Medical Xpress

Metabolic 'reprogramming' by the p53 gene family leads to tumor regression

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Scientists have found that altering members of the p53 gene family, known as tumor suppressor genes, causes rapid regression of tumors that are deficient in or totally missing p53. Study results suggest existing diabetes drugs, which impact the same gene-protein pathway, might be effective for cancer treatment.

The University of Texas MD Anderson Cancer Center investigation showed that, in vivo, the genes p63 and p73 can be manipulated to upregulate or increase levels of IAPP, a protein important for the body's ability to metabolize glucose. IAPP is found in some diabetes drugs already on the market.

The research findings were published in today's issue of *Nature*.

The study, led by Elsa R. Flores, Ph.D., associate professor of molecular and cellular oncology, centered on p63 and p73 because of the genes' ability to cause tumor regression or spur its growth due to their unique genetic makeup.

"P53 is altered in most human cancers and p53 reactivation suppresses tumors in vivo in mice. This strategy has proven difficult to implement therapeutically. We examined an alternative approach by manipulating the p53 family members, p63 and p73," said Flores.

Flores described two "warring" versions of p63 and p73 that are at odds when it comes to tumor suppression. One version, known as

transactivation domain-bearing, is structurally and functionally similar to p53 in their ability to suppress tumors. The other version, which lacks this transactivation domain, actually prevents p53 from stopping tumor growth. Transactivation domains are specific regions within a protein known as a transcription factor that effect further downstream cellular responses.

"The p53 family interacts extensively in cellular processes that promote tumor suppression," said Flores. "Thus, a clear understanding of this interplay in cancer is needed to treat tumors with p53 alterations."

Flores' team found that by deleting the p63 and p73 versions that lacked transactivation domains, they were able to metabolically reprogram cells so that the cancer progression was stopped and reversed in p53-deficient tumors. This was accomplished through increasing levels of IAPP, a gene important to the body's use of insulin. IAPP encodes amylin, chains of amino acids that are co-secreted with insulin. Flores sees IAPP as significant in trying new therapeutic approaches for treating p53-deficient tumors.

"We found that IAPP is involved in tumor regression and that amylin, the protein encoded by the IAPP gene, stops a cell's ability to metabolize glucose, leading to programmed cell death," said Flores. "Pramlintide, a synthetic type of amylin that is currently used to treat type 1 and type 2 diabetes, caused rapid tumor regression in p53-deficient lymphomas of the thymus."

Flores tested Pramlintide on a variety of human cancer cell lines with p53 deletions and mutations and found the drug to be highly effective in inhibiting glucose metabolization and causing programmed cell death.

"This represents a novel strategy to target p53-deficient and mutant cancers," said Flores. She and her team also identified critical receptors

on tumor cells with p53 deletions and mutations needed for Pramlintide to induce tumor regression. The receptors represent a potential prognostic marker for determining if Pramlintide will be effective in treating cancer patients with p53 deletions or mutations.

More information: IAPP-driven metabolic reprogramming induces regression of p53-deficient tumours in vivo , DOI: 10.1038/nature13910

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