Potential for targeted therapy in prostate cancers with ERG abnormalities

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ince the recent identification of recurrent gene fusions in prostate cancer between members of the ETS family of genes and transmembrane protease, serine 2 (TMPRSS2),¹,² a tremendous amount of interest has developed in the pathways through which these fusions contribute to prostatic carcinogenesis, as well as their diagnostic utility, prognostic value and therapeutic implications.¹–⁶ Most commonly, fusion of the transcriptional regulator gene ERG (ETS-related gene) with TMPRSS2 is seen, present in half or more of prostate cancers, although other partner genes, such as ETV1, ETV4 and ETV5, may be involved in translocations.¹,²,⁷ Subsequent studies have found these gene fusions to appear early in prostate cancer development,²⁸ present in a subset of cases of prostatic intra-epithelial neoplasia and putative precursor lesions.²,⁸,⁹ Likewise, ERG fusions are present throughout the spectrum of the various microscopic manifestations of prostate cancer,⁶,¹⁰,¹¹ supporting their role as a key step in the pathogenesis of prostate cancer in general. However, other genetic alterations appear to be contributory components of tumor development, such as loss of PTEN and activation of the PI3–kinase pathway, particularly in the setting of progression from an intraepithelial neoplasm to invasive adenocarcinoma.²,⁴,¹² Although abnormalities of ETS genes are sometimes found in tumors of other organs, ERG–TMPRSS2 fusion is not seen in common neoplasms of other sites, both epithelial and non-epithelial.³ As such, these abnormalities have begun to demonstrate tremendous potential for broad applications in diagnosis, prognostication and treatment of prostate cancer.⁷,⁸

With regard to therapy, however, gene rearrangements involving transcription factors have unfortunately been largely considered poor targets for pharmacologic therapy, due to their lack of enzymatic activity, location within the nucleus and complex interaction with other proteins required for function.¹³,¹⁴ Nonetheless, in a recent study by Brenner et al.,⁷ the authors identified a potential avenue of utility for poly(ADP-ribose) polymerase 1 (PARP1) inhibition in treatment and prognostication for patients with ETS-abnormal prostate cancer, opening the door for a wide spectrum of potential applications.

The group sought to identify proteins interacting with the TMPRSS2–ERG fusion product in prostate cancer cells harboring the rearrangement. Interacting proteins of high probability included components of the DNA-dependent protein kinase complex, as well as peptides for PARP1, both of which they confirmed to physically interact with the ERG gene fusion product endogenously. Inhibition of these enzymes leads to decreased invasion in prostate cancer cell lines with ETS gene abnormalities compared to those without, suggesting a key role in ERG-mediated prostate cancer progression.⁷ Since inhibition of PARP1 via a number of pharmacologic agents has been investigated as a potential cancer therapy,¹⁵,¹⁶ the interaction of PARP1 with the ERG fusion product is of particular interest. Specifically, cancers with BRCA1 and BRCA2 mutations are deficient in DNA repair. In this setting, PARP1 inhibition results in accumulation of double-strand DNA breaks that are unable to be repaired by homologous recombination, resulting cumulatively in cell death, sometimes referred to as synthetic lethality. However, this tumor cell susceptibility to PARP inhibition may not be limited to cancers with BRCA1/2 abnormalities. Tumors with other abnormalities of double-strand break repair proteins may also yield a similar outcome under PARP inhibition.¹⁶ Of such agents, olaparib has begun to show promise, particularly as many of the toxic effects associated with traditional chemotherapy have been lacking in preliminary studies.¹⁵ With this in mind, Brenner and colleagues also investigated its impact on prostate cancer xenograft growth. They examined the effect of olaparib on prostate cancer cell lines with and without ERG abnormalities, finding a significant reduction of tumor growth in the ETS-rearranged cells. Interestingly, overexpression of the TMPRSS2–ERG fusion product in cell lines without the rearrangement also led to sensitization to PARP inhibition. Combination treatment with olaparib and temozolomide resulted in a greater, significant growth reduction, without signs of overt toxicity, suggesting a potential role for addition of PARP inhibition to existing chemotherapy regimens.

In another recent study, Vainio et al.¹⁷ found that several genes: PLA2G7, HPGD, EPHX2 and CYP4F8, members of the arachidonic acid pathway, are highly expressed in prostate cancer. In particular, PLA2G7 appears to be involved in the cell’s response to oxidative stress. These authors found the enzyme encoded by PLA2G7 to be especially over-expressed in tumors with the ERG translocation and required for viability of ERG-positive cancer cells. Silencing of PLA2G7 increased the sensitivity of ERG-positive prostate cancers to oxidative stress, suggesting a utility of PLA2G7 as a potential therapeutic target or biomarker for prostate cancer.

In another study by Rahim and colleagues,¹⁸ the authors hypothesized that YK-4-279, a small molecular inhibitor of EWS-FLI1, may have inhibitory effects on prostate cancer, as the ERG and ETV1 proteins belong to the same class of ETS factors as FLI1. They
Based upon their conclusions, in the setting of breast and ovarian cancer, inhibition has already undergone significant inhibition by YK-4-279 in the prostate. Motility studies also showed significant inhibition by YK-4-279 in the prostate cancer cell lines. Notably, reduction of ERG protein expression abrogated these effects of YK-4-279 in ETS-abnormal cell lines. Similarly, transient expression of ERG in fusion-negative cells resulted in a more invasive phenotype that was inhibited by YK-4-279. Motility studies also showed significant inhibition by YK-4-279 in the prostate cancer cell lines.

Although studies such as these have begun to investigate the therapeutic implications of ERG fusions, the study by Brenner et al. may be of particular interest, in that PARP1 inhibition has already undergone significant investigation as a potential cancer treatment in the setting of breast and ovarian cancer. Based upon their conclusions, inhibition of PARP1 may have important therapeutic applications via synthetic lethality by the way of increased DNA double-strand break formation, as well as reduction of ERG-mediated transcription and invasion. Going forward, awareness of ETS abnormalities in prostate cancer in general as well as the novel identification of sensitivity to PARP inhibition may lead to advances in not only the therapy of ETS-rearranged prostate cancer but also risk stratification, prediction of therapy response and use as a biomarker.