 and DNA-PKcs are both critical for activation of *ERG*-mediated transcription of a number of target genes, some of which are increased in metastatic disease.[99] In the same study, it was shown that prostate cancer cells are susceptible to olaparib when they express the *ERG* gene through potentiation of DSBs.[99] On the basis of these results, it was suggested that the *TMPRSS2–ERG* gene fusion could predict for sensitivity to PARP inhibition. Interestingly, Chatterjee *et al.*[100] showed that PARP inhibition increased sensitivity to radiation therapy, especially in prostate cancer cells expressing the *TMPRSS2–ERG* fusion gene and deficient in *PTEN*, supporting this hypothesis. However, a recent phase I clinical trial conducted in *BRCA1* mutation carriers and patients with sporadic prostate cancer showed no correlation between the activity of niraparib, another PARP inhibitor, and *ETS* rearrangements.[101] Further studies are needed to clarify this question but this concept also highlights the importance of developing novel biomarkers of HR dysfunction to predict sensitivity to PARP inhibitors such as olaparib and niraparib.

The role of AR in DDR regulation

As described above, AR has been implicated in activation of DDR.[6,7,42] The finding of Bowen *et al.*[47] that AR target gene *NKX.3.1* activates ATM suggests that AR may stimulate ATM-mediated DDR. Recent reports support the role of AR in DDR regulation during prostate cancer progression, highlighting multiple therapeutic opportunities provided by combining hormonal manipulation with DNA-damaging approaches such as radiation therapy.

Schiewer *et al.*[102] demonstrated that PARP1 mediates AR binding to chromatin, promoting transcription of AR target genes such as *PSA*, *TMPRSS2* and *ERG*. The authors showed that PARP1 activity is essential to maintain AR function in genetically modified mouse embryonic fibroblasts and that PARP1 activity is upregulated in CRPC, enhancing the AR activity under ADT.[102] Moreover, according to that report, PARP1 inhibition sensitizes only AR-positive prostate cancer cells to genotoxic agents such as irradiation and docetaxel, while veliparib (ABT-888), a PARP1 inhibitor, enhances the effects of castration *in vivo* in VCaP and LNCaP C4-2 xenografts and decreases prostate cancer cell proliferation in explants from human primary prostate tumors.[102] Given that PARP1 has a spectrum of activities, these data suggest that PARP1 promotes prostate cancer growth and survival, in part, by enhancing AR activity and regulating DDR, suggesting that PARP1 inhibition may improve the efficacy of hormonal therapy in patients with prostate cancer.

As previously described, the DNA-PK complex, consisting of the Ku-70–Ku-80 heterodimer and DNA-PKcs, is a key component of NHEJ. Ku proteins detect DSB ends and join them together, promoting DSB repair. Al-Ubaidi *et al.*[103] in a recent report identified an interaction between AR and Ku-70 in prostate cancer tissues, while castration was found to be associated with reduction in Ku-70 protein levels. Interestingly, low Ku-70 levels were related

to low prostate-specific antigen levels and increased numbers of γ*H2AX* foci in prostate cancer samples.[103] These results support the role of AR regulation of DDR, particularly NHEJ activities and that ADT can inhibit the repair of DSBs, leading to increased DNA damage in the absence of a genotoxic agent.

Goodwin *et al.*[7] evaluated the hypothesis that AR regulates DSB repair and that AR inhibition may sensitize prostate cancer cells to DNA-damaging therapies such as irradiation. They showed that ADT and radiation synergize to decrease growth of androgen-sensitive and -insensitive AR-positive prostate cancer cells *in vitro*, while this combined therapeutic approach increases the incidence of DSBs as indicated by increased numbers of γ*H2AX* and *53BP1* foci in LNCaP C4-2 cells. Interestingly, data presented in this report suggest that irradiation induced AR transcriptional activity, an effect that was reduced by addition of *N*-acetylcysteine, a reactive oxygen species scavenger, and by administration of ADT.[7] The authors discovered that three genes were regulated by both androgens and radiation and upregulated in CRPC, namely, *XRCC2* and *XRCC3,* which encode the XRCC2 and XRCC3 proteins that promote strand transfer at the sites of DNA damage during HR,[104] and *PRKDC,* which encodes the DNA-PKcs involved in the recruitment of repair factors in the sites of DNA damage during NHEJ.[9] Chromatin immunoprecipitation analysis showed that androgens promote expression of these genes under radiation. Moreover, the presence of androgens and radiation enhanced the activity of DNA-PK-dependent repair of DNA damage caused by radiation through NHEJ.[7] These results further support the role of AR in the regulation of multiple genetic activities and pathways that influence DDR and DNA repair under genotoxic stress.

