MedicalXpress

Protein 'switches' could turn cancer cells into tiny chemotherapy factories

September 23 2011

Johns Hopkins researchers have devised a protein "switch" that instructs cancer cells to produce their own anti-cancer medication.

In lab tests, the researchers showed that these switches, working from inside the cells, can activate a powerful cell-killing drug when the device detects a marker linked to cancer. The goal, the scientists said, is to deploy a new type of weapon that causes cancer cells to self-destruct while sparing healthy tissue.

This new cancer-fighting strategy and promising early lab test results were reported this week in the online early edition of Proceedings of the National Academy of Sciences. Although the switches have not yet been tested on human patients, and much more testing must be done, the researchers say they have taken a positive first step toward adding a novel weapon to the difficult task of treating cancer.

One key problem in fighting cancer is that broadly applied chemotherapy usually also harms healthy cells. In the protein switch strategy, however, a doctor would instead administer a "prodrug," meaning an inactive form of a cancer-fighting drug. Only when a cancer marker is present would the cellular switch turn this harmless prodrug into a potent form of chemotherapy.

"The switch in effect turns the cancer cell into a factory for producing the anti-cancer drug inside the cancer cell," said Marc Ostermeier, a Johns Hopkins chemical and biomolecular engineering professor in the

Whiting School of Engineering, who supervised development of the switch.

"The healthy cells will also receive the prodrug," he added, "and ideally it will remain in its non-toxic form. Our hope is that this strategy will kill more cancer cells while decreasing the unfortunate side effects on healthy cells."

To demonstrate that these switches can work, the research team successfully tested them on human colon cancer and breast cancer cells in Ostermeier's lab and in the laboratory of James R. Eshleman, a professor of pathology and oncology in the Johns Hopkins School of Medicine.

"This is a radically different tool to attack cancers," said Eshleman, a co-author of the PNAS journal article, "but many experiments need to be done before we will be able to use it in patients."

The next step is animal testing, expected to begin within a year, Ostermeier said.

Ostermeier's team made the cancer-fighting switch by fusing together two different proteins. One protein detects a marker that cancer cells produce. The other protein, from yeast, can turn an inactive prodrug into a cancer-cell killer. "When the first part of the switch detects cancer, it tells its partner to activate the chemotherapy drug, destroying the cell," Ostermeier said.

In order for this switch to work, it must first get inside the cancer cells. Ostermeier said this can be done through a technique in which the switch gene is delivered inside the cell. The switch gene serves as the blueprint from which the cell's own machinery constructs the protein switch. Another approach, he said, would be to develop methods to deliver the

switch protein itself to cells.

Once the switches are in place, the patient would receive the inactive chemotherapy drug, which would turn into a cancer attacker inside the cells where the switch has been flipped on.

Although many researchers are developing methods to deliver anti-cancer drugs specifically to cancer cells, Ostermeier said the protein switch tactic skirts difficulties encountered in those methods.

"The protein switch concept changes the game by providing a mechanism to target production of the anti-cancer drugs inside cancer cells instead of targeting delivery of the anti-cancer drug to cancer cells," he said.

More information: The paper, "A protein therapeutic modality founded on molecular recognition," can be viewed online at: www.pnas.org/content/early/201 … 803108.full.pdf+html

Provided by Johns Hopkins University

Citation: Protein 'switches' could turn cancer cells into tiny chemotherapy factories (2011, September 23) retrieved 29 April 2024 from https://medicalxpress.com/news/2011-09-protein-cancer-cells-tiny-chemotherapy.html

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