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The resounding effect of DNA repair deficiency in prostate cancer

Heather H. Cheng, M.D., Ph.D.[a,b,*]

[a] Division of Medical Oncology, University of Washington, Seattle, WA
[b] Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA

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Abstract

An estimated one-fifth or more of metastatic castration-resistant prostate cancer (mCRPC) harbor defects in genes involved in DNA repair pathway (e.g., *BRCA2, BRCA1*, and others). Early evidence suggests these alterations may be predictive of therapeutic response to PARP inhibitors and platinum chemotherapy, thought to reflect principles of synthetic lethality and are currently being investigated in an increasing number of prospective clinical trials. Other studies have examined these alterations as prognostic biomarkers and in association with response to currently available treatments. A smaller fraction of men (5%–10%) with mCRPC have evidence of microsatellite instability and defects in the DNA mismatch repair pathway, which may predict therapeutic response to immune checkpoint inhibitors. Loss of function of these 2 critical DNA repair pathways serves as new candidate predictive biomarkers for treatment strategies that represent net gains in the treatment toolbox for prostate cancer. Additionally, more than one-tenth of men with mCRPC carry genetic alterations of DNA repair in their germline DNA, which may indicate high- to moderate-penetrance heritable cancer risk and have important implications for family members. Cascade genetic testing of family can, in some cases, direct modified strategies for screening and prevention of multiple cancers. Further study in each of these arenas is ongoing, although the potential for resounding effect is clear. © 2018 Elsevier Inc. All rights reserved.

Keywords: Prostate Cancer; DNA repair; Biomarker; PARP inhibitor; Germline

New precision targets

The prostate cancer research field has recently witnessed a series of important discoveries revolving around genes critical to DNA repair and is beginning to harness the potential of these findings in earnest. In 2015, the Cancer Genome Atlas Research Network reported findings from 333 primary prostate cancers and the identification of 19% of primary tumors with mutations in DNA repair genes, including 3% in the homologous recombination repair gene, *BRCA2* [1]. In the same year, the International SU2C/PCF/AACR Prostate Cancer Dream Team applied exome sequencing to 150 metastatic biopsies and found approximately 20% of metastatic prostate cancers with alterations in genes critical to DNA repair, notably involving homologous recombination repair (*BRCA2, ATM*, and *BRCA1*) as well as mismatch repair (*MLH1* and *MSH2*) [2]. Other studies have validated the high prevalence of DNA repair alterations in metastatic castration-resistant prostate cancers (mCRPC) [3,4].

Deficiencies in specific DNA repair pathways have been characterized in other cancers where treatments exploit these deficiencies using principles of synthetic lethality (Fig). The basic rationale is that cancers with specific inactivation of one of a number of DNA repair pathways will render the cancer more reliant on the remaining intact repair pathways. However, drugs such as PARP inhibitors can inactivate one of the remaining DNA repair pathways, which is lethal in cancer cells (where there is insufficient DNA repair capacity to compensate), while being relatively less toxic in noncancerous cells (where there is sufficient remaining intact DNA repair capacity to compensate). These discoveries are major strides in the field, as they represent molecular subsets that may benefit from precision therapies and thus are promising candidate predictive biomarkers.

Homologous recombination deficiency

Following on the discovery that a significant proportion of mCRPC harbors defects in DNA repair was early,

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* Corresponding author. Tel.: +1-206-606-7595.
E-mail address: hhcheng@uw.edu

