Loss of Function Mutations in ETS2 Repressor Factor, ERF, Reveal a Balance Between Positive and Negative ETS Factors Controlling Prostate Oncogenesis

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Background and Objectives: half of prostate cancers are caused by a gene-fusion that enables androgens to drive expression of the normally silent ETS transcription factor ERG in luminal prostate cells. Recent prostate cancer genomic landscape studies have reported rare but recurrent point mutations in the ETS repressor ERF. The objective of this study is to understand the significance of these mutations and to understand how ERF may promote prostate cancer.

Methods: ERF expression was inhibited using CRISPR and shRNA technology and the androgen receptor cistrome and transcriptome was probed via ChIP-seq and RNA-seq respectively, in normal prostate organoids, patient-derived organoids, as well as existing TMPRSS2-ERG positive models. Results: here we show these ERF mutations cause decreased protein stability and ERF mutant tumors are mostly exclusive from those with ERG fusions. ERF loss recapitulates the morphologic and phenotypic features of ERG gain in primary mouse prostate tissue, including expansion of the androgen receptor repertoire, and ERF has tumor suppressor activity in the same genetic background of Pten loss that yields oncogenic activity by ERG. Furthermore, in a human prostate cancer model of ERG gain and wild-type ERF, ChIP-seq studies indicate that ERF inhibits the ability of ERF to bind DNA at consensus ETS sites. Consistent with a competition model, ERF loss rescues ERG-positive prostate cancer cells from ERG dependency. Conclusion: collectively, these data provide evidence that the oncogenicity of ERG is mediated, in part, by displacement of ERF and raises the larger question of whether other gain-of-function oncogenic transcription factors might also inactivate endogenous tumor suppressors. Implications: further work needs to be performed, but ERF loss may serve as a predictive marker of response to anti-androgen therapy.

Conflict of Interest: none to report.

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