

NEW FINDINGS ON BREAST CANCER REPORTED AT AAAS

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BERKELEY, CA — New experimental findings by Lawrence Berkeley National Laboratory (Berkeley Lab) cell biologist Mary Helen Barcellos-Hoff show that **exposure to ionizing radiation creates a microenvironment in the tissue surrounding breast cells that can cause even nonirradiated cells and their progeny to become cancerous. The discovery suggests new and possibly more effective means for preventing breast cancer.**

Speaking in Boston at the annual meeting of the American Association for the Advancement of Science (AAAS), Barcellos-Hoff described her study in which a special line of nonirradiated, nonmalignant breast cells were transplanted into irradiated mammary glands. Nearly 75 percent of the transplanted glands developed tumors, and the effect persisted up to 14 days after the radiation exposure. Tumors developed in less than 20 percent of the glands when Barcellos-Hoff transplanted the same type of cells into nonirradiated mice.



Mary Helen Barcellos-Hoff, a cell biologist with the Lawrence Berkeley National Laboratory, has shown that exposure to ionizing radiation can cause breast cancer by pathways other than genetic mutations.

"Our studies demonstrate that radiation elicits rapid and persistent global alterations in the mammary gland microenvironment," says Barcellos-Hoff. "We believe that these radiation-induced microenvironments lead to changes in the physical characteristics (phenotypes) of cells and their progeny that promote carcinogenesis. In other words, **radiation exposure can cause breast cancer by pathways other than genetic mutations.**"

Studies by Barcellos-Hoff and her research group indicate that one of these alternative pathways is damage to the tissue that surrounds a breast cell. This surrounding tissue, which includes a network of fibrous and globular proteins called the extracellular matrix (ECM), normally acts to suppress cells from becoming cancerous.

"Repairing damaged tissue so that it once again suppresses instead of promotes carcinogenesis is a simpler strategy for stopping the cancer process, compared to trying to repair individual damaged cells," says Barcellos-Hoff. **"Our data is pointing to the tissue surrounding breast cells as a primary target of ionizing radiation damage."**

Ionizing radiation is a well-established carcinogen, but previous studies of its cancer-causing effects have largely focused on damage to the breast cells' DNA. If repaired improperly, this damage gives rise to genetic mutations or chromosome damage that if passed on to daughter cells leads to cancer. In that context, the question for medical researchers has been: How do cells become cancerous?

Barcellos-Hoff has pursued a different tack. "It takes a tissue to make a tumor," she says. "Cells don't become tumors without cooperation from the surrounding tissue. Cancer is a process that occurs at the tissue level and the question we ought to be asking is: How do tissues become tumors?"

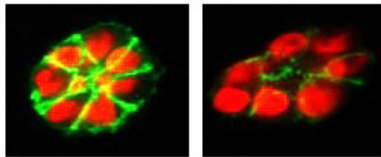
To answer that question, Barcellos-Hoff and her group, which includes postdoctoral fellow Rhonda Henshall-Powell, have focused their attention on the extracellular signaling that takes place between a cell and the microenvironment of its surrounding tissue. Their studies and others have shown that proper communications between the cell and its microenvironment are crucial to normal functioning. The director of Berkeley Lab's Life Sciences Division, Mina Bissell, has shown that breakdown in these communications can initiate the cancer process or cause an abnormally high rate of

apoptosis³/₄programmed cell death³/₄another significant factor in the development of breast and other cancers.

"Ionizing radiation is like a wound, in that it produces a defensive response from the affected tissue. Usually this helps to protect undamaged cells and eliminates those that have become abnormal," Barcellos-Hoff says. "However, if there is too much damage, the defense response can become a problem."

For example, exposure to just the right dose of ultraviolet radiation will cause skin tissue to respond by producing melanin, the protective skin-darkening pigment. Too much exposure at once, however, leads to sunburn, and repeated exposures over time will damage the tissue, causing wrinkles and possibly skin cancer. In the case of mammary glