**Activation of Notch1 synergizes with multiple pathways in promoting castration-resistant prostate cancer**

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**Background:** Metastatic castration-resistant prostate cancer (CRPC) is the primary cause of prostate cancer specific mortality. Thus, identifying new mechanisms that drive lethal CRPC is critical. These mechanisms can give us insights into novel therapeutic targets and strategies for CRPC. Here, we set to determine the role of Notch1 receptor in prostate tumorigenesis.

**Methods:** To evaluate the role of Notch receptors in prostate tumorigenesis, we used human tissue microarrays (TMAs) and tissue regeneration model using naïve mouse prostate epithelial cells.

**Results:** Our study demonstrates that localized high-risk prostate cancer and metastatic CRPC but not benign prostate tissues or low/intermediate-risk prostate cancer express high levels of Notch1 receptor intracellular domain (NICD1). Chronic activation of Notch1 synergizes with multiple oncogenic pathways altered in early disease to promote the development of prostate adenocarcinoma. These tumors display features of epithelial to mesenchymal transition, a cellular state associated with increased tumor aggressiveness. Consistent with its activation in clinical CRPC, tumors driven by NICD1 in combination with multiple pathways altered in prostate cancer are metastatic and resistant to androgen deprivation.

**Conclusion:** Our study provides functional evidence that the Notch1 signaling axis synergizes with alternative pathways in promoting metastatic CRPC, and may represent a new therapeutic target for advanced prostate cancer.

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