Beyond Hormone Therapy for Prostate Cancer with PARP inhibitors

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In this issue of *Cancer Cell*, Brenner et al. describe that the poly-(ADP) ribose polymerase (PARP) may mediate ERG function and that PARP blockade has antitumor activity in ETS gene-rearranged prostate cancer models. These data support the clinical evaluation of PARP inhibitors for treating ETS gene-rearranged prostate cancers.

The hormone dependence of prostate cancer was described seven decades ago. More recently, trials of drugs targeting continued androgen receptor (AR) signaling have confirmed the critical role of the AR in driving prostate cancer across the entire spectrum of the disease through to the fatal phenotype (Attard et al., 2009a). However, despite improvements in treatment, resistance to these next-generation therapies invariably develops. Novel treatment approaches for prostate cancer, particularly treatments sparing hormone function, remain an unmet medical need.

The discovery of gene fusions that result in hormone-regulated overexpression of oncogenes (Tomlins et al., 2005) suggested that a main mechanism underlying the response to hormone treatment was downregulation of the 3′ gene fusion partner. This is supported by preclinical evidence that ERG knockdown in AR-dependent cancer cells with a *TMPRSS2-ERG* gene fusion inhibits cell growth and invasion (Tomlins et al., 2008), and by the re-expression of high levels of ERG in *ERG*-rearranged, progressing, castration-resistant tumors (Attard et al., 2009b). Although the presence of a *TMPRSS2-ERG* gene fusion (the most common gene fusion type) does not appear sufficient for prostate cancer initiation, prostate cancer cells with this rearranged gene may be ''addicted'' to it.

The discovery and development of compounds targeting ERG (or the less common ETS fusion proteins ETV1, ETV4, or ETV5) signaling may be many years from becoming reality. The identification of proteins that interact with these oncogenes, and are key to their function, and can be targeted by therapeutics in clinical development is an attractive alternative approach. With this aim in mind, Brenner and Ateeq (2011) have identified a number of proteins with a high probability of interaction with ERG, including as top hits the DNA-dependent protein kinase (DNA-PKcs) complex of DNA repair enzymes. An immediate appeal of this discovery is the advanced stage of the clinical development of drugs inhibiting Poly(ADP-Ribose) Polymerase (PARP), a key DNA repair protein identified in these studies to interact with ERG through a DNA-independent mechanism. These data indicate that PARP1 is critically important to ETS protein function and that PARP1 inhibitors may block ETS-mediated transcription. Moreover, these authors have shown that PARP inhibitors have antitumor activity in ETS gene-driven prostate cancer models.

Studies have previously shown that potent PARP inhibitors such as olaparib and MK4827 have significant and durable antitumor activity in ovarian, breast, and prostate cancer patients whose tumors lack competent homologous recombination DNA repair, for example, due to loss-of-function BRCA1 or BRCA2 mutations (Fong et al., 2009; Yap et al., 2011). Although BRCA loss-of-function mutations may be relatively uncommon in cancer cells in sporadic tumors, DNA repair defects are probably much more common. It has been postulated that defective homologous recombination (HR) DNA repair with proficient, lower fidelity, nonhomologous end-joining (NHEJ) DNA repair may be important in accelerating the generation of DNA double strand breaks (DSB) that result in the ''driver'' rearrangements reported in prostate cancer (Lin et al., 2009) (e.g., *TMPRSS2-ERG*). These DSBs may be a result of ligand-bound androgen receptor inducing topological changes to DNA, resulting in genes like TMPRSS2 and ERG being brought to the same transcription factory loci, and activating topoisomerase IIβ to cleave DNA at specific androgen response elements, which results in the development of genomic rearrangements by NHEJ (Haffner et al., 2010). The key question is therefore what comes first: defective HR DNA repair leading to ETS gene rearrangements and PARP inhibitor sensitivity, or ETS gene rearrangements leading to PARP inhibitor sensitivity and increased DNA DSB. It may be that both of these explanations are correct.

Although further evidence is required to prove that prostate cancers have an underlying early defect in high fidelity HR DNA repair, predisposing these cells to acquiring ETS gene rearrangements, it is clear that PARP inhibitors merit evaluation in the treatment of ETS gene-rearranged prostate cancers. Brenner and Ateeq (2011) propose two mechanisms for PARP inhibitors' antitumor activity in ETS gene-driven prostate cancers: 1) inhibition of the PARP1-ETS complex that is key to ERG-mediated invasion and cell growth, and 2) synthetic lethality secondary to the accumulation of DNA DSB. Further support for the clinical evaluation of PARP inhibition in prostate cancer comes from studies showing that PTEN loss of function is associated with an inability to elicit RAD51 foci in the presence of DNA strand breaks, an accumulation of DNA DSB, and an increased sensitivity to PARP inhibitors (Dedes et al., 2010), as well as a poor prognosis (Reid et al., 2010, Mendes-Pereira et al.,

2009). This could be of enormous clinical significance due to the high prevalence of PTEN loss of function in cancer, including in prostate cancer with ERG rearrangements. Overall, therefore, the appeal of these findings is obvious: ETS-rearranged prostate cancer is very common and can be relatively easily identified in tumor biopsies, urine (untreated patients), or circulating tumor cells, allowing patient selection for treatment (Attard et al., 2009b). Interestingly, the in vivo antitumor activity of PARP inhibition in combination with the chemotherapy temozolomide is greater than PARP inhibition alone in a preclinical model. A concern of these results is, however, that the significant antitumor activity observed with temozolomide alone in this model is not observed in patients. The synergism between PARP inhibition and radiotherapy has not been tested in these models but, based on Brenner and Ateeqs' (2011) results, certainly merits further evaluation in prostate cancer patients. It is envisioned, however, that single agent antitumor activity will be important to the successful clinical development of these agents.

PARP inhibitors are now undergoing clinical evaluation in advanced sporadic prostate cancer both as single agents and in combination with chemotherapy. It is therefore probable that the relevance of Brenner and Ateeqs' study will soon become apparent. The careful design of these trials will be critically important to maximize the likelihood of their successful evaluation: 1) patient selection based on validated ETS gene breakapart fluorescence in situ hybridization (FISH) assays is required; 2) evaluation of PTEN loss in pretreatment tumor tissues is recommended, although the degree of PTEN reduction that would result in sensitivity to PARP inhibitors remains to be clarified; 3) evaluation of the impact of PARP inhibitors on γH2AX and RAD51 foci formation in post-treatment cancer cells is also recommended in pharmacodynamic studies as well as studies evaluating ETS gene signaling; and 4) finally, it is possible that PARP inhibitors will not result in immediate falls in the circulating prostate cancer tumor marker Prostate Specific Antigen (PSA), since these agents decrease ERG signaling without directly impacting androgen receptor signaling. Other endpoints evaluating the impact of PARP inhibitors on radiologic disease measurements, circulating tumor cells, and symptoms are therefore necessary to evaluate the antitumor activity of these agents. Finally, Brenner and Ateeqs' study also identifies other proteins that significantly interact with ERG that could represent therapeutic candidates, such as Hsc70. Ultimately, if proven to be effective, PARP inhibitors could be the first of a generation of novel therapeutic strategies that improve on or possibly avoid the use of hormone therapy for prostate cancer.

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