Editorial

The future of prostate cancer precision medicine: anti-ERG therapies

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Prostate cancer (PCa), the most common, non-cutaneous male malignancy (1), is primarily driven by androgen signaling. Thus, clinical management of the disseminated disease is dominated by ever-improving androgen receptor (AR) pathway inhibitors (ARPIs) that have contributed to 30–40% decline in disease-specific mortality observed over the last two decades (2). Nonetheless nearly all ARPI therapy patients eventually develop resistance to these agents (2,3), calling for the development of novel targeted therapeutics for additional molecular lesions in PCa.

Although confounded by disease heterogeneity, PCas harbor a number of specific genomic alterations linked to the disease occurrence, progression, and outcome (1,3,4). Some of the most prevalent lesions correlated with metastatic castration-resistant PCa (mCRPC) include: AR overexpression and mutations, loss/mutations of key tumor suppressors [including TP53, RB and phosphatase tensin homologue (PTEN) among others], and prominent gene fusions that direct aberrant expression of members of the E26 transformation-specific (ETS) family, such as TMPRSS2-ERG (5,6). These fusion events have been observed in approximately half of PCas, and represent the most common PCa-associated abnormality documented to date (7).

ERG is one of several members of the ETS transcription factor family known to have oncogenic potential (8,9) and the fusion of androgen-responsive elements of TMPRSS2 with open reading frame sequences of ERG (TMPRSS2-ERG) directs aberrant AR-driven ERG expression (1). It is broadly accepted that TMPRSS2-ERG rearrangements represent early events in PCa initiation and are strongly associated with higher Gleason score, aggressive disease, and poor prognosis due to activation of aberrant ERG-driven transcriptional programs that promote migration, invasion and epithelial-mesenchymal transition (10). Importantly, ERG expression has been shown to persist during disease progression and to regulate taxane sensitivity in PCa. Thus, it is expected that therapeutic targeting of ERG could have immense clinical significance (11).

While TMPRSS2-ERG diagnostic and prognostic methods undergo very active development, there are yet no approved ERG-directed therapeutics. The absence of agents targeting any ETS factors makes developing therapeutics targeting these major oncoproteins a critical step towards new therapeutics for PCa and other ETS factor-driven malignancies. With urine tests available to detect the TMPRSS2-ERG fusion event (12,13), the development of ERG-targeted drugs would offer a specific 'precision medicine' approach for PCa patients. Here we discuss the recent report by Wang *et al.* "*Development of Peptidomimetic Inhibitors of the ERG Gene Fusion Product in Prostate Cancer*" (14), and that effort to develop such needed ERG-targeted therapy.

Using a phage display random peptide library screen, Wang *et al.* identified ERG inhibitory peptides (EIP) that bound directly to the DNA binding (ETS)-domain of ERG and disrupt ERG-ETS domain/DNA interactions. Mutagenesis of the ETS domain and peptides demonstrated reciprocal requirements for the selective affinity. Furthermore, cell permeable peptides prepared via conjugation of HIV-TAT sequence to EIPs retained ERG-ETS affinity, exhibited nuclear co-localization with ERG, and blocked invasive properties of ERG-expressing PCa models. While retro-inverso (RI) EIP

versions exhibited no significant effect on angiogenesis in several models, they promoted ERG degradation, decreased ERG target gene expression, offered improved stability when delivered via intraperitoneal administration, and demonstrated inhibition of tumor growth and metastasis.

The results of this study represent a significant step towards the development of an ERG-targeted therapeutic and bolster the ever-increasing recognition of the importance of persistent ERG expression in TMPRSS2-ERG PCas. The lack of overt murine toxicity of the developed candidates is encouraging; however, there is a need to characterize the affinity of these peptides with other ETS family members since these genes are involved in maintenance and oncogenesis in several tissue types and target selective peptidomimetic agents would undoubtedly be of value. The details of molecular interactions between the developed EIPs and ERG-ETS target as well as the specifics of the competition with DNA binding remain to be described. For the latter, as for any mutational efficacy study, the lack of observed activity in the binding assay needs to be considered with respect to differential domain folding, or indirect allosteric changes to the protein structure. Finally, ERG is a key regulator of fate determination and differentiation of several tissues, including chondrogenesis (15), hematopoiesis (10) and, as tested by Wang *et al.*, endothelial development. It is perplexing that a potent ERG antagonist would not exhibit an impact on the array of angiogenic assays performed.

As has been previously reviewed (16,17), peptidomimetics have several advantages and disadvantages in their use as therapeutic agents. While complexity of peptide-based therapeutics affords their high target affinity and specificity, as well as generally low side effect and toxicity, the important issues of tissue accumulation of the corresponding drug candidates, their metabolic stability and solubility, membrane permeability and delivery obstacles, along with rapid clearance and high cost of development, represent well-known drawbacks for their clinical development (16). With that being said, it is important to stipulate that the use of peptides as ERG-directed therapeutic agents represents an exciting avenue for PCa treatment and that result by Wang *et al.* provide an important stepping stone for overcoming limitations associated with the use of peptides as therapeutic agents.

On another hand, it should also be noted that there are concurrent efforts to develop small molecule ERG antagonists as a more clinically viable alternative for peptide-based agents. The first reported small molecule ERG inhibitor YK-4-279 was initially discovered as an antagonist for FLI1 protein, a close homologue of ERG and a known oncotarget implicated in Ewing's sarcoma (18-21). The pre-clinical development of its derivative TK216 is currently in phase 1 trial (ClinicalTrials.gov Identifier: NCT02657005) (22) that is expected to significantly impact the future development of ETS targeted therapies.

Other recent efforts to directly target ERG protein with small molecules include rational computer-aided discovery of a compound VPC-18005. It has been shown that this compound directly binds the ERG-ETS domain and suppresses ERG transcriptional activity at low micromolar concentrations, while it is also capable of suppressing metastatic potential of ERG-expressing PCa cells (23). Other small molecules include ERGi-USU, a small molecule that can selectively suppress growth of ERG-expressing cancer cells (24), and heterocyclic dithiophene diamidines that target the ETS consensus DNA motif to block ERG-DNA interactions (25).

To conclude, it is important to outline, that therapeutic targeting of ERG, as well as other oncogenic ETS family members represents a promising avenue for the development of novel precision oncology strategies. It is anticipated that an entirely novel class of ERG inhibitors (whether peptide- or small molecule-based) are urgently needed and can be used as alternative or complimentary agents for the current ARPIs and chemotherapeutics to treat PCa even in its most deadly resistant and metastatic form.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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