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Discoveries Thrust Cancer-Initiating Stem Cells Into A Larger Role In Cancer Biology And Treatment

Apr. 19, 2007 — Recent discoveries about the role of stem cells in cancer have altered the landscape of cancer research. With each new study, scientists are learning more about cancer-initiating properties of stem cells at organ sites and throughout the body. Increasingly, stem cells are examined as the cause -- and potential target of treatment -- for many, if not all, cancers. At the 2007 Annual Meeting of the American Association for Cancer Research, researchers present new discoveries about stem cells in leukemia, breast and colon cancer that add to the growing evidence that perhaps cancer is, fundamentally, a stem cell problem.

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PTEN and HER2 regulate self-renewal and invasion of human mammary stem cells: Abstract 1287

Two genes associated with aggressive breast cancer are linked to a key property of mammary stem cell function, according to researchers at the University of Michigan. The genes, PTEN and HER2, both are involved in the biochemical pathways that mediate stem cell self-renewal, a defining property of stem cells.

According to the researchers, understanding the pathways that regulate stem cell self-renewal is important in developing therapeutics that target the tumor stem cell pool. These genes might also become targets of interest in the treatment of tumors resistant to the drug Herceptin.

"We now believe that our results show further evidence that breast cancer arises from signaling errors in the biochemical pathways that control mammary stem cell self-renewal" said Hasan Korkaya, D.V.M., Ph.D., a research fellow at the University of Michigan's Comprehensive Cancer Center. "Since only stem cells have the ability to self-renew, deregulation of either PTEN or HER2 expands the stem cell populations with self-renewing ability."

According to Korkaya, cells with deregulated – or increased – self-renewing ability will then initiate and maintain tumors that are resistant to current therapies.

The two genes appear to influence stem cell self-renewal by controlling two different arms of the pathway, says Korkaya. In breast cancer, the loss of PTEN is linked to nearly a quarter of all cases, while the overproduction of HER2 is associated with nearly 40 percent of all cases. Patients with a combined defect of PTEN loss and HER2 amplification represent worse prognosis than either defect alone.

To replicate this clinical phenomenon and study the link between stem cell self-renewal and tumorigenesis, the researchers altered the expression of the two genes in a line of human breast carcinoma cells. In experimental settings, their results confirmed this clinical data that either defect increases stem cell population by three to five times. Furthermore, Korkaya observed an additive effect and an approximate 10-fold increase in stem cell population when they created a cell line with deleted PTEN and HER2 overexpression. Another property of aggressive tumors is metastasis; the team also found that these cells had increased invasive capacity in a matrigel invasion assay.

"In general, tumors are heterogeneous including stem and non-stem cell populations in a given malignancy," Korkaya said. "If the stem cells acquired mutations in their self-renewing

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pathways, they will then begin reproducing at an accelerated rate, leading to a particularly aggressive form of cancer."

The researchers believe further studies will identify new biomarkers that will enable physicians to clinically screen patients for mammary stem cells and provide specific treatments designed to target these cells.

Local Radiotherapy Might Contribute to Leukemia Risk in Breast Cancer by Recruitment of Hematopoietic Stem Cells: Abstract 5050

Radiation therapy affects not only the cancer mass, but also the surrounding tissues, including the bone marrow. Signals from the cells in the bone marrow damaged by cancer radiotherapy could be involved in the development of secondary acute myeloma by drawing hematopoietic stem cells, the blood-producing cells of the bone marrow, from distant sites into the irradiated bone marrow, according to researchers from the Ontario Cancer Institute. Their findings suggest that local radiotherapy leads to leukemia, even though radiotherapy directly affects only a small fraction of the bone marrow.

While often effective in treating breast cancer, localized radiation therapy increases the risk of developing secondary cancer, which most frequently manifests in the form of acute myeloid leukemia. In breast cancer, less than 10 percent of bone marrow is exposed to radiation therapy, yet a much higher percentage of hematopoietic stem cells could be affected.

To understand this effect, the researchers labeled and tracked the movement of hematopoietic stem cells in an animal model. Following local radiation therapy, they found that more than four times more hematopoietic stem cells accumulated in the irradiated bone marrow, compared to the non-irradiated bone marrow. Through molecular screening, they found that cells in the area were creating an overabundance of three protein signals known to recruit hematopoietic stem cells: SDF1, MMP2 and MMP9.

