MedicalXpress

New discoveries about tumor-suppressing protein could help to reduce treatment side effects

May 12 2011

Researchers at the Stanford University School of Medicine have untangled two distinct ways in which a common, naturally occurring "tumor-suppressor" protein works. The separation of these two functions — which can have quite different consequences — could enhance efforts to develop treatment approaches that mitigate the sometimes-devastating side effects of radiotherapy and chemotherapy.

The protein, p53, is mutated or missing in more than half of all human cancers, and most cancers involve at least some compromise in its function.

Cancer is caused by two categories of mutations: those that activate oncogenes, whose protein products drive cells into overzealous replication, and those that disable tumor-suppressor genes, which code for proteins that sense this abnormal behavior and put the brakes on it.

"We knew that p53 responds to two different types of signals: DNA damage and oncogene activity," said Laura Attardi, PhD, associate professor of radiation oncology and of genetics. "We wanted to know if p53 responds to both in the same way." Attardi is senior author of a study to be published May 13 in *Cell* that throws light on crucial molecular details about how p53 works.

It is widely understood that p53 can temporarily or permanently shut

down cell division in response to either acute damage to a cell's DNA or biochemical signals within a cell that suggest it's prone to becoming a cancer cell. In extreme cases, p53 convincingly counsels the cell to commit suicide, thereby preventing the possibility of a tumor arising.

Attardi and her colleagues created bioengineered mice in which various parts of p53 were incapacitated. This allowed them to determine which genes are activated by different parts of the protein, and to show that p53's aggressive DNA-damage response and its gentler tumor-suppression response are separable functions.

"We've determined, for the first time, that the gene expression program p53 requires in its tumor-suppression role is distinct from that which it requires in the context of acute DNA damage," Attardi said. "Separating these responses may allow the identification of ways to inhibit the detrimental effects of radiotherapy and chemotherapy — both of which damage DNA —without putting a patient at risk for developing new tumors."

While most tumors lack a working p53 protein, radiotherapy and chemotherapy activate the p53 present in healthy tissues, producing serious side effects by destroying cells in the gastrointestinal tract, blood, hair follicles and brain. That's because these treatments cause profound DNA damage, a trigger for p53 action.

It's known that p53 is a transcription factor: a protein that can regulate the production of numerous other proteins inside a cell. According to scientists, p53 recognizes and perches upon a particular DNA sequence found near large numbers of genes. Once p53 has seated itself near such a gene, two different regions of the protein, called TAD1 and TAD2, can serve as landing beacons that attract mammoth molecular copying machines to the gene — a key early step in protein generation.

But the response is very different depending on which of the two beacons, TAD1 or TAD2, is calling in the copying machinery.

Attardi's group used bioengineered mice in which TAD1, TAD2 or both had been disabled by mutations. This allowed the investigators to show that these two beacons flag different sets of genes.

The genes that TAD1 turns on are the ones involved in p53's show-stopping response to DNA-damage. More than 100 such genes had already been identified.

But when the investigators disabled TAD1 while leaving TAD2 intact, they were able to unmask a set of 50 or so genes turned on by TAD2. These genes, the team showed, mediate p53's ability to stimulate cells' somewhat more nuanced tumor-suppression response, which shuts down a cell only upon sensing oncogene activity, a more direct sign of potential cancer than mere DNA damage.

"When we treated the TAD1-disabled mice with high-dose radiation, they didn't suffer the DNA-damage-induced side effects that we saw in wild-type mice," said the study's lead author, Colleen Brady, a PhD student in Attardi's lab. "But TAD1-disabled mice were resistant to tumor development."

"This is an important advance," said molecular biologist and oncologist Arnold Levine, PhD, a professor at the Institute of Advanced Studies in Princeton, N.J. "The team has uncovered half of what the biggest player in human cancers does." Levine, who didn't participate in the study but is familiar with it, is one of three scientists credited for p53's discovery in 1979.

The finding that p53 can suppress tumors, even when the part of it that shuts down cells in response to DNA damage has been disabled, holds

significant implications for therapy. If the two distinct activities of p53 in healthy cells can be decoupled — say, by a drug impairing TAD1's function but sparing TAD2's — it might be possible to avoid the massive healthy-cell die-off responsible for nausea, hair loss, immune deficiency and nerve damage that usually occur during radiotherapy or chemotherapy, without promoting new tumor development. Disabling p53's TAD1 region would allow cells that have sustained DNA damage in the course of these therapies to live to another day, but TAD2's still-intact tumor-suppressor function in those otherwise normal cells would guard against those cells becoming cancer cells.

Provided by Stanford University Medical Center

Citation: New discoveries about tumor-suppressing protein could help to reduce treatment side effects (2011, May 12) retrieved 26 April 2024 from https://medicalxpress.com/news/2011-05-discoveries-tumor-suppressing-protein-treatment-side.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.