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RESEARCH HIGHLIGHT

Potential for targeted therapy in prostate cancers with *ERG* abnormalities

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Since 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,[6] 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.[2,5]

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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 are 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[7] 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 chemotherapeutic 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

did not find expression of FLI1 in prostate cancer cells to account for a potential cause of inhibition, yet cell exposure to YK-4-279 resulted in reduced mRNA and protein levels of several ERG and ETV1 target genes without significant decrease in ERG or ETV1 protein levels themselves. Using an impedance-based endothelial cell invasion assay, YK-4-279 significantly inhibited invasion in ETS-abnormal prostate cancer cell lines, without demonstrable inhibition in ETS fusion-negative prostate cancer cells. 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.*[7] 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.[15,19–21] 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.

1 Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R *et al*. Recurrent fusion of *TMPRSS2* and *ETS* transcription factor genes in prostate cancer. *Science* 2005; **310**: 644–8.
2 Kumar-Sinha C, Tomlins SA, Chinnaiyan AM. Recurrent gene fusions in prostate cancer. *Nat Rev Cancer* 2008; **8**: 497–511.
3 Scheble VJ, Braun M, Beroukhim R, Mermel CH, Ruiz C *et al*. ERG rearrangement is specific to prostate cancer and does not occur in any other common tumor. *Mod Pathol* 2010; **23**: 1061–7.
4 Carver BS, Tran J, Gopalan A, Chen Z, Shaikh S *et al*. Aberrant *ERG* expression cooperates with loss of *PTEN* to promote cancer progression in the prostate. *Nat Genet* 2009; **41**: 619–24.
5 Tomlins SA, Bjartell A, Chinnaiyan AM, Jenster G, Nam RK *et al*. *ETS* gene fusions in prostate cancer: from discovery to daily clinical practice. *Eur Urol* 2009; **56**: 275–86.
6 Andreoiu M, Cheng L. Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. *Hum Pathol* 2010; **41**: 781–93.
7 Brenner JC, Ateeq B, Li Y, Yocum AK, Cao Q *et al*. Mechanistic rationale for inhibition of poly(ADP-ribose) polymerase in *ETS* gene fusion-positive prostate cancer. *Cancer Cell* 2011; **19**: 664–78.
8 Clark J, Attard G, Jhavar S, Flohr P, Reid A *et al*. Complex patterns of *ETS* gene alteration arise during cancer development in the human prostate. *Oncogene* 2008; **27**: 1993–2003.
9 Mosquera JM, Perner S, Genega EM, Sanda M, Hofer MD *et al*. Characterization of *TMPRSS2–ERG* fusion high-grade prostatic intraepithelial neoplasia and potential clinical implications. *Clin Cancer Res* 2008; **14**: 3380–5.
10 Han B, Mehra R, Suleman K, Tomlins SA, Wang L *et al*. Characterization of *ETS* gene aberrations in select histologic variants of prostate carcinoma. *Mod Pathol* 2009; **22**: 1176–85.
11 Williamson SR, Zhang S, Yao JL, Huang J, Lopez-Beltran A *et al*. *ERG–TMPRSS2* rearrangement is shared by concurrent prostatic adenocarcinoma and prostatic small cell carcinoma and absent in small cell carcinoma of the urinary bladder: evidence supporting monoclonal origin. *Mod Pathol*; e-pub ahead of print 15 April 2011; doi: 10.1038/modpathol.2011.56.
12 King JC, Xu J, Wongvipat J, Hieronymus H, Carver BS *et al*. Cooperativity of *TMPRSS2–ERG* with PI3-kinase pathway activation in prostate oncogenesis. *Nat Genet* 2009; **41**: 524–6.
13 Palanisamy N, Ateeq B, Kalyana-Sundaram S, Pflueger D, Ramnarayanan K *et al*. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat Med* 2010; **16**: 793–8.
14 Darnell JE Jr. Transcription factors as targets for cancer therapy. *Nat Rev Cancer* 2002; **2**: 740–9.
15 Fong PC, Boss DS, Yap TA, Tutt A, Wu P *et al*. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009; **361**: 123–34.
16 Dedes KJ, Wilkerson PM, Wetterskog D, Weigelt B, Ashworth A *et al*. Synthetic lethality of PARP inhibition in cancers lacking *BRCA1* and *BRCA2* mutations. *Cell Cycle* 2011; **10**: 1192–9.
17 Vainio P, Gupta S, Ketola K, Mirtti T, Mpindi JP *et al*. Arachidonic acid pathway members *PLA2G7*, *HPGD*, *EPHX2*, and *CYP4F8* identified as putative novel therapeutic targets in prostate cancer. *Am J Pathol* 2011; **178**: 525–36.
18 Rahim S, Beauchamp EM, Kong Y, Brown ML, Toretsky JA *et al*. YK-4-279 inhibits ERG and ETV1 mediated prostate cancer cell invasion. *PLoS One*. 2011;**6**e19343
19 Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet* 2010; **376**: 245–51.
20 O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D *et al*. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011; **364**: 205–14.
21 Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 2010; **376**: 235–44.