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PROSTATE CANCER

Hand in hand — *Rb1* and *Trp53* cooperate to suppress resistance

> "...therapeutic epigenetic modulation could reverse or delay lineage plasticity..."

New data presented in *Science* indicate that *Rb1* and *Trp53* cooperate to suppress lineage plasticity, metastasis, and resistance to antiandrogens in prostate cancer. These findings, and the development of mouse models of *Rb1* and *Rb1* and *Trp53* (also known as *Tp53*) loss, will be useful for testing the hypothesis that lineage plasticity drives prostate cancer progression to castration resistance. Furthermore, these results show that epigenetic modulation using Ezh2 inhibitors can reverse resistance to antiandrogen therapy and resensitize resistant disease to antiandrogen treatment, potentially offering a new treatment strategy.

The authors of this study developed double-knockout and triple-knockout mice (with *Rb1* deletion and *Rb1* plus *Trp53* deletion, respectively) using a *Pten*-null mouse model of prostate cancer. Describing their findings, corresponding author David Goodrich told *Nature Reviews Urology:* "Using these genetically engineered mice and also human prostate cancer cell lines, we found that eliminating *RB1* in prostate adenocarcinoma drives transformation to a variant expressing neuroendocrine lineage markers, but this variant remains sensitive to antiandrogen therapy." Leigh Ellis, another corresponding author, continued, "Loss of *Rb1* drives increased epigenetic deregulation, metastatic progression, and lineage plasticity." Goodrich explained: "However, additional loss of *TRP53* converts the disease into a fully antiandrogen-resistant, neuroendocrine variant. Loss of these genes also causes upregulation of stem cell reprogramming factors."

The investigators believe that expression of these reprogramming factors creates a stem-cell-like epigenetic state that underlies lineage plasticity, and that the transformation from antiandrogen-sensitive disease to an antiandrogen-resistant state is potentially reversible, owing to the epigenetic nature of these changes.

To test this hypothesis they treated cells isolated from their mouse models of prostate cancer and also engineered LNCaP cells lacking *RB1* or *RB1* and *TRP53* with Ezh2 inhibitors (Ezh2 methylates lysine 27 of histone H3) and antiandrogens). Goodrich explained: "Treatment with Ezh2 inhibitors drove neuroendocrine-variant cells back to an *AR*-expressing, antiandrogen-sensitive phenotype." Ellis expanded, "Ezh2 seems to mediate epigenetic catastrophe, lineage plasticity, and antiandrogen resistance that is caused by *Rb1* and *Trp53* loss." "This observation suggests a novel therapeutic approach — using epigenetic drugs to delay or reverse neuroendocrine transformation and extend the duration of clinical responses to antiandrogen therapies like enzalutamide," Goodrich added.

These data indicate that loss of both *Rb1* and *Trp53* causes epigenetic changes that result in a stem-cell-like epigenetic environment that enables lineage plasticity, which is hypothesized to drive prostate cancer progression. The mouse models developed in this study could be used to test this hypothesis and study the molecular mechanisms behind lineage plasticity. The results also suggest that therapeutic epigenetic modulation could reverse or delay development of resistance to antiandrogen treatment, and extend the duration of clinical benefit of these drugs.

Future studies will include characterizing the epigenetic landscape of the mouse models to determine the effects of *Rb1* and *Trp53* loss; optimizing Ezh2 inhibitor plus antiandrogen combination therapy in preclinical models and translating this treatment combination to the clinic; clinically validating whether Ezh2 inhibition reverses or stabilizes lineage plasticity and resensitizes prostate cancer to antiandrogen therapy; and treating patients with Ezh2 inhibitors to see if progression to castration resistance is delayed.

The authors also want to investigate whether their findings can be generalized to other models of prostate cancer and whether resistance to targeted therapies in other diseases could involve similar genetic or epigenetic mechanisms.

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