MedicalXpress

An Achilles heel in cancer cells

December 8 2008

A protein that shields tumor cells from cell death and exerts resistance to chemotherapy has an Achilles heel, a vulnerability that can be exploited to target and kill the very tumor cells it usually protects, researchers from the University of Illinois at Chicago show in a new study published in the Dec. 9 issue of *Cancer Cell*.

Akt is a signaling protein, called a kinase, that is hyperactive in the majority of human cancers.

"Akt is perhaps the most frequently activated oncoprotein (cancer-promoting protein) in human cancer," says Nissim Hay, professor of biochemistry and molecular genetics at the UIC College of Medicine. Pharmaceutical companies have been trying to find ways to inhibit Akt to improve cancer therapy, he said, but most candidate drugs have acted too broadly and proved toxic.

"One of Akt's major functions in tumor cells is promoting cell survival," Hay said. "Tumor cells with hyperactive Akt are not only resistant to the external stresses that can induce cell death but also to chemotherapy."

But Akt is also required for metabolism and the proliferation of cancer cells, and it was as a byproduct of its role in metabolism that the researchers were able to exploit Akt hyperactivity against the tumor cell.

"We found that cells with hyperactive Akt have increased intracellular levels of reactive oxygen species (ROS) and at the same time impaired ability to scavenge ROS," Hay said. These ROS are highly reactive

byproducts of metabolism that can damage the cell. Cells usually respond to high levels of ROS by undergoing cell suicide, or apoptosis.

"And, to our surprise, we found that although Akt can protect cancer cells from many of the external signals that would ordinarily induce cell death, including many chemotherapy drugs, it cannot protect from ROS inducers," said Hay.

The researchers found that if they treated cancer cells with chemicals that raise ROS levels, the cells die. Akt could not protect cells from this form of apoptosis and, indeed, because Akt impaired the normal ROS scavenging in the cell, hyperactive Akt actually had the effect of making the cells more vulnerable to these ROS inducers. This enabled selective killing of cancer cells, expressing hyperactive Akt, and not normal cells.

The researchers also devised another strategy to exploit Akt's Achilles heel to successfully target and kill cancer cells.

An FDA-approved chemotherapy drug called rapamycin can be used to arrest cell tumor growth. A drawback of this drug is that it doesn't kill the cells, it just arrests the growth of the tumor. When the drug is removed the tumor may grow again.

"Rapamycin's other drawback is complicated feedback regulation that we turn to our advantage," Hay said. "It turns out rapamycin's target and Akt talk to each other in the cell." If the rapamycin target is hyperactive, Akt is inhibited, and if Akt is active, the rapamycin target is activated.

"So even though cancer cells treated with rapamycin stop dividing, they activate Akt, which makes the cells more resistant to other chemotherapy drugs," said Hay. "But we use that to our advantage. Because overactivation of Akt sensitizes the cells to ROS mediated cell death, if we treat the cells with ROS inducers and rapamycin together we

can now kill the cells, not just arrest their growth."

The new study "provides a proof of the principle that Akt's Achilles heel -- a consequence of its role in metabolism -- can be exploited in at least these two ways to selectively target and kill cancer cells," Hay said.

Source: University of Illinois at Chicago

Citation: An Achilles heel in cancer cells (2008, December 8) retrieved 20 April 2024 from https://medicalxpress.com/news/2008-12-achilles-heel-cancer-cells.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.