Rb1 Suppresses Prostate Cancer Metastasis and Lineage Plasticity Underlying Castration Resistance

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Background: Lethal neuroendocrine prostate cancer variants increasingly arise in patients relapsing from improved androgen deprivation therapies like enzalutamide. Underlying mechanisms are incompletely understood and experimental models are limited, hindering development of effective countermeasures.

Methods: We used genetically engineered mouse models with specific prostate deletion of *Pten* and/or *Rb1*. Aging, castration and gene expression studies were performed to investigate the contribution of Rb1 deletion in combination with Pten deletion. We further conducted combination preclinical therapy studies based on our findings.

Results: We find Rb1 and Pten loss in the mouse causes metastatic prostate adenocarcinoma with lineage plasticity and neuroendocrine transformation comparable to neuroendocrine variants arising in human patients. Additional Trp53 mutation drives resistance to androgen deprivation therapy. Neuroendocrine transformation is accompanied by increased expression of epigenetic reprogramming factors like Sox2 and Ezh2. Clinically relevant Ezh2 inhibitors reverse lineage transformation and restore sensitivity to enzalutamide.

Conclusions: These findings uncover genetic mutations driving prostate cancer lineage plasticity and suggest an epigenetic approach for extending the beneficial clinical responses of androgen deprivation therapy.

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Conflict of Interest
N/A