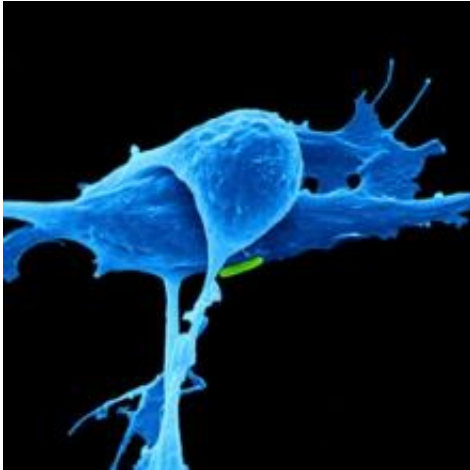


Tumor-suppressor p53 regulates protein that stifles immune attack on cancer

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A crucial tumor-thwarting gene protects an immune attack against lung cancer by blocking the key to an off switch on T cells, the customized warriors of the immune system, a team led by researchers at The University of Texas MD Anderson Cancer Center reports in the *Journal of the National Cancer Institute*.

"Identifying this role for tumor-suppressing [p53](#) provides both a potential biomarker for response to important new [cancer](#) immunotherapy drugs and a possible new therapeutic pathway for treatment," said James Welsh, M.D., associate professor of Radiation Oncology at MD Anderson and senior author.

This preclinical research shows an experimental drug currently in phase I clinical trials can replace the immunity-protecting role lost when p53 fails.

The [p53 gene](#) is damaged, missing or under-expressed in 42 percent of common cancers and 70 percent of lung cancers. It's by far the most common mutation in cancer. Lung cancer is the leading cause of cancer death in the United States,

with an estimated 221,200 new diagnoses and 158,040 deaths in 2015, according to the National Cancer Institute.

Scientists have long known that p53 plays a central role in cancer control by regulating a process that forces abnormal cells to repair themselves and, failing that, to kill themselves.

Welsh and colleagues found that p53 also blocks a protein called PDL1 that tumor cells can wield to halt immune attack. Like a key, PDL1 connects with and activates a checkpoint molecule called PD1 found on the surface of T cells that shuts down those killer white blood cells. Two PD1-inhibiting drugs, pembrolizumab (Keytruda) and nivolumab (Opdivo) were approved this year for treatment of metastatic [lung cancer](#). Both drugs help a significant fraction of patients, but not all.

p53 launches miR-34a to thwart PDL1

First author Maria Angelica Cortez, Ph.D., instructor of Experimental Radiation Oncology, identified the mechanism by which p53 blocks expression of PDL1.

"The interaction is specific: p53 activates the micro RNA miR-34a, which in turn directly blocks expression of PDL1," said Cortez. "If you lose [p53 function](#), then miR-34a is lost and PDL1 is over-expressed."

Unlike messenger RNAs produced by genes that lead to production of specific proteins, micro RNAs do not code for proteins but instead regulate other genes.

While p53 had been linked to other aspects of immune response, the JNCI paper is the first to connect it to immune evasion by tumors and regulation of PDL1.

The team conducted a series of experiments in cell

lines, miRNA target-predicting databases and tumor samples from non-small cell lung cancer patients. Then in a mouse model of NSCLC they showed that MRX34, alone or with radiation therapy, reduced PDL1 expression, preventing T cell exhaustion.

MRX34, a first-in-class miR-34-based cancer therapy being developed by Mirna Therapeutics in Austin, Texas, packages a synthetic version of natural miR-34a in a fatty nanoparticle called a liposome. The drug is in phase I clinical trials for advanced solid tumors, liver cancer and hematological malignancies at MD Anderson and other cancer clinics.

The researchers analyzed tumor samples from The Cancer Genome Atlas of 181 patients with NSCLC. Expression of p53 and PDL1 were inversely correlated, when one was high, the other was low and vice-versa. Tumors with p53 mutated had higher levels of PDL1 and lower levels of miR-34a.

High levels of p53, miR-34a increase survival

Patients with either low PDL1 and high p53 expression or with high p53 and miR-34a levels had longer median survival than those with low expression of p53 and miR-34a and higher PDL1.

Forced expression of miR-34a in NSCLC cell lines suppressed PDL1. Injecting MRX34 into lung cancer tumors in mice increased levels of miR-34a and reduced levels of PDL1. The team also showed that miR-34a binds to a specific site on the PDL1 gene to block its expression.

The researchers randomized mice to control, MRX34, radiation therapy or a combination of MRX34 and radiation. The treatment arms all led to increased numbers of T cells infiltrating the tumor, reduced numbers of T cells positive for the PD1 checkpoint, and slowed tumor growth, with the combination having the strongest effects.

Next steps

Studies under way include a retrospective analysis of the clinical outcome of patients treated with PD1 inhibitors to see whether p53 or miR-34a status at

While patients with PDL1 in their tumors have a higher response rate to PD1 checkpoint inhibitors, a fraction of patients without the biomarker also respond to these drugs. So additional biomarkers are sought to further guide treatment, Cortez said.

In the lab, the team is combining MRX34 with a PD1 inhibitor to see if the combination improves tumor response, Welsh said.

Provided by University of Texas M. D. Anderson Cancer Center

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