"Cells within the bone marrow send out these chemical signals as a sort of call for help, which recruits a large number of hematopoietic stem cells into the affected areas, supposedly to replace damaged cells," said Carlo Bastianutto, Ph.D., a scientific associate at the Ontario Cancer Institute. "In effect, this becomes a trap for this specific population of stem cells, drawing them into the bone marrow present in the radiation field and getting them exposed to the following radiation cycles. This story might repeat at every cycle of radiation therapy, therefore increasing the chance of producing a leukemic stem cell."

According to the OCI researchers, the recruiting signal might be stopped by chemical blockers, which was shown to inhibit the signals experimentally. "Conceivably, it could be possible to inhibit these chemical signals, and this could reduce the risk of secondary acute myeloid leukemia, but much more research needs to be done," Bastianutto said.

The researchers believe this model could help prevent acute myeloid leukemia in patients with malignancies other than breast cancer.

Prospective identification of highly tumorigenic colon adenocarcinoma cells enriched for stem-like properties: Abstract 1288

Colon cancer could join the growing list of stem cell-related cancers with the discovery of a population of highly tumorigenic primary human colon tumor cells, according to researchers from Biogen Idec.

"Such stem cells could be responsible for the perpetuation of colon cancer and its relapse following successful therapy," said Peter Chu, Ph.D., researcher at Biogen Idec. "Our goal is to improve cancer survival rates by identifying these cancer stem cells in order to pave the way for therapeutics to prevent the relapse or metastasis of cancer."

To identify potential cancer stem cells, also known as cancer-initiating cells, the researchers screened a population of human colon cancer cells for molecular markers that differentiated some cells from others. They found a certain subset of cells produced an exceptional amount of CD44 cell surface receptor protein, a well-studied protein involved in many forms of cancer.

According to Chu, to be identified as cancer stem cells, they had to be highly tumorigenic, creating new tumors quickly and from very few starting cells; had to be self-renewing, possessing a capacity to regenerate; and they had to produce tumors similar to the tumor of origin. "These CD44-producing cells fit the bill, although there is evidence to believe that CD44 overexpression is not the sole marker for colon cancer stem cells," said Chu.

Chu and his colleagues discovered that as few as 10 cells producing high amounts of CD44 were capable of creating tumors in an animal model. In contrast, other tumor cells were 10 to 50 times less tumorigenic. The fact that they were tumorigenic at all, the researchers say, indicates that CD44 alone is unlikely to be the sole indicator of stem cell-ness

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among the tumor cell population. However, according to Chu, the discovery that high CD44 producing cells have cancer stem cell properties provides an entry point into further research into cancer-causing stem cells.

BRCA1 regulates human mammary stem cell self-renewal and differentiation: Abstract 5700

Mutations in the well-known breast cancer susceptibility gene BRCA1 have a role in the propagation of aggressive stem cell-driven cancer. The findings, according to researchers at the University of Michigan, offer further evidence that breast cancer treatment strategies require a stronger focus on the stem cells that drive the disease.

"Our lab previously identified the presence of mammary stem cells and, since BRCA1 is such a strong predictor of breast cancer, we were interested in the involvement of the gene in stem cells," said Suling Liu, Ph.D., a researcher at the University of Michigan's Comprehensive Cancer Center. "If mammary stem cells are, indeed, the driving force of breast cancer, then we need to know more about their function if we hope to create more effective therapies."

To investigate the role of the gene in stem cells, the team engineered a lentivirus to carry small interfering RNA segments that, in effect, silence the BRCA1 gene. They then observed how a population of mammary stem cells functioned without the ability to produce BRCA1. When BRCA1 was inhibited, the number of stem cells was increased by 75 percent. These new cells, in turn, produced three times the normal amount of a stem cell marker protein ALDH1.

In an animal model of the disease, the knockdown of the BRCA1 gene increased the number of stem cells, which then propagated in the fatty tissues of the breast.

These studies suggest that loss of BRCA1 function leads to a block in cell differentiation, expanding the stem cell pool. Since BRCA1 also regulates DNA repair, this may then produce genetically unstable stem cells which in turn generate tumors in these women.

According to Liu, the loss of a single BRCA1 gene can lead to stem cell propagation. The researchers believe their findings might lead to better BRCA1 screening in women with a family history of breast cancer.

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