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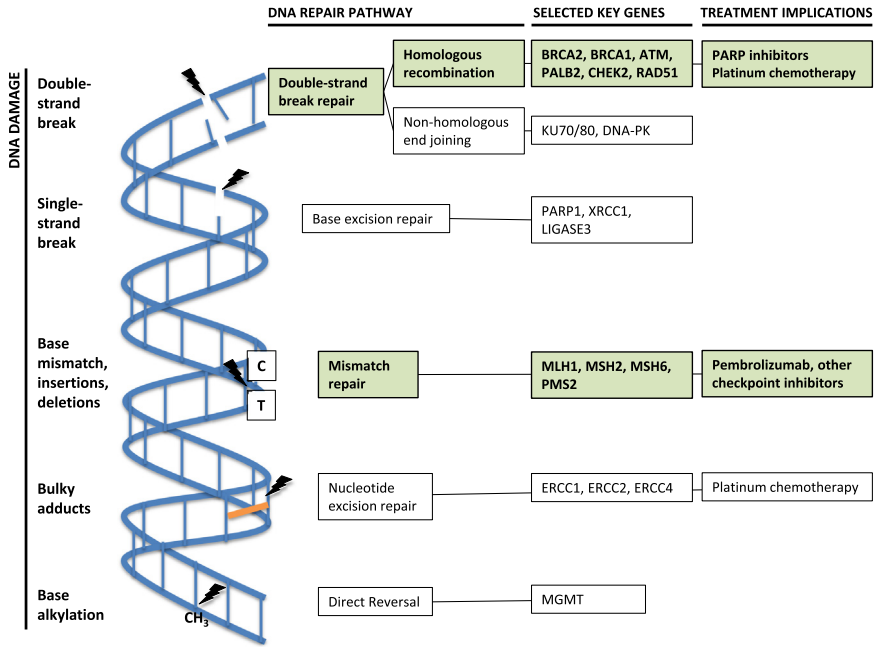

Fig. Schematic overview of major types of DNA damage, along with the corresponding DNA damage repair mechanisms, key genetic drivers, and treatment implications. Boxes denote components with particular new relevance to advanced prostate cancer. (Color version of figure is available online.)

biologically plausible evidence of clear therapeutic consequence–that not only PARP inhibitors but also platinum chemotherapy may have particular efficacy in prostate cancer with homologous recombination repair deficiency [5–7]: the TOPARP-A study showed that 14/16 (88%) of heavily pretreated patients with mCRPC who had defects in DNA repair genes had a response to the poly ADP ribosylase (PARP) inhibitor olaparib [5]. There are now a substantial number of clinical trials underway investigating PARP inhibitors in mCRPC with evidence of homologous DNA repair inactivation (Table).

In addition, several reports show notably improved response to platinum chemotherapy in patients with metastatic prostate cancer containing inactivating mutations of *BRCA2,* germline and somatic-only. In our case series from the University of Washington and Fred Hutchinson Cancer Center, 3 heavily pretreated patients observed to have exceptional responses to addition of carboplatin chemotherapy (up to 30 mo of PSA-progression-free survival) underwent tumor next generation sequencing and all were found to have evidence of biallelic inactivation of *BRCA2.* Notably, 2 patients had underlying germline *BRCA2* pathogenic mutations [6]. In another single-institutional study of 141 men treated with at least 2 cycles of carboplatin and docetaxel for mCRPC, pathogenic germline *BRCA2* variants were observed in 8/141 men (5.7%; 95% CI, 2.5%–10.9%). Six of 8 *BRCA2* mutation carriers (75%) experienced PSA declines >50% within 12 weeks, compared with 23 of 133 noncarriers (17%; absolute difference, 58%; 95% CI, 27%–88%; $P < 0.001$) [8]. There are also prospective clinical trials underway examining treatment with platinum chemotherapy for patients with mCRPC (Table).

Mismatch repair deficiency and microsatellite instability

In May of 2017, the U.S. Food and Drug Administration granted approval to pembrolizumab for patients with unresectable or metastatic solid tumors with progression or no alternative treatments that have microsatellite instability (MSI) or mismatch repair deficiency, agnostic of tissue/site indication—in this regard, the first FDA-approval of its kind. A small subset of advanced prostate cancers have been reported to have complex *MSH2* or *MSH6* structural rearrangements resulting in hypermutation [2,8]. Preliminary findings from a combination study adding pembrolizumab at time of resistance to enzalutamide revealed one exceptional responder with evidence of tumor MSI (www.clinicaltrials.gov; NCT02312557) [9]. Thus, MSI/mismatch repair deficient suggests that immune checkpoint inhibition may be another precision-guided treatment avenue for a subset of men with advanced prostate cancer. It remains to be determined whether the combination of enzalutamide and pembrolizumab exerts a different effect on prostate cancer compared to monotherapy with pembrolizumab alone, and whether there are therapeutic differences between different timing and sequences of combinations. Other novel approaches include combination of immune checkpoint inhibitors and PARPi, with the goal of forcing errors in tumor replication and potentially rendering greater tumor antigenicity and visibility to the immune system.

Therapeutic opportunities

These findings have proven exhilarating to the prostate cancer field that has eagerly awaited delivery on the

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