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Dual-Lineage dTAG-AR Degradation Models to Characterize Acute AR-Bypass Kinetics and Resistance Mechanisms in Castration-Resistant Prostate Cancer

Saurabh Verma, PhD^{1,a}

¹ Fred Hutch Cancer Center, P.O. Box 19024, Seattle, WA, United States

Corresponding author

^a Saurabh Verma, PhD, Fred Hutch Cancer Center, P.O. Box 19024, Seattle, WA, United States

Email: sverma@fredhutch.org

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Abstract

Background

Androgen receptor (AR) signaling drives castration-resistant prostate cancer (CRPC), but resistance inevitably emerges via AR splice variants, mutations, or amplification. Characterizing the immediate, compensatory bypass pathways activated upon AR inhibition is essential to developing next-generation pathway-directed strategies and designing effective combination regimens. To isolate these rapid survival networks without the confounding genomic adaptations of chronic selective pressure, we established chemically inducible dTAG (degron TAG)-based AR degradation platforms in two distinct models of aggressive CRPC: 22Rv1 and C4-2B.

Methods

We stably expressed an HA-tagged AR-dTAG fusion construct to enable rapid, chemically induced, and reversible AR degradation. A dual-guide, single-vector CRISPR/Cas9 approach was used to generate AR-knockout (ARKO) clones in 22Rv1 and C4-2B lines, confirmed by targeted amplicon sequencing. Temporal and dose-dependent AR loss was validated via immunoblotting, immunofluorescence, and

canonical downstream target gene expression. To capture acute versus long-term compensatory transcriptomic remodeling, we performed RNA-seq profiling at 3, 6, and 15 days post-dTAG treatment.

Results

Ligand-induced dTAG treatment mediated rapid, near-complete AR degradation in both cell lines, outperforming clinical AR degraders. AR loss induced G1 cell-cycle arrest and significantly reduced cell viability and proliferation. RNA-seq revealed highly dynamic transcriptional rewiring. Comparing these lineages differentiated acute, transient transcriptional stress responses from sustained bypass pathways driving long-term survival in 22Rv1 and C4-2B genetic backgrounds.

Conclusion

We established and validated a tunable, dual-lineage dTAG-AR-KO platform that models distinct clinical archetypes of CRPC. By capturing both the acute cellular response and subsequent chronic adaptations to AR depletion, this platform recapitulates clinical resistance trajectories while circumventing the confounding mutations of long-term selective pressure. Ultimately, this work provides a robust preclinical

framework to screen next-generation degraders, guide patient-specific combination therapies. map co-occurring escape pathways, and can

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