Cell context dependency and vulnerabilities of ERG-driven prostate cancer

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Background

Translocations of the ETS family transcription factor ERG are found in half of primary prostate cancers but is challenging to directly target, underscoring the importance of defining the mechanism by which ERG promotes prostate epithelial transformation.

Methods

To gain insight into how ERG causes prostate cancer, we performed single cell transcriptional profiling of an autochthonous mouse model at an early stage of disease initiation, in combination with lineage tracing, primary prostate tissue transplantation, *ex vivo* organoids modeling, and functional validation *in vivo*.

Results

We find that tumor initiating activity resides in a subpopulation of basal cells that co-express the luminal genes Tmprss2 and Nkx3.1 (which we call Basal^{Lum}) but not in the larger population of classical Krt8+ luminal cells. Upon ERG activation, Basal^{Lum} cells give rise to a small population of cells with a highly proliferative multi-lineage state (basal/luminal/hillock/club), which subsequently transition to the larger population of KRT8+ luminal cells that are characteristic of ERG-positive human cancers. Cells within this proliferative population have a novel chromatin state enriched for ETS, NFkB, AP-1, STAT and NFAT transcription factor binding sites and elevated epigenetic regulators, which collectively contribute to the ERG dependent tumor phenotype.

Conclusions

Thus, the tumorigenic potential of ERG is cell context dependent, resulting in unique chromatin landscape that enables cooperativity with several potentially druggable partner transcription factor pathways and chromatin modifying enzymes.

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Disclosure

Dr. Sawyers serves on the Board of Directors of Novartis, is a co-founder of ORIC Pharmaceuticals and co-inventor of enzalutamide and apalutamide. He is a science advisor to Beigene, Blueprint, CellCarta, Column Group, Foghorn, Housey Pharma, Nextech and PMV.