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PROSTATE CANCER

Transdifferentiation results in resistance

New data have shown that transdifferentiation is a mechanism of treatment resistance in castration-resistant prostate cancer (CRPC). These observations could be helpful in stratifying patients who are likely to fail antiandrogen therapy.

Zou and colleagues generated a mouse model of *Pten* and *Tp53* loss of function based on an inducible *Nkx3.1*^{CreERT2} driver. Phenotypic analysis of this model and mice with *Pten*-only deletion showed features similar to human CRPC, specifically features associated with a luminal phenotype of adenocarcinoma. Cross-species computational investigations revealed conservation of the molecular drivers of CRPC. Gene-set enrichment analysis showed that the molecular drivers of cancer in double-knockout mice are conserved within metastatic CRPC. Furthermore, a high degree of master regulator conservation was observed between this model and human prostate cancer with low *PTEN* and *TP53* expression.

Treatment with abiraterone resulted in different responses to treatment in double-knockout mice than were seen in mice with *Pten*-only deletion; specifically, CRPC was not inhibited in double-knockout mice, whereas it was in single-knockout mice. Moreover, in some instances, abiraterone treatment accelerated tumour growth in double-knockout mice and metastasis only occurred in these mice. Gene-set enrichment analysis of tumours from these mice and human CRPC showed strong positive correlation. Thus, these mice were termed "exceptional nonresponders". The master regulator signature of these mice was significantly positively correlated with human CRPC and also neuroendocrine prostate cancer. Furthermore, patients with increased activity of this master regulator signature have poor cancer-specific outcomes.

> "abiraterone treatment accelerated tumour growth in double-knockout mice"

Molecular analysis showed that exceptional nonresponders have significant upregulation of genes that have increased expression in neuroendocrine prostate cancer. Specifically, *Sox11* was particularly upregulated in cell lines developed from double-knockout mice and correlated with expression of the neuroendocrine marker neuron-specific enolase. Silencing of *Sox11 in vitro* resulted in reduced expression of neuroendocrine markers.

Tumours from abiraterone-treated, double-knockout mice that were not exceptional nonresponders showed significantly increased expression of synaptophysin, but no coexpression of proliferation markers. Synaptophysin-positive cells were observed in small patches within regions of adenocarcinoma, similar to focal differentiation. However, synaptophysin-positive cells comprised the majority of tumour cells in samples from exceptional nonresponders; these cells lacked androgen receptor expression and were highly proliferative. Lineage tracing showed that these cells were derived from luminal cells.

These data suggest that dual loss of function of *PTEN* and *TP53* could be a mechanism of resistance to abiraterone treatment. Moreover, this combined loss could actually increase tumour aggressiveness and result in neuroendocrine differentiation. These results could aid in selecting appropriate treatments for men with prostate cancer, specifically identifying those likely to fail antiandrogen therapy.

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