

## Researchers find surprising role for enzyme in tumor cell division and new drug to combat it

November 13 2011



This is a diagram of "allosteric" approach. Credit: UC San Diego School of Medicine

Researchers at the University of California, San Diego School of Medicine and the UC San Diego Moores Cancer Center have identified a new drug discovery approach enabling the destruction of the most highly proliferative tumors. The discovery, published in the Nov. 13 online issue of the journal *Nature Medicine*, points to an effective, alternative method for killing fast-growing cancer cells without causing some of the negative effects of current therapies.

The scientists, led by David A. Cheresh, PhD, professor of pathology



and associate director for translational research at the Moores Cancer Center, used an innovative chemical and biological approach to design a new class of drugs that arrests division in virtually all tumor cells by binding to and altering the structure of an enzyme called RAF.

RAF has been long-studied, but its role in <u>cell division</u> – critical to cell proliferation and tumor growth – was a surprise. "By designing a new class of drugs that changes the shape of RAF, we were able to reveal this previously undiscovered role for RAF in a wide range of highly proliferative tumors," Cheresh said.

Current cancer drugs that target enzymes like RAF are generally designed to interact with the active site of the enzyme. Unfortunately, these drugs often lack specificity, Cheresh said. "They hit many different targets, meaning they can produce undesired side effects and induce dose-limiting toxicity." More of a concern is that tumor cells often develop resistance to this class of drugs rendering them inactive against the cancer.

Cheresh and colleagues pursued development of a new class of RAF inhibitors that do not bind to the active site of the enzyme and so avoid the limitations of current drugs. Instead, this new class, called allosteric inhibitors, changes the shape of the target enzyme and in doing so, renders it inactive. The specific drug tested, known as KG5, singles out RAF in proliferating cells, but ignores normal or resting cells. In affected <u>tumor cells</u>, RAF is unable to associate with the mitotic apparatus to direct cell division, resulting in cell cycle arrest leading to apoptosis or programmed cell death. KG5 in a similar manner effectively interferes with proliferating blood vessels, a process called angiogenesis.

"It's an unusual discovery, one that really challenges current dogma," said Cheresh. "Before this drug was designed, we had no idea RAF could



promote <u>tumor</u> cell cycle progression. This may be only one example of how, by designing drugs that avoid the active site of an enzyme, we can identify new and unexpected ways to disrupt the growth of tumors. In essence, we are attacking an important enzyme in a whole new way and thereby discovering new things this <u>enzyme</u> was intended for."

KG5 produced similar results in tests on cancer cell lines, in animal models and in tissue biopsies from human cancer patients. The research team has since developed variants of KG5 that are 100-fold more powerful than the original drug. They hope one of these more powerful compounds will soon enter clinical trials at Moores Cancer Center.

The new RAF targeted compounds are being developed by Amitech Therapeutic Solutions, Inc a start-up company in San Diego.

Provided by University of California - San Diego

Citation: Researchers find surprising role for enzyme in tumor cell division and new drug to combat it (2011, November 13) retrieved 5 May 2024 from <u>https://medicalxpress.com/news/2011-11-role-enzyme-tumor-cell-division.html</u>

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.