The cellular root of colorectal cancers?

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Researchers at Children's Hospital Boston have found a marker called ABCB5 that both tags a small proportion of cells within colorectal cancers and fuels resistance in those cells to standard treatments. The results indicate that eliminating ABCB5-expressing cells is crucial for successful colorectal cancer treatment, while adding to the growing body of evidence for a theory of cancer growth called the cancer stem cell hypothesis.

An international team led by Brian J. Wilson, PhD, Tobias Schatton, PhD, and Markus Frank, MD, of the Transplantation Research Center at Children's Hospital Boston, and Natasha Frank, MD, of the VA Boston Healthcare System and Brigham and Women's Hospital, and colleagues at the University of Wurzburg in Germany reported the findings online in the journal Cancer Research on June 7, 2011.

An estimated 141,000 Americans will be diagnosed with colorectal cancer this year. While its mortality has been dropping over the last two decades thanks to screening and improved treatment options, colorectal cancer is still the second leading cause of cancer-related death in the United States.

Recognizing ABCB5's role as a marker of tumor recurrence in melanoma and liver cancer, and knowing from previous studies that the gene for ABCB5 is also active in colorectal cancer, the Franks' team studied the protein's expression in both normal and cancerous colorectal tissue specimens. They found that ABCB5 is found only rarely in healthy colorectal tissue, but is present at levels 23 times greater in cancerous

tissue.

Underscoring its preferential expression on stem cells, ABCB5 was frequently accompanied on both healthy and cancerous cells by a second protein, CD133, which is thought to be a marker of both healthy intestinal stem cells and colorectal cancer stem cells. CD133 is also associated with aggressiveness in colorectal cancer.

To understand ABCB5's role in treatment resistance, the team examined biopsies gathered from colorectal cancer patients both before and after treatment with 5-fluorouracil (5-FU), a standard chemotherapeutic for this tumor. They found that the percentage of cells expressing ABCB5 increased more than five fold after treatment.

Using a mouse model of colorectal cancer, the researchers also found that cells expressing ABCB5 were markedly resistant to 5-FU. Knocking down ABCB5 expression both blocked the growth of these cells and restored their sensitivity to the drug, showing that ABCB5 is not only a marker of treatment resistance but actually drives it.

"With ABCB5, we have a molecule that is present at higher levels in colorectal cancers than in healthy cells, that marks the subset of cancer stem cells in human patients that will resist therapy, and that mediates that resistance at a functional level," said Markus Frank, a staff scientist Children's Department of Medicine and an assistant professor of pediatrics at Harvard Medical School. "It's a new mechanism of 5-FU resistance with very significant translational and therapeutic relevance," added Natasha Frank, a research associate at Children's Hospital Boston, an associate physician in the Division of Genetics at Brigham and Women's Hospital, and director of the Genetics Clinic at the VA Boston Healthcare System. "We think that these are the cells that need to be eliminated for successful treatment of colorectal cancer."

The cancer stem cell hypothesis holds that a fraction of the malignant cells in a tumor have characteristics associated with normal stem cells, namely the ability to self-renew and to give rise to other cell types. The hypothesis also holds that in order to successfully eliminate a tumor, the cancer stem cells must be eliminated as well; if they are not, they could serve as seeds for the tumor to regrow or spread.

"When the cancer stem cell concept was first posited, it was thought that the stem cell subset might coincide with the subset that remains after therapy and that metastasizes," Markus Frank said. "This subset has historically been a hidden target, because we have not been able to define and isolate it. But therapies capable of killing off those cells at the root of the cancer would be much more effective than those that miss this subset."

Provided by Children's Hospital Boston