**Rb1 loss, lineage plasticity, and antiandrogen resistance in prostate cancer**

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**Background:** Prostate adenocarcinoma relapsing from improving antiandrogen therapies can exhibit variant histology with altered lineage marker expression. These variants share clonal origin with the original adenocarcinoma, indicating they arise by lineage transformation. The mechanisms underlying this transformation and resulting therapeutic resistance are incompletely understood. Loss of the Rb1 tumor suppressor gene is rare in prostate adenocarcinoma, but common in variants relapsing from antiandrogen therapy. This observation inspires the hypothesis that Rb1 loss is a genetic driver of prostate cancer lineage plasticity and antiandrogen resistance.

**Methods:** Genetically engineered prostate cancer mouse models, organoid cultures, and cell lines are used to test the hypothesis, identify relevant molecular mechanisms, and suggest therapeutic approaches for treating these aggressive prostate cancer variants.

**Results:** Engineered Rb1 loss in vivo causes transformation of prostate adenocarcinoma to a variant form with cells expressing either neuroendocrine or luminal epithelial lineage markers. Highlighting inherent lineage plasticity, organoids developed from these tumors are heterogeneous, exhibiting either luminal, basal, or neuroendocrine phenotypes depending on culture conditions. Gene expression profiling indicates the mouse tumors resemble human neuroendocrine prostate cancer variants, both expressing elevated levels of epigenetic reprogramming factors like Ezh2 and Sox2. The mouse prostate cancers are sensitive to antiandrogen therapy, but relapse with spontaneously acquired Trp53 mutations and loss of Ar expression. Engineered Ezh2 deficiency alters disease course in vivo while Ezh2 inhibitors or Ezh2 silencing restores androgen receptor expression and sensitivity to antiandrogen therapy in vitro.

**Conclusions:** These findings identify Rb1 and Trp53 mutation as genetic drivers of prostate adenocarcinoma lineage plasticity and acquired resistance to antiandrogen therapy. Antiandrogen resistance in this case is a reversible, epigenetic process. This conclusion suggests the use of epigenetic modulating therapy to extend beneficial clinical responses to antiandrogen therapy.

**Conflict of Interest:** C.L.S. is a co-inventor of enzalutamide and may be entitled to royalties. Enzalutamide is commercially available from Selleck Chemicals. C.L.S. serves on the Board of Directors of Novartis and is a paid consultant to ORIC Pharmaceuticals.

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