Researchers discover new molecular pathway for targeting cancer, disease

20 July 2009

(PhysOrg.com) -- A UCLA study has identified a way to turn off a key signaling pathway involved in physiological processes that can also stimulate the development of cancer and other diseases. The findings may lead to new treatments and targeted drugs using this approach.

In the study, which is currently available in the online edition of the journal *Molecular Endocrinology*, scientists found that by activating a receptor in cells called the liver X receptor (LXR), they were able to inhibit the hedgehog (Hh) signaling pathway, which is involved in the maintenance of tissue integrity and stem cell generation. When stimulated in an unregulated manner, however, the Hh pathway can also cause cancers of the brain, lung, blood, prostate, skin and other tissues.

Blocking such unregulated stimulation of the Hh pathway had previously been shown in animal studies to prevent cancers, according to the researchers. How LXR was able to inhibit tumor cell growth by impeding the Hh pathway was previously unknown.

"Our finding shows that activation of LXR signaling is a novel strategy for inhibiting Hh pathway activity and for targeting various cell types, including cancer cells, which may provide important clues as to how we might be able to intervene with tumor formation," said Farhad Parhami, a professor of medicine at the David Geffen School of Medicine at UCLA and the study's principal investigator.

During the study, researchers performed various tests activating LXR receptors in cells and found that specific gene expression induced by the Hh pathway could be inhibited. This finding was also confirmed in mice.

"Since Hh signaling plays a major role in other physiological and pathological processes, we may be able to impact other diseases as well," Parhami said.

Dr. William Matsui of Johns Hopkins Medical Institute, an expert on Hh signaling in cancer development, noted the importance of the UCLA study and its significance for the next stages of research — finding a pharmaceutical drug or substance molecule to act as an agonist, which would stimulate LXR activity to inhibit aberrant Hh signaling.

"The hedgehog Hh signaling pathway is an important regulator of tumor formation, and these findings suggest that LXR agonists may be novel treatments for a wide variety of human cancers," Matsui said.

According to researchers, utilizing this new treatment pathway could have broad applications in the cancer field.

"This discovery identifies an entirely new and unexpected mechanism of hedgehog pathway modulation," said study author Dr. James A. Waschek, an expert on Hh signaling in brain tumor development and a professor of psychiatry and biobehavioral sciences at the David Geffen School of Medicine at UCLA. "This has great potential in offering other options, because current hedgehog pathway inhibitors have severe side effects which preclude their use in many cancer patients, especially children."

Waschek also noted that this discovery may reveal new details on how Hh signals within the cell, which is currently poorly understood.

The next stage of the research will focus on activating the LXR pathway using various pharmacological molecules to inhibit tumor formation. Matsui will be a collaborator in this follow-up research.

In addition, the team has started a medicinal

chemistry program to design and test small molecules that activate the LXR pathway while avoiding the adverse effects that may be caused when LXR is activated in tissues such as the liver.

Source: University of California - Los Angeles

APA citation: Researchers discover new molecular pathway for targeting cancer, disease (2009, July 20) retrieved 11 October 2022 from https://medicalxpress.com/news/2009-07-molecular-pathway-cancer-disease.html

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