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PROSTATE CANCER

Loss of PTEN promotes progression of prostate cancer in an androgen-independent manner

The development of castration-resistant prostate cancer (CRPC) involves the loss of androgen receptor (AR) activity, which is compensated for by alternative signaling pathways that lead to androgen-independent cell proliferation. Altered PI3K–AKT–mTOR signaling is one potential alternative pathway. PTEN is a negative regulator of this axis, and its expression is frequently lost during progression of prostatic malignancy. David Mulholland and colleagues have used a conditional *Pten*$^{-/-}$ mouse model and human specimens to characterize these interactions.

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PTEN$^{-/-}$ mice developed prostate cancer even when they underwent orchidectomy at an early age, suggesting that PTEN loss sensitizes the AR to reduced androgen levels. Furthermore, the PTEN$^{-/-}$ tumors were less dependent on AR signaling, despite the fact that *Pten*$^{-/-}$ prostate cancer epithelial cells could proliferate under castrate conditions.

Rather than sensitizing AR to the greatly reduced androgen levels or negating the need for androgens altogether, PTEN loss suppressed the transcription factor activity of AR. This effect was shown to be mediated by enhanced expression of EGR1, c-JUN and EZH2, which led to downregulation of AR-associated genes. Thus, PTEN loss regulated AR activity via several other coregulators, resulting in a greatly diminished or abolished dependency on androgen signaling for proliferation. Indeed, progression of *Pten*$^{-/-}$ prostate cancer to a castration-resistant state was shown to be independent of the presence of epithelial AR. This suggests that PTEN loss provides an 'escape' mechanism whereby castration-resistant growth can occur in the absence of the AR signaling axis.

The findings of this study indicate a role for PTEN in crosstalk between the AR and PI3K–AKT–mTOR signaling pathways in CRPC development. Therapeutic targeting of these pathways might, therefore, lead to better outcomes in men with prostatic malignancy initiated by PTEN loss.

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Original article Mulholland, D. J. *et al.* Cell autonomous role of PTEN in regulating castration-resistant prostate cancer growth. *Cancer Cell* **19**, 792–804 (2011)