

Understanding Lineage Plasticity Risk in Lethal Prostate Cancer

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OVERVIEW

A tool for predicting androgen receptor independent castrate prostate cancer (CRPC)

- Identification of therapeutic targets in the treatment of androgen receptor independent CRPC
- A promising biomarker of lineage plasticity risk and tumor aggressiveness

BACKGROUND

Prostate cancer remains the second most prevalent and the second most deadly cancer in men. The initiation and progression of prostate cancer relies on signaling through the androgen receptor (AR). The treatment of prostate cancer may therefore include androgen deprivation therapy (ADT) which inhibits androgen signaling in tumor cells. One complexity of prostate cancer treatment results from acquired resistance to ADT over time. The ability of prostate cancer cells to grow during ADT signifies the development of castration-resistant prostate cancer (CRPC), with survival in this patient subgroup falling to less than three years. The loss of AR signaling may cause CRPC, providing a focus for research that would elucidate this mechanism for resistance. Studies suggest that up to 15% of CRPC results from a change in behavior of the tumor cells to a different subtype, signifying a circumstance known as lineage plasticity. A need exists to delineate the mechanism that drives prostate cancer cells to become AR-independent.

INNOVATION

Researchers have identified a gene signature enriched in prostate cancer cells that was associated with a risk for lineage plasticity. The investigators determined that high expression of this genetic signature was strongly associated with poor survival from the time of AR signaling inhibitor treatment. Using Master Regulator Inference analysis and pathway analysis of recovered samples, they also determined that specific transcription factors and pathways linked to stemness were more activated in baseline tumors from patients whose tumors underwent lineage plasticity. Furthermore, this signature was enriched in a patient-derived xenograft that undergoes castration-induced lineage plasticity versus other patient-derived xenografts that do not, strongly suggesting this signature is linked to poor patient outcome and risk of lineage plasticity after AR signaling inhibitor therapy. Through the evaluation of tumor cell resistance to an AR signaling inhibitor enzalutamide (ENZA), the researchers were able to confirm heterogeneity of ENZA resistant tumors. The discovery therefore implicates specific tumor-related genetic factors that predispose prostate cancer to undergo ENZA-induced lineage plasticity.

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Diagnostics
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