

Researchers discover gene that permanently stops cancer cell proliferation

August 1 2012

Researchers at Case Western Reserve University School of Medicine have discovered a mutant form of the gene, Chk1, that when expressed in cancer cells, permanently stopped their proliferation and caused cell death without the addition of any chemotherapeutic drugs. This study illustrates an unprecedented finding, that artificially activating Chk1 alone is sufficient to kill cancer cells.

"We have identified a new direction for cancer therapy and the new direction is leading us to a reduction in toxicity in cancer therapy, compared with chemotherapy or radiation therapy," said Dr. Zhang, assistant professor, Department of Pharmacology at the School of Medicine, and member of the university's Case Comprehensive Cancer Center. "With this discovery, scientists could stop the proliferation of [cancer cells](#), allowing physicians time to fix cells and [genetic errors](#)."

While studying the basic mechanisms for genome integrity, Dr. Zhang's team unexpectedly discovered an active mutant form of human Chk1, which is also a non-natural form of this gene. This mutation changed the protein conformation of Chk1 from the inactive form into an active form. Remarkably, the research team discovered that when expressed in cancer cells, this active mutant form of Chk1 permanently stopped cancer [cell proliferation](#) and caused cell death in [petri dishes](#) even without the addition of any [chemotherapeutic drugs](#).

The biggest advantage of this potential strategy is that no toxic chemotherapeutic drug is needed to achieve the same cancer killing

effect used with a combination of Chk1 inhibitors and chemotherapeutic drugs.

Cells respond to [DNA damage](#) by activating networks of signaling pathways, termed cell cycle checkpoints. Central to these genome pathways is the protein kinase, called Chk1. Chk1 facilitates cell survival, including cancer cells, under stressful conditions, such as those induced by chemotherapeutic agents, by placing a temporary stop on the cell cycle progression and coordinating repair programs to fix the DNA errors.

It has long been suggested that combining Chk1 inhibition with chemotherapy or radiotherapy should significantly enhance the anticancer effect of these therapies. This idea has served as the basis for multiple pharmaceutical companies searching for potential Chk1 inhibitors that can effectively combine with chemotherapy in cancer therapy. To date, no Chk1 inhibitor has passed the clinical trial stage III. This led Dr. Zhang's team to look for alternative strategies for targeting Chk1 in [cancer therapy](#).

Future research by Dr. Zhang and his team will consider two possible approaches to artificially activating Chk1 in cancer cells. One possibility is to use the gene therapy concept to deliver the active mutant form of Chk1 that the team discovered, into cancer cells. The other is to search for small molecules that can induce the same conformational change of Chk1, so that they can be delivered into cancer cells to activate Chk1 molecules. The consequence of either would be permanent cell proliferation inhibition and cancer.

This study is published in *Cancer Research*.

Provided by Case Western Reserve University

Citation: Researchers discover gene that permanently stops cancer cell proliferation (2012, August 1) retrieved 20 March 2024 from <https://medicalxpress.com/news/2012-07-gene-permanently-cancer-cell-proliferation.html>

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