

Targeting a stress-adaptive, stem-like tumor state in metastatic castration-resistant prostate cancer with uPAR-directed cell therapy

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Background. Metastatic castration-resistant prostate cancer (mCRPC) remains incurable, and the incidence of double-negative prostate cancer (DNPC) and stem-like CRPC (CRPC-SCL) is rising. These tumors, characterized by loss or reduction of androgen receptor signaling without neuroendocrine lineage commitment, are enriched for TP53 and MAPK/PI3K pathway alterations and display stress-adaptive, stem-like phenotypes associated with therapeutic resistance and metastatic progression. Despite extensive molecular characterization, no FDA-approved targeted therapies exist for these subtypes. Because such tumors are defined by an adaptive cell state rather than a stable lineage, we asked whether a state-associated surface antigen could provide a therapeutic target where lineage-directed approaches have not.

Methods. We integrated genomic, cell-surface proteomic, and spatial analyses across multiple tumor types to identify surface antigens marking conserved adaptive states, and examined their distribution in CRPC cohorts. Functional dependence on uPAR was tested by genetic ablation in vivo. uPAR-directed chimeric antigen receptor (CAR) T cells were generated and evaluated in DNPC xenografts and additional solid tumor models, with on-target toxicity assessed in humanized and syngeneic systems. Antigen induction was measured following therapeutic stress.

Results. We identified a conserved uPAR-expressing, progenitor-like tumor cell state enriched in TP53-deficient and MAPK/PI3K-driven cancers, including a subset of CRPC tumors with DNPC and CRPC-SCL features. uPAR, a GPI-anchored surface protein involved in tissue remodeling, marked a stress-induced niche associated with fibrosis and immune suppression, spanning malignant, fibroblast, and myeloid compartments. Genetic ablation of uPAR impaired metastatic progression in vivo, indicating that this state depends functionally on uPAR rather than merely expressing it. uPAR-directed CAR T cells produced potent antitumor activity across solid tumor models, including DNPC xenografts, with durable regressions and minimal hematopoietic toxicity in humanized and syngeneic models. Therapeutic stress further increased uPAR expression, indicating that treatment can enhance the targetable state.

Conclusions. uPAR marks a stress-adaptive, progenitor-like state that is functionally required for metastatic progression and is shared across malignant and stromal compartments in a subset of mCRPC. Targeting this state rather than a lineage antigen addresses antigen heterogeneity, tumor plasticity, and microenvironmental resistance simultaneously. Ongoing work is evaluating uPAR-directed cell therapy in organoid and patient-derived xenograft models, defining safety parameters in metastatic and adjuvant settings, and testing induction-based combination schedules, toward a biomarker-guided framework for clinical development in double-negative prostate cancer.

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Conflicts of Interest Disclosure. S.W.L. and M.S. are named inventors on patent applications related to uPAR-directed cell therapy and have financial interests in companies developing these approaches. Z.Z. is a named inventor on patent applications related to uPAR-directed cell therapy. The remaining authors declare no competing interests.