Study offers way to increase immune checkpoint inhibitor effectiveness in patients with MTAP-deleted cancers

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Loss of the "housekeeping" gene methylthioadenosine phosphorylase, or MTAP, is a common event in cancer. Patients with melanoma or bladder cancer whose tumor cells lack a functioning version of the gene tend not to respond to immune checkpoint inhibitors, although the reasons haven't been clear.

In a study published in the journal Cancer Cell, researchers at Dana-Farber and the University of Texas MD Anderson Cancer Center found that the deletion of MTAP creates a buildup of the protein MTA within tumor cells. The cells secrete most of the MTA into the extracellular space, where it impedes the growth and activity of cancer-fighting T cells of the immune system.

The researchers hypothesized that MTA-degrading enzymes could reduce MTA levels in the tumor microenvironment, restoring T cell function and improving the effectiveness of immune checkpoint inhibitors. Tests of this approach in tumor models showed this to be the case: the number of active T cells rose, and tumor growth slumped.

The deletion of MTAP is primarily responsible for the decline in T cell function and lack of response to immune checkpoint inhibitors in patients whose tumor cells lack working copies of this gene. Drugs that deplete MTA have the potential to enhance the effectiveness of checkpoint inhibitors in these patients.

More information: Donjeta Gjuka et al, Enzyme-mediated depletion of methylthioadenosine restores T cell function in MTAP-deficient
tumors and reverses immunotherapy resistance, Cancer Cell (2023).
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