

## ERG orchestrates chromatin interactions driving prostate cell fate reprogramming

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### BACKGROUND:

Lineage plasticity have been proved as the extensively mechanism which involved in multiple cancer progression stages, facilitating the growth and drug resistance acquisition of cancer cells. Primary prostate cancer is generally characterized with luminal cells expansion and loss of basal cells. Cumulative evidence with detailed mechanisms suggested that therapeutics induced lineage alterations with the transition from luminal cell lineage towards neuroendocrine and basal differentiation. Numerous studies have focused on lineage transition in CRPC. However, the lineage determining mechanism of therapy sensitive primary prostate luminal cancer is largely unknown.

### METHODS:

We integrated two prostate cancer subtyping methods including PAM50 classifier and integrative epigenetics classifier, which were performed on the basis of prostate cell lineage markers and epigenetic features respectively. This integrative method ensured that the transcription factors to be further identified would highly correlate with both prostate cancer lineage and epigenetics modification. To investigate the relationship between ERG and prostate cell lineage, we performed *in vitro* organoids formation assay and *in vivo* prostate organoids transplantation assay. To further test whether gene expression changes induced by ERG correlated with global changes in chromatin interactions, we performed BridgeLinker-Hi-C (BL-Hi-C) in Luminal, Luminal-ERG, *Pten*<sup>-/-</sup> and *Pten*<sup>-/-</sup>;*R26-ERG* organoids.

### RESULTS:

Through the integration of two prostate cancer subtyping methods including PAM50 classifier and integrative epigenetics classifier, we found that ERG highly correlated with prostate cancer subtyping. ERG over-expression

maintained luminal-cell-derived organoids and allografts with luminal histology. Pten loss enforced prostate cells basal differentiation in organoids and genetic engineered mouse model (GEMM), while ERG expression in prostate organoids, allografts and GEMM led to prostate cancer cell luminal differentiation in Pten loss context. Moreover, prostate cancer cell luminal phenotype was more dependent on ERG, in the meanwhile AR knock-out had no significant effects on prostate cancer cell luminal lineage determination. ERG DNA binding significantly correlated with differential chromatin interactions, indicating the potential role of ERG in transcription regulation by re-organizing chromatin interactions to facilitate cell fate reprogramming. The number of chromatin interaction loops between Trp63 and the region of distal ERG binding site in ERG-positive prostate organoids significantly decreased comparing to ERG-negative prostate organoids. In both luminal-ERG and *Pten*<sup>-/-</sup>; *R26-ERG* organoids, the deletion the distal ERG binding site resulted in lineage alteration, reflecting that ERG orchestrates prostate luminal lineage plasticity through chromatin interaction. We also confirmed the existence of the distal ERG binding site in human prostate cells, indicating the conserved role of ERG in the regulation of prostate luminal lineage.

### **CONCLUSIONS:**

Taken together, our findings identify ERG as a master regulator transcription factor, manipulating prostate cell lineage plasticity towards pro-luminal program through chromatin interactions. These findings proposed a novel model with detailed mechanisms for elucidating a fundamental and long-standing question how prostate cancer cells maintain luminal lineage identity, also provided further support for the role of lineage plasticity in cancer progression.

### **CONFLICT OF INTEREST:**

No related conflict of interest to this study.

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