HIF1A inhibition as a therapeutic strategy to overcome castration-resistance in PTEN-deficient prostate cancer

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2nd most common cancer affecting men worldwide
- In 2020: >1.4M new cases;
- >560,000 deaths

- Androgen deprivation therapy (ADT) leads to initial tumor regression, but many tumors progress to an androgen-independent state called castration-resistant prostate cancer (CRPC).
- Despite the identification of various tumor cell-intrinsic and extrinsic mechanisms driving castration-resistance, the therapeutic landscape for metastatic CRPC remains insufficient.
- Identification of novel therapeutic targets for the management of CRPC is in demand.

Androgen-deprivation further enhances HIF1α signaling and promotes plasticity of luminal-C cells

Results

1. Experimental strategy

Identification of potential mediators enabling survival under androgen-deprivation conditions by single-cell RNA sequencing

2. Results

Luminal HIF1α inactivation provides durable therapeutic responses to castration

Pharmacological HIF1α inhibition sensitizes PTEN-deficient tumors to androgen deprivation

Conclusions

- Pten<sup>1cre</sup> mice develop CRPC and are a valuable tool to study resistance mechanisms to ADT.
- HIF1A signaling is further activated in Luminal-C cells of castrated Pten<sup>1cre</sup> mice and promotes androgen deprivation-induced cellular plasticity.
- Genetic and pharmacological HIF1A inhibition sensitizes prostatic tumors to androgen deprivation.

⇒ HIF1α and ADT combined treatment as a promising strategy to treat CRPC patients