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Blocking cancer in its path: New cellular defect discovered

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(PhysOrg.com) -- UCSF researchers have discovered that a key cellular defect that disturbs the production of proteins in human cells can lead to cancer susceptibility. The scientists also found that a new generation of inhibitory drugs offers promise in correcting this defect.

According to the study team, this discovery has broad clinical implications in the fight against cancer and could affect treatment of lymphoma and many other forms of the disease, including prostate cancer, breast cancer, colorectal cancer, brain cancer and multiple myeloma.

The findings are featured as the cover story in the March 16, 2010 issue of the scientific journal *Cancer Cell*.

The discovery was made in the laboratory of UCSF faculty scientist Davide Ruggero, PhD, whose lab team is doing research in the burgeoning field of study on how defects in protein synthesis can lead to cancer susceptibility.

"Our work has the potential to create real, tangible benefits for the medical community," said Ruggero, an assistant professor of urology at the UCSF Helen Diller Family Comprehensive Cancer Center and senior author of the paper.

The researchers focused on a multi-protein unit known as mTOR, which stands for the "mammalian target of rapamycin." mTOR controls several

important processes in mammalian cells, including cell survival and proliferation.

One of the most significant of these processes is the production of proteins within a cell, the control of which is known as translational control. mTOR integrates information about the cell's nutritional and energy needs, and prompts the cell to manufacture key proteins for cell growth. Cancer cells exploit this signal for their own growth.

According to the researchers, when the cells in the body lose the ability to control mTOR activity, mTOR is considered "hyperactivated." This hyperactivation causes protein synthesis rates to climb. Cells begin to proliferate without limits and simultaneously become immortal, all of which leads to tumor formation.

"Our findings show that for a cancer cell, normal cellular functions such as protein synthesis can be specifically hijacked for tumor growth," explained first author Andrew Hsieh, a clinical fellow at the UCSF School of Medicine and the Department of Urology at the Helen Diller Family Comprehensive Cancer Center.

Ruggero said that the "dismal" clinical results seen with first generation mTOR inhibitor drugs like rapamycin "stemmed in part from the inadequate limit on unhealthy protein synthesis that is caused by hyperactivated mTOR."

Researchers in his laboratory made this key discovery through genetic tests that demonstrate that healthy genes in charge of protein production can become cancerous when mTOR is hyperactivated. To combat this, the scientists employed a new drug called PP242. This drug was discovered at UCSF in the lab of Kevan Shokat, PhD, Howard Hughes Medical Investigator and professor of cellular and molecular pharmacology at UCSF.

"This drug has shown promising results by bringing protein synthesis and cell proliferation levels back down to normal rates," Ruggero said. "In addition, PP242 helps fight the process of immortalization that cancer cells go through."

In their findings, PP242 proved to be more effective than similar drugs in its ability to jumpstart translational control in both live mice and human cells tested in the lab. PP242 is currently in Phase 1 clinical trials.

"We demonstrated that the drug kills the cancer cells more effectively because it blocks the abnormal production of proteins," said Ruggero. "The other drugs we tested did not show clinical effectiveness in blocking cancer development in this manner."

The authors say that PP242 could become a potent cancer treatment. The findings are a positive step, Ruggero said, because what have previously been considered unresponsive tumors can now be treated with the second generation of inhibitors that halt mTOR's action on protein production.

"We are extremely excited about our findings and the potential of targeting aberrant protein synthesis and mTOR in cancer as we should be able to block cancer's main source of growth," said Ruggero. "We are working with clinicians to test our hypothesis in a variety of human tumors."

More information: http://www.cell.com/cancer-cell/issue?pii=S1535-6108%2810%29X0004-6

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