ERG finally has something to YAP about in prostate cancer

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ERG is a transcription factor of the ETS (erythroblastosis virus E26) family that is rearranged and overproduced in approximately 50% of all human prostate tumors. ERG overproduction appears to be important because knockdown of ERG in a human prostate cancer cell line (VCaP) that overexpresses ERG has been shown to decrease cell invasion, a hallmark of metastasis. Conversely, overexpression of ERG in non-cancerous prostate epithelial cells (RWPE-1) results in a marked increase in cell invasion. However, whether overexpression of ERG is sufficient for prostate cancer development and the potential molecular mechanisms of ERG in prostate cancer have not been determined. A new Fred Hutch study from Dr. Valeri Vasioukhin’s Laboratory (Human Biology...
Division), in collaboration with Dr. Pete Nelson’s Laboratory (Human Biology, Clinical Research, and Public Health Sciences Divisions), tackled this question by providing a detailed characterization of a mouse model wherein ERG is overexpressed in the prostate epithelium at levels comparable to those observed in ERG-rearranged human prostate cancers. This study was recently published in Cancer Cell.

The authors first generated a mouse model that expressed clinically relevant levels of ERG specifically in the prostate epithelium. They found that these mice were short-lived, and that half of them developed late-onset prostate tumors. This finding demonstrated that overproduction of ERG in prostate epithelial cells in vivo is sufficient for prostate cancer development, indicating that rearrangement and overproduction of ERG plays a causal role in prostate cancer initiation. The researchers then analyzed expression of gene targets of major signaling pathways known to regulate cancer development, and found that even before tumor development, the ERG-overexpressing prostate epithelial cells exhibited high activity of YAP1 (Yes-associated protein 1). Because YAP1 is a transcriptional regulator and a key effector of the Hippo signaling tumor suppressor pathway, the investigators used RNA sequencing to compare the transcriptional profiles of RWPE-1 cells overexpressing either ERG, a constitutively active form of YAP1 (YAP1S127A), or both ERG and YAP1S127A. Gene set enrichment analysis of the RNA sequencing data revealed strong overlap between the ERG and YAP1 transcriptional programs.

Next, the researchers investigated the functional relevance of YAP1, and its close relative TAZ, using a 3D prostate organoid culture system. These experiments revealed that knockdown of either YAP1 or TAZ blunted both the proliferation and the invasive properties of human RWPE-1 cells that overexpressed ERG. To address the mechanism by which ERG promotes high YAP1 activity, the authors performed chromatin immunoprecipitation followed by high throughput DNA sequencing (ChIP-seq) to identify DNA sequences bound by ERG and TEAD4, a YAP1 binding partner. ChIP-seq experiments in both VCaP and RWPE-1 cells revealed that ERG and TEAD4 were co-bound at many Hippo pathway genes, and that ERG increased both histone acetylation and gene activation at these sites. Importantly, 44% (52 of 116) of primary human prostate cancers analyzed co-expressed ERG and YAP1, and expression of nuclear YAP1 was linked to tumor recurrence after treatment.

To evaluate the role of YAP1 in ERG-driven tumors in vivo, the investigators administered an FDA-approved inhibitor of YAP1 (Verteporfin) to pre-established human orthotopic xenografts tumors, and found that Verteporfin treatment suppressed the growth of ERG-positive, but not ERG-negative, prostate tumor xenografts. Finally, the authors addressed whether activation of YAP1 was sufficient for tumor formation by driving expression of YAP1S127A in the prostate epithelium, which resulted in
late-onset prostate tumors that were strikingly similar to ERG-driven tumors, both in histology and transcriptional profile.

Said Dr. Vasioukhin, "ERG is overexpressed in ~50% of human prostate cancers, but the role and mechanisms of ERG in prostate cancer remained poorly understood. This study demonstrated that ERG expression is sufficient to cause prostate cancer development in aged individuals and revealed a connection between ERG and the Hippo signal transduction pathway, which can explain the molecular mechanisms of ERG in prostate cancer initiation." In conclusion, this important study showed that overexpression of either ERG or YAP1 results in late-onset prostate tumors and it revealed the mechanism responsible for oncogenic function of ERG. Furthermore, since YAP1 activity is required for ERG-driven tumors both in vitro and in vivo, it suggests that the YAP1 antagonist Verteporfin may provide novel therapeutic opportunities.


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