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PROSTATE CANCER

ETS factors in the balance

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A new paper in *Nature* shows that a competitive balance of two members of the ETS family of transcription factors, the transcriptional regulator ERG and the ETS domain-containing transcription factor ERF, has a role in prostate oncogenesis.

Increased expression of *ERG* is common in prostate cancers and is a driver of malignant transformation. Sequencing studies have shown that 1–3% of men with this disease have mutations in *ERF*, another ETS family member, whose DNA-binding domain is similar to that of the ERG subfamily but contains a transcription repression domain.

In their paper, the researchers describe that mutations or focal deletions of *ERF* are mostly exclusive to tumours without *TMPRSS2–ERG* fusion and question whether ERF loss results in a phenotype similar to ERG gain. *Erf* knockdown in mouse prostate organoids resulted in morphological characteristics similar to ERG overexpression, regardless of *Pten* status, and tumour formation when *Pten*$^{-/-}$ organoids were injected into mice. In a human prostate cancer cell line without *TMPRSS2–ERG* fusion, *ERF* knockdown increased the number of differentially expressed androgen receptor (AR) target genes and the extent of expression changes, but did not change AR mRNA or protein levels. Analysis of data from human cohorts showed that *ERF* mRNA levels were inversely correlated with androgen transcriptional activity in normal and primary malignant prostate samples, and in metastatic tumours that lacked amplification or mutation of *AR*, regardless of *TMPRSS2–ERG* fusion.

The team then knocked down *ERG* and *ERF* separately in VCaP cells, which are ERG-fusion-positive. ERG inhibition resulted in a contracted androgen transcriptome, whereas ERF inhibition doubled the androgen transcriptome, without affecting each other's expression, or AR levels and localization. Analysis of ERF binding to canonical ETS motifs showed a nearly tenfold increase in binding sites when ERG was knocked down. The majority of sites overlapped with those of ERG or AR. In normal prostate, ERF and AR binding site overlap was much lower, consistent with AR binding site redistribution during tumorigenesis.

Finally, the researchers demonstrated that ERF deletion or ERF induction resulted in increased or absent tumour formation, respectively, in a mouse xenograft model of *Pten*$^{-/-}$, ERG-fusion-positive organoids. In human ERG-positive prostate cancer cells, ERG deletion stopped proliferation and previous ERF knockdown rescued cells from ERG dependency. The team propose that loss of ERF activity (through mutation or through competition with the *TMPRSS2–ERG* gene product) leads to AR pathway activation and prostate cancer.

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ORIGINAL ARTICLE Bose, R. *et al.* ERF mutations reveal a balance of ETS factors controlling prostate oncogenesis. *Nature* http://dx.doi.org/10.1038/nature22820 (2017)