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Stem Cells May Be at Root of Cancer

New Research May Explain Why So Many Tumor-Fighting Treatments Now Fail

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WebMD Medical News

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April 20, 2007 (Los Angeles) -- Are most current cancer treatments -- as well as many in development -- aimed at eradicating the wrong cancer cells?

That's the position of some leading researchers, who say that cancer is, fundamentally, a stem cell problem -- and that therapy should be targeted at so-called cancer stem cells.

"The models we currently use to develop cancer treatments are fundamentally flawed," says Max Wicha, MD, director of the University of Michigan Comprehensive Cancer Center in Ann Arbor.

"Most approaches up to now are targeting the wrong population of cancer cells," which explains why so many fail to produce a cure, he tells WebMD.

At the annual meeting of the American Association for Cancer Research here this week, Wicha moderated a session during which researchers discussed new discoveries suggesting that stem cells in leukemia, breast, and colon cancer are at the root of many tumors.

A Primer on Cancer Stem Cells

All stem cells -- regardless of their source -- share some general properties: They can reproduce and make exact copies of themselves, they live longer than ordinary cells, and they can give rise to other cells in our bodies.

Embryonic stem cells are a hot, if controversial, area of research. They are at such an early stage of development that they have potential to become many different types of cells, including those of the heart or brain, for example.

Adult stem cells, on the other hand, are generally limited to differentiating into cell types of their tissue of origin. Under typical conditions, for example, adult stem cells in liver tissue can only form liver cells, Wicha explains.

In labs worldwide, scientists are working furiously to figure out how to use both embryonic and adult stem cells to produce virtually unlimited quantities of healthy cells to replace the damaged ones in patients suffering from disorders ranging from Alzheimer's to Parkinson's disease.

Cancer stem calls are a perversion of other adult stem cells. "They are cells that have

the ability to reproduce themselves and develop into cancer cells," Wicha says.

A New Model for Cancer

Wicha says that the current model of what causes cancer assumes that cells become malignant after a series of mutations disables their genetic control system.

"In this theory, any cell that gets the right series of mutations can become cancer," he says.

In the stem cell hypothesis, cancer is driven by specific cells that contain stem cell properties, Wicha says. These cells then reproduce and replenish malignant tumors.

Currently, most treatments target cancer cells, but not necessarily cancer stem cells, he says. While the treatment may shrink the tumor and keep it in check for a while, eventually, the untreated cancer stem cells proliferate into cancer cells, leading to a return of the tumor and death, he says.

If the treatments targeted the cancer stem cells, however, the tumor would lose the ability to generate new cancer cells, eventually resulting in a cure, Wicha says.

Think dandelions, says researcher Peter Chu, PhD, of Biogen Idec in San Diego. "If you cut a weed and don't get the root, it will grow back," he tells WebMD. "So if you don't [kill off] cancer stem cells, you're not going to see better long-term survival."

Wicha notes that the concept that stem cells cause cancer is not new. But recent advances in molecular biology -- such as the development of tests that allow researchers to locate and measure the cancer stem cells -- are giving it new credibility, he says.

Stem Cells Drive Aggressive Breast Tumors

Experiments in Wicha's lab show that two genes, PTEN and HER2/neu, that are associated with aggressive breast cancers have stem cell properties. Defects in either gene are tied to faster-growing tumors that are more likely to return.

The researchers studied three types of genetically altered breast cancer cells: One had the PTEN defect, one had the HER2/neu defect, and one had both genetic alterations.

Results showed that that either defect increases the stem cell population by two to five times. Furthermore, there was an approximately tenfold increase in the stem cell population when they created a cell line with both PTEN and HER2/neu defects.

Then, the researchers injected the three types of genetically altered cells into mice. Cells with either defect induced the growth of tumors that were four to six times more aggressive than normal. Injection of the cells with both alterations caused tumors that were 10 times more aggressive.

Wicha believes the experiments may help explain why Herceptin, the biologic therapy that targets the HER2 protein on cancer cells, works so well.

"We believe that knocking out the tumor-causing cancer stem cells explains why Herceptin reduces that chance of cancer coming back by 50% [in women with HER2 positive breast cancer], although that remains to be proven," he says.

Stem Cells Drive Colon Cancer

In another experiment, Chu and colleagues sorted colon cancer cells according to a molecular marker known as CD44 that appears on their surface.

The marker was chosen because it fit the bill for a cancer stem cell, with earlier studies showing it "possessed a capacity to reproduce itself, regenerate, and produce tumors similar to the tumor of origin," he says.

Then, the researchers injected cells producing various amounts of CD44 into mice. Results showed that the mice developed tumors after being injected with as few as 10 cells producing high amounts of CD44. That's not many, when you consider there are billions of cells in the body, Chu says.

Cancer cells that did not have CD44 on their surface were far less driven. Researchers had to inject 5,000 or more of these cells into the mouse to induce tumor growth, he says.

Wicha notes that CD44 is present on the surface of lung, breast, and many other types of cancers as well. What this suggests, he says, is that novel drug treatments blocking CD44 would curb the growth of many tumor types, not just that of the colon.

Radiation Enhances Cancer Stem Cell Growth

In a third study reported at the meeting, researchers from the Ontario Cancer Institute found that cancer stem cells may help explain why women with breast cancer who are successfully treated with radiation are at increased risk of developing leukemia down the road. Radiation therapy in mice enhanced blood stem cell growth which could lead to increased risk for leukemia.

Wicha cautions that while all the research is exciting, there's still a long way to go. "This is obviously a very important and exciting area of research with great potential," says Len Lichtenfeld, MD, deputy chief medical officer of the American Cancer Society in Atlanta.

"A lot of people believe, and rightly so, that it may help provide the answers we have been looking for," he tells WebMD.

At the same time, "we do have to be cautious," says Lichtenfeld, noting that researchers have had other promising theories about how cancer develops that did not prove to hold true after rigorous examination.

SOURCES: 2007 Annual Meeting of the American Association for Cancer Research, Los Angeles, April 14-18, 2007. Max Wicha, MD, director, University of Michigan Comprehensive Cancer Center, Ann Arbor. Peter Chu, PhD, Biogen Idec, San Diego. Carlo Bastianutto, PhD, Ontario Cancer Institute.

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