

Targeting cancers' 'addiction' to cell-cycle proteins shuts down tumors in mice

October 16 2012

In what they say is a promising and highly selective treatment strategy, scientists at Dana-Farber Cancer Institute have safely shut down breast cancer and a form of leukemia in mice by targeting abnormal proteins to which the cancers are "addicted," according to a new study.

Even though the investigators genetically silenced the proteins or blocked them with a drug in normal as well as cancerous tissues, the animals remained healthy, they report in the Oct. 16 issue of the journal [Cancer Cell](#). Peter Sicinski, MD, PhD, of Dana-Farber is the paper's senior author.

The experiments targeted two related proteins, cyclin D1 and cyclin D3, that control cells' growth cycle. Many [types of cancer](#) have abnormal amounts of the proteins, spurring the cells to grow too rapidly and form tumors. The new results shown that the cancers' addiction to these proteins is an Achilles' heel that can be safely targeted with an inhibitor drug that halts [cancer growth](#) or causes cancer cells to die.

Based on the results, the Dana-Farber scientists are planning a clinical trial, using an experimental cyclin-inhibiting drug called PD0332991 that has already been tested in a form of lymphoma.

"It was impressive to find that you could target a single cyclin [protein](#) and completely clear the leukemia and the mouse remained healthy," said Yoon Jong Choi, PhD, the study's lead author. "We're excited because we think this approach is very promising" as a potential

treatment for some [cancer types](#), she added.

Some of the experimental mice had been engineered to develop a type of [breast cancer](#) driven by the ErbB2 oncogene. Others were modified to develop a type of T-cell [acute lymphoblastic leukemia](#) (T-ALL) that is driven by an abnormal pathway known as Notch1. In one experiment, human T-ALL cells were infused into mice that then developed the disease.

Blocking cyclin D1 in the mice drove the [breast cancer cells](#) into a kind of permanent retirement called senescence, an irreversible halt to their growth cycle. Inhibiting cyclin D3 in the T-ALL leukemia mice caused the cancer cells to self-destruct—a programmed death process called apoptosis.

In addition to these tests with mouse cancers, the scientists found that the cyclin-D-inhibiting drug had similar effects on human blood cancer cells in the laboratory.

Cyclin proteins act as "checkpoint" guards to control cell's cycle of rest, growth and division. The D-cyclins determine when a cell begins making DNA in preparation for dividing to form new cells. In many types of cancer, an excess of cyclins allows cells to grow too fast and form tumors. Abnormal cyclins D1, D2 and D3 are found in breast, lung, endometrial, pancreatic, and testicular cancers and in multiple myeloma and other blood cancers.

In a key report in Nature in 2001, Sicinski showed that mice engineered to lack cyclin D1 were resistant to developing breast cancer. It wasn't known for many years, however, whether knocking out cyclin D1 could halt an established cancer, or if breast cancer needed the protein long-term.

Also unknown was whether normal cells could get along without cyclin D1: If not, treating cancer by targeting the protein might be too dangerous.

To test these questions, Choi and her Dana-Farber colleagues developed a strain of mice with cyclin D proteins that could be inactivated at any time by treating the mice with the drug tamoxifen.

"By generating these 'conditional' knockout mice, we could address these questions for the first time," said Choi. The effect was global, affecting all the body cells, not just those that were cancerous. When the cyclin D proteins were turned off using this technique, the addicted cancer cells shut down while normal cells were unaffected.

The authors say the results show that blocking cyclin D "represents a highly selective anticancer strategy that specifically targets [cancer cells](#) without significantly affecting normal tissues."

Provided by Dana-Farber Cancer Institute

Citation: Targeting cancers' 'addiction' to cell-cycle proteins shuts down tumors in mice (2012, October 16) retrieved 4 May 2024 from <https://medicalxpress.com/news/2012-10-cancers-addiction-cell-cycle-proteins-tumors.html>

<p>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.</p>
--