

Stem cells may look malignant, not act it

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Call it the cellular equivalent of big glasses, a funny nose and a fake mustache. Bone marrow stem cells attracted to the site of a cancerous growth frequently take on the outward appearance of the malignant cells around them, University of Florida researchers report in a paper to be published in the August issue of *Stem Cells*.

But whether that enables them to fuel cancer's ability to develop and then spread, as some scientists suspect, is not entirely clear. The findings, available early in this month's online edition of the journal, actually contest the increasingly popular theory that bone marrow stem cells seed cancer. Instead, these cells might simply look like cancer, not act like it.

"They have the same kind of surface proteins," said study author Chris Cogle, M.D., an assistant professor of medicine at the UF's College of Medicine Program in Stem Cell Biology and Regenerative Medicine. "They have the same skin. The next question is 'Do they have the same guts?'

"Our results indicate these cells act as developmental mimics; they come in and look like the surrounding neoplastic tissue, but they aren't actually the seed of cancer," said Cogle, who also is affiliated with the UF Shands Cancer Center. "At the worst, these cells could help support cancerous tissue by providing it with growth factors or proteins that help the cancer grow and survive. At the very least, these marrow cells are just being tricked into coming into the cancerous environment and then made to walk and talk like they don't usually do."



The researchers have coined the term "developmental mimicry" to describe the phenomenon, which could have implications for the integrity of the cell lines scientists use to test new cancer drugs in the lab.

Up to 5 percent of cancerous tissue contains marrow-derived cells that look just like surrounding cancer. So when malignant tissue is grown in the laboratory for experiments that test the effects of new drugs, it's possible the results are muddied, Cogle said. Drugs, if effective, may be targeting the marrow cell mimics, not actual cancer cells.

"If there are bone marrow cells in this cancerous tissue, these cells may actually contaminate our cancer studies and could make a difference as to whether or not investigational drugs we're testing work or don't work," he said. "The significance of this is new treatments may work in the culture dish but may not translate to the clinic or the hospital room, and for many reasons. One of the reasons could be bone marrow contamination."

In their study, UF researchers evaluated two women who underwent bone marrow transplantation and subsequently developed colonic adenomas, four women who developed skin cancer and one who developed lung cancer.

"We questioned where the cancer was coming from — was it really from the patient or could it have been from the donor bone marrow that we transplanted in the patient?" Cogle said.

Each patient received infusions of bone marrow cells from a brother or an unrelated male donor. That enabled physicians to track the transplanted cells by screening for the Y male chromosome.

They found that the cancers were mostly of female origin, but the



malignant tissue often contained small areas of male marrow cells.

"This led us to question the extent the donor marrow was participating in these cancers," Cogle said. "A tumor consists of a mixed bag of cells, not just one solid same-celled block of tissue. What we're trying to study is the role of these marrow-derived cells within the neighborhood of cancer."

The researchers then studied mice who underwent bone marrow transplant and developed the same cancers as the women. When they viewed the cancerous tissues under the microscope, they found marrow cells shared outward features of the cancer cells.

Cogle said research conducted elsewhere suggests marrow cells flock to a cancerous site to help set up a blood vessel-friendly environment that feeds the tumor. The current findings, supported by grants from the National Institutes of Health and the James & Esther King Biomedical Research Program, might be an aftereffect of this supporting role, he said.

UF researchers — who collaborated with scientists from Beth Israel Medical Center at New York's Albert Einstein College of Medicine, Yale University School of Medicine, St. Francis Hospital in Indianapolis and the Penn State Milton S. Hershey Medical Center — are now analyzing whether marrow cells that look like cancer are able to spawn tumors in animals, and whether they harbor the characteristic internal genetic defects of tumor cells.

Some patients who undergo bone marrow transplant later develop secondary cancers because of the high doses of radiation and chemotherapy they receive to prepare them for the procedure, said Mariusz Ratajczak, M.D., Ph.D., director of the Stem Cell Developmental Biology Program at the University of Louisville James



Graham Brown Cancer Center and a member of the journal's editorial board.

"Transplanted cells which are derived initially from the bone marrow can include a population of stem cells which can on one hand do nice things and contribute to regeneration, and on the other hand if something goes wrong, these cells can also contribute to cancer development, of course in very rare cases," Ratajczak said. "This study has very nicely shown that that possibility exists, and it actually describes a new, novel mechanism. Somehow we know these cells contribute to growing tumor. They may not initiate it but they somehow contribute by developmental mimicry to these secondary malignancies."

Source: University of Florida

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