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Histone deacetylase inhibitors enhance immunotherapy in lung cancer models, researchers say

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Several new immunotherapeutic antibodies that inhibit checkpoint receptors on T cells to restimulate the immune system to target tumors have been approved to treat advanced stage lung cancer and melanoma; however, only 20 percent of lung cancer patients show a response to these agents. Moffitt Cancer Center researchers have identified a class of drugs that improve the activity of immunotherapeutic antibodies by stimulating the movement of T cells into a tumor and enhancing their activity.

Tumors avoid detection by the immune system by increasing levels of immune-suppressive molecules, such as PD-L1. Antibodies that inhibit PD-1 and PD-L1 interaction can reactivate the immune system to target cancer cells.

Clinical studies have shown that not all patients respond to PD-1-targeted antibodies. Low levels of a type of immune cell called a T cell within a tumor are associated with a poor response to agents that target PD-1. Moffitt researchers hypothesized that small molecule drugs that could stimulate the movement of T cells into tumors could enhance the activity of PD-1-targeting drugs.

The researchers analyzed a panel of 97 FDA-approved agents for their ability to increase expression of chemical messengers called chemokines that stimulate T cell tumor infiltration and activity. They discovered that

only one class of drugs called histone deacetylase (HDAC) inhibitors was capable of inducing T cell chemokine expression in vitro.

The team further demonstrated that the HDAC inhibitor romidepsin significantly decreases lung tumor growth in mice. They showed that romidepsin's anti-tumor effects are due to its ability to induce chemokines and T cell infiltration into tumors.

These observations suggest that HDAC inhibitors, including romidepsin, could work in conjunction with other immune-stimulating agents to enhance an immune response against tumors. The researchers confirmed this by showing that romidepsin combined with an antibody that targets PD-1 results in greater anti-tumor activity than either agent alone and increases the levels of T cells within the tumor and their activity.

Several HDAC inhibitors, including romidepsin, have been approved to treat hematologic malignancies; however, their single-agent activity in solid tumors, such as lung cancer, has not been as great.

"These results suggest that combination of HDAC inhibitors with PD-1 blockade represents a promising strategy for lung cancer treatment," said Amer Beg, Ph.D., senior member of the Immunology Program at Moffitt.

A clinical trial to test combination therapy of an HDAC inhibitor and a PD-1 inhibitor in stage IV non-small cell lung cancer has been initiated at Moffitt and is currently recruiting participants.

More information: H. Zheng et al. HDAC inhibitors enhance T cell chemokine expression and augment response to PD-1 immunotherapy in lung adenocarcinoma, *Clinical Cancer Research* (2016). DOI: 10.1158/1078-0432.CCR-15-2584

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