SOX2 utilizes FOXA1 as a heteromeric transcriptional partner to drive proliferation in therapy-resistant prostate cancer

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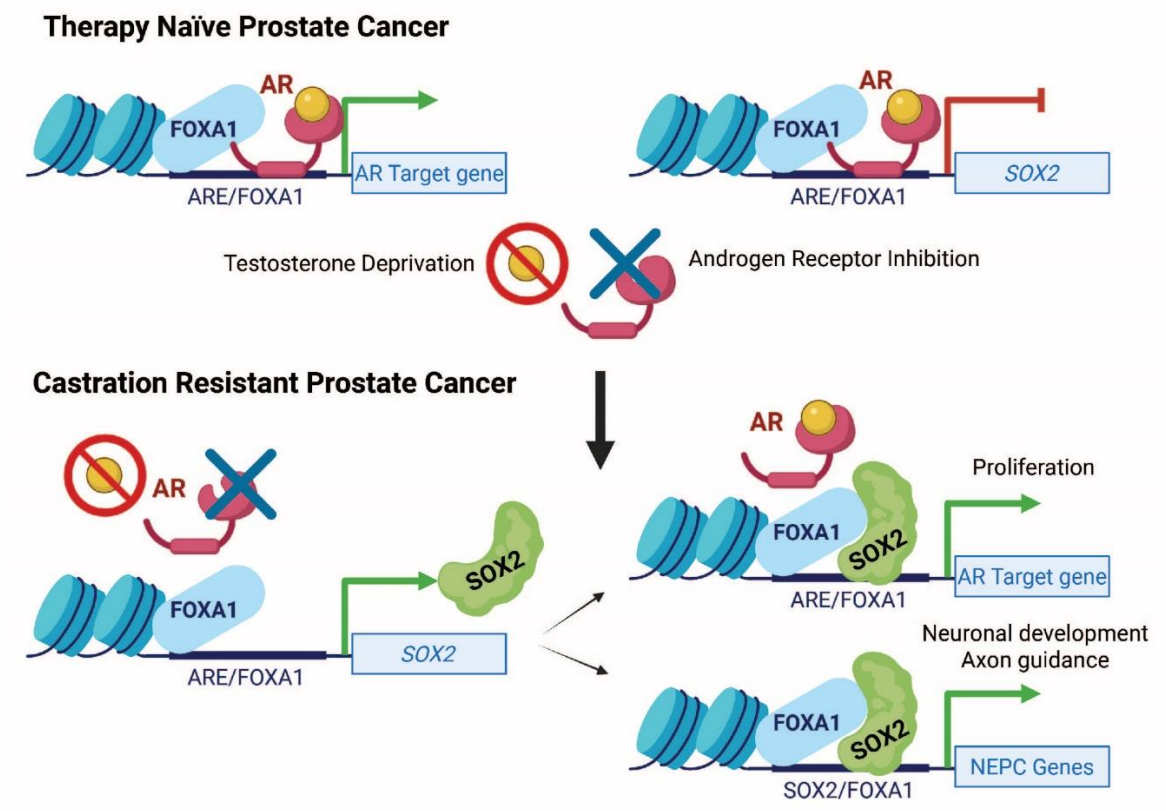
Background: Despite advances in targeting the androgen receptor (AR), the emergence of lethal forms of prostate cancer (PCa) with acquired resistance to AR-signaling inhibition (ARSI) and lineage plasticity remains a significant clinical burden. In this study, we investigate a shared function of FOXA1, AR's pioneering cofactor that remains essential when AR-expression is lost in late-stage PCa, and SOX2: an AR-repressed transcription factor, driver of ARSI-resistance, and neuroendocrine prostate cancer (NEPC) marker. This study defines the functional role of SOX2 and FOXA1 in ARSI-resistant PCa.

Methods: We assayed cell viability after SOX2 knockdown, probed PCa patient transcriptome datasets, employed biochemical approaches to detect protein-protein interactions, and assayed genomic occupancy of AR, FOXA1, and SOX2 in castration-resistant adenocarcinoma and NEPC cells. We also performed functional enrichment and gene ontology (GO) analyses on transcription factor binding and validated downstream SOX2 targets.

Results: SOX2 knockdown decreases survival of both adenocarcinoma and NEPC cells. We demonstrate SOX2 and FOXA1 engage in direct physical interaction and exhibit ~90% overlap in DNA binding. These co-bound regions are also AR-bound in adenocarcinoma cells and GO reveals enrichment of cell cycle progression and neuronal pathways. We show decoupling of AR and FOXA1-regulated gene networks in NEPC patient transcriptomes, and establishment of SOX2 and FOXA1-regulated gene networks. SOX2 seldom has conserved DNA binding sites in cancers compared to its canonical environment in pluripotent cells and in prostate basal epithelial cells. Altogether, our results demonstrate physical and functional cooperation of SOX2 and FOXA1, whose DNA-binding occurs near genes responsible for ARSI-resistance, lineage plasticity, and NEPC phenotypes.

Conclusions: Here we provide the first evidence of direct SOX2 dependency within a representative NEPC system. Protein interaction assays, in silico modeling, and ChIP-seq analyses mechanistically establish SOX2 and FOXA1 as heteromeric transcriptional partners who occupy DNA near genes which promote cell proliferation and confer lineage plasticity, regardless of AR status. Altogether, we assert that SOX2's interaction with FOXA1 and downstream target genes might provide a novel therapeutic opportunity in deadly, ARSI-resistant PCa.


Therapy Naïve Prostate Cancer
AR
FOXA1
AR Target gene
ARE/FOXA1
AR
FOXA1
SOX2
ARE/FOXA1
Testosterone Deprivation
Androgen Receptor Inhibition
Castration Resistant Prostate Cancer
AR
FOXA1
SOX2
ARE/FOXA1
AR
FOXA1
SOX2
Proliferation
AR Target gene
ARE/FOXA1
Neuronal development
Axon guidance
FOXA1
SOX2
NEPC Genes
SOX2/FOXA1