

A genome-scale CRISPR screen nominates LSD1 inhibition as a strategy to increase STEAP1 expression and enhance STEAP1-directed therapy in prostate cancer

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⁵In memoriam

Background

Prostate cancer treatment centers on androgen receptor (AR) signaling, but resistance is common and outcomes in advanced disease remain poor, motivating therapeutic targets beyond AR. Six-Transmembrane Epithelial Antigen of the Prostate 1 (STEAP1) is a cell surface protein that is overexpressed across all stages in prostate cancer. STEAP1-directed agents, including bispecific T-cell engagers (TCE), chimeric antigen receptor (CAR) T cells, and antibody-drug conjugates, have shown preclinical and clinical activity. Xaluritamig (a STEAP1-directed T-cell engager) has shown encouraging responses in early studies in late-stage disease and further studies are evaluating STEAP1-directed therapy in earlier disease settings. One strategy to enhance the efficacy of STEAP1-targeted therapies is to increase STEAP1 surface expression by targeting pathways that upregulate its expression.

Methods

To identify regulators of STEAP1 expression in an unbiased approach, we performed a FACS-based genome-scale CRISPR interference (CRISPRi) screen in AR-positive C4-2B prostate cancer cells, using an anti-STEAP1 antibody to sort cells by top/bottom 20% of STEAP1 expression for sequencing. Hits were cross-referenced with the West Coast Prostate Cancer Dream Team (WCDDT) dataset for clinical relevance and prioritized for regulators that were pharmacologically targetable. We validated selected candidates with small molecule inhibitors and nominated the LSD1 (KDM1A) inhibitors bomedemstat (BMD) and iadademstat (IAD) for further testing. To determine whether LSD1 inhibition enhanced response to STEAP1-targeted therapies, we pretreated prostate cancer models with an LSD1 inhibitor and co-cultured with a STEAP1-directed TCE (xaluritamig biosimilar) or STEAP1 CAR-T cells in C42B and PC3 cells in vitro and 3 ex vivo patient-derived xenograft organoid (PDXO) models LuCaP 96CR, LTL313HR, and a UCSF intraductal-carcinoma PDX.

Results

In WCDDT cohorts, STEAP1 expression was correlated with AR-positive subtypes of mCRPC and AR-signaling pathways. The CRISPRi screen nominated multiple candidate regulators of STEAP1, including chromatin modifying genes and transcriptional factors: KDM1A, GNB2L1, SWI/SNF members, MYC, ZIC4, and HOXB13, whose perturbation altered surface STEAP1 expression. Among these, LSD1 (KDM1A) was most clinically actionable. LSD1 knockdown increased STEAP1, and pharmacologic inhibition with bomedemstat or iadademstat increased STEAP1 mRNA as well as surface/total protein in prostate cancer models. Pretreating tumor cells with an LSD1 inhibitor enhanced STEAP1-directed killing by both TCE and STEAP1 CAR-T cells in PC3 (baseline STEAP1-low) co-culture and in the LuCaP 96CR, LTL313HR, and intraductal-carcinoma patient derived PDXO models. Pretreating T-cells with LSD1 inhibitor alone also enhanced TCE and CAR-T effect.

Conclusions

Using a genome-scale CRISPR screen, we nominated candidate regulators of STEAP1 in prostate cancer and identified LSD1 (KDM1A) inhibition as a feasible approach to enhance STEAP1-directed therapies. Across in vitro and ex vivo PDXO models, LSD1 inhibition increased STEAP1 cell surface expression and enhanced killing by STEAP1-directed T-cell engager and CAR-T therapy. The cellular mechanism underlying this interaction is under investigation.

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