These results were further confirmed by Polkinghorn *et al.*,[6] who showed that androgens induce expression of DDR genes, promoting repair of DNA damage caused by ionizing radiation. In contrast, novel anti-androgens such as ARN 509 inhibit the repair of DSBs. Moreover, the combination of AR inhibition and radiation decreases the clonogenic survival of prostate cancer cells.[6] The authors also presented evidence that AR promotes expression of genes implicated in sensing DNA damage and other components of DDR such as base excision repair and MMR.[6] A recent report by Li *et al.*[105] showed that MYB is transcriptionally activated by androgen deprivation or genetic silencing of AR, and that AR and c-Myb share a subset of target genes that encode DDR proteins. These results indicate that c-Myb may supplant AR as the dominant regulator of their common DDR target genes in prostate cancer cells that are resistant to AR inhibition.[105] Collectively, these data highlight the role of AR as a regulator of DDR and support the hypothesis that combining AR inhibition with genotoxic agents represents a rational approach for advanced prostate cancer.

THERAPEUTIC IMPLICATIONS

While the concept of synthetic lethality is inherently plausible in rare familial prostate cancers carrying germline alterations in DDR genes (for example, *BRCA1/2*), mutations of DDR genes are rare in sporadic cancers. However, AR-mediated regulation of DDR genes provides a rationale of synergistic combinations using novel androgen synthesis inhibitors and anti-androgens such as abiraterone and enzalutamide, respectively to inhibit or impair DDR. More specifically, inhibition of AR leads to downregulation of DDR function to create a DNA damage repair defect. If AR-inhibited tumors are then treated with an agent(s) that promotes DNA damage, synthetic lethality or synergistic cytotoxicity may result. In support of this hypothesis, combination of ADT with a PARP inhibitor (such as olaparib or niraparib) is one approach that has demonstrated encouraging results in preclinical models.[102] A clinical trial is currently underway (ClinicalTrials.gov ID

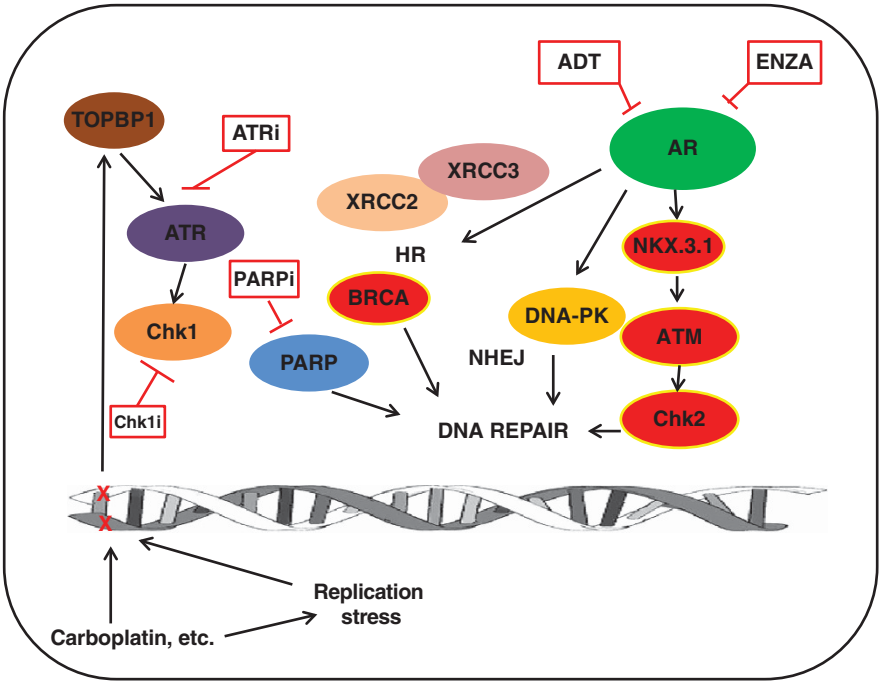

Figure 2. Strategies for combination therapies in aggressive prostate cancers focusing on AR inhibition and androgen depletion. Androgen receptor (AR) regulates multiple aspects of DDR during prostate cancer development. DNA damage induced by replication stress and DNA-damaging agents such as carboplatin activate DDR, many aspects of which, such as ATM-Chk2 signaling and NHEJ, are mediated by AR. Mutations and deletions of BRCA and ATM-Chk2 signaling (molecules represented by red ovals with yellow outline) render ATR-Chk1 signaling and PARP critical for prostate cancer cell survival. Inhibition of AR by androgen-depletion therapy (ADT) or enzalutamide (ENZA) is expected to render prostate cancer cells particularly sensitive to inhibition of PARP (PARPi) and AR-independent DDR signaling such as ATR-Chk1 signaling (Chk1i and ATRi) with targeted agents. Finally, combination of DNA-damaging agents such as carboplatin with inhibition of DDR may be a reasonable therapeutic approach for anaplastic (AR negative) disease. HR, homologous repair; NHEJ, nonhomologous end joining.

NCT01576172) in which patients with mCRPC receive abiraterone with or without veliparib (ABT-888). Patients are stratified by their *ETS* gene fusion status (positive or negative) and then randomized to receive abiraterone alone or abiraterone+velaparib. We believe that this trial will inform about the potential for synergistic effects with combined ADT+PARP inhibition, although this is not a primary objective.

Since AR regulates ATM-Chk2 signaling, a second approach would be to combine ADT with ATR and/or Chk1 inhibitors, especially those bearing *p53* mutations and characterized by increased replication stress and genomic instability. A third approach would be to combine DDR inhibition with a cytotoxic DNA-damaging agent. Platinum-based chemotherapy regimens are active in aggressive prostate cancers with neuroendocrine and anaplastic features.[106] Thus, combining an inhibitor of DDR with a platinum agent may represent a novel and promising approach for treating this lethal disease (Figure 2).

CONCLUSION

DNA damage is considered one of the most frequent events contributing to development of both hematologic and epithelial neoplasms, including prostate cancer. Mutations and deletions of critical DDR 'signaling nodes' regulated by ATM and Chk2 have been shown to increase the risk of prostate cancer development, while p53, an important mediator of DDR, is inactivated in many sporadic prostate cancers. Recent studies provide evidence supporting the role for AR in DDR activation and repair of DNA damage in prostate cancer cell survival through regulation of relevant genetic activities and pathways. Although there is controversy in the literature, the activation of oncogenic signaling such as Akt and c-Myc has been in general shown to increase DNA damage through replication stress enhancing genomic instability and disease aggressiveness. In cancer cells bearing defective DDR genes, the remaining active component of DDR becomes critical for tumorigenesis, since further inhibition of DDR may lead to genomic instability incompatible with cancer cell survival. Given the potential for AR to regulate genetic activities and pathways that influence DDR gene, particularly those related to ATM-Chk2 signaling, combination therapy with ADT plus a PARP inhibitor or ADT plus ATR and/or Chk1 inhibitors represents a rational therapeutic strategy. Combination of a DDR-targeted agent with a cytotoxic DNA-damaging agent (for example platinum agents) is another approach to be considered. Clinical trials based on these concepts are critical to determine which agents, conditions and combinations of agents will benefit patients' quality and longevity of life. It should also be noted that introducing DDR-targeted agents into clinical management of heterogeneous diseases, such as metastatic castration-resistant prostate carcinoma, is not without potential consequences, as evidenced by the emergence of *de novo* neoplasias following exposure to DNA-damaging agents. However, characterizing specific DDR defects in each patient should provide a unique opportunity for personalized medicine utilizing rational therapy combinations that promote synthetic lethality or synergistic cytotoxicity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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