Researchers Build Colony of Colon Cancer Stem Cells to Test New Approach to Therapy

AACR

• Colon cancer stem cells may be the root of therapy resistance.
• Idea is to shut down cells that continually revive tumors.
• First model that shows how a single colon cancer stem cell behaves.

PHILADELPHIA — University of Pittsburgh researchers have devised a three-dimensional system in laboratory culture that mimics the growth patterns of colon cancer stem cells in patients. Their findings were presented at the American Association for Cancer Research special conference on Colorectal Cancer: Biology to Therapy, held Oct. 27-30, 2010.

The assay, which uses green fluorescent “reporter” proteins to watch the process of stem cell differentiation, is designed to understand how these cancer stem cells behave, and to identify and test therapies that could halt production of the endless generations of new cancer stem cells that continually revive a tumor.

“Colon cancer stem cells are thought to be the root of therapy resistance, metastases and recurrence in colon cancer, so our approach is to find a way to remove the ability of these stem cells to self-renew,” said the study’s lead investigator, Julie Chandler, a graduate student in pathology.

“While many labs have investigated notch inhibitors and others have investigated cancer stem cells, our unique approach combines both in a three-dimensional culture that mimics what happens in patients,” she said. Animal models, which are immunodeficient and use human xenografs, may not provide accurate information about colon cancer stem cell behavior, Chandler added.

Colon cancer stem cells have the ability to repopulate a tumor after treatment, using stem cells that are resistant to treatment. Such treatment forces a response in these cells, which are genetically unstable, forcing the cells to adapt and pass on resistance to daughter stem cells.

In the same way that adult intestinal stem cells self-renew, colon stem cells give rise to different kinds of cells, including daughter stem cells and fully differentiated cells, such as the goblet epithelial cells that line the colon. Researchers would like to force cancer stem cells to differentiate and behave like goblet cells because these cells do not self renew. Chandler said the notch pathway that controls differentiation in stem cells is inactivated in goblet cells. One way to possibly do that is to use agents that shut down the notch pathway, such as gamma secretase inhibitors, she said. Cancer treatment may then be able to destroy tumors that are now populated by fully differentiated goblet cells.

In their new assay, Chandler used a three-dimensional culture matrix in which she could watch a single cancer stem cell divide and produce progeny, which is called an “independent organoid.”

To see the kind of cells a colon cancer stem cell produces, they labeled a protein that is specific only to goblet cells. To date, the researchers have found that some colon cancer stem cells produce many differentiated cells, such as goblets and others, while others produce more primitive, self-renewing cells.

In this way, the researchers can test the ability of notch pathway inhibitors to force progeny cancer stem cells to differentiate into harmless goblet cells.

“Green goblet cells are no longer capable of promoting cancer growth,” Chandler said. “It may be that a certain notch inhibitor or similar drug is all that is needed to prevent cancer recurrence and metastasis that so often follows an initial response to treatment. This new tool will help us determine if that is so.”

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The mission of the American Association for Cancer Research is to prevent and cure cancer. Founded in 1907, the AACR is the world’s oldest and largest professional organization dedicated to advancing cancer research. The membership includes 32,000 basic, translational and clinical researchers; health care professionals; and cancer survivors and advocates in the United States and more than 90 other countries. The AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, diagnosis and treatment of cancer through high-quality scientific and educational programs. It funds innovative, meritorious research grants, research fellowships and career development awards. The AACR Annual Meeting attracts more than 18,000 participants who share the latest discoveries and developments in the field. Special conferences throughout the year present novel data across a wide variety of topics in cancer research, treatment and patient care. The AACR publishes six major peer-reviewed journals: *Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; Cancer Epidemiology, Biomarkers & Prevention*; and *Cancer Prevention Research*. The AACR also publishes *CR*, a magazine for cancer survivors and their families, patient advocates, physicians and scientists, providing a forum for sharing essential, evidence-based information and perspectives on progress in cancer research, survivorship and advocacy.

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