Treatment strategy for certain advanced prostate cancers shows promise in preclinical models

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Epigenetic changes can cause prostate cancer to resist treatment by switching genes on or off. One epigenetic mechanism tags genes with DNA methylation marks. This process is mediated by molecules called DNA methyltransferases. These tags can alter gene expression in ways

that promote tumors to grow and transition into advanced forms of the disease.

Researchers from Dana-Farber Cancer Institute discovered, in experiments using patient-derived preclinical models of advanced prostate cancer, that inhibition of DNA methylation with decitabine, a medicine used in the treatment of certain blood cancers, slows tumor growth specifically in a subset of advanced prostate cancers that have neuroendocrine features or loss of the gene RB1. The work has been published in *Science Translational Medicine*.

It also results in decreased methylation and elevated expression of a gene that produces a receptor called B7-H3. This receptor is the target of an antibody-drug conjugate currently in evaluation in clinical trials called DS-7300a.

In prostate cancers with high levels of B7-H3, DS-7300a was effective on its own. However, DS-7300a alone was less effective when B7-H3 levels are low. The researchers observed that when the drugs are combined, decitabine sensitizes tumors to DS-7300a and improves efficacy.

Patients with advanced prostate cancer with tumors harboring RB1 gene loss or neuroendocrine features often have a poor prognosis and limited treatment options. This research opens the door to a potential treatment strategy geared specifically toward this population that involves decitabine, B7-H3 targeted therapy, or the two in combination.

More information: Yasutaka Yamada et al, DNA methylation as a therapeutic target in RB1-deficient and neuroendocrine prostate cancer, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.adf6732.
www.science.org/doi/10.1126/scitranslmed.adf6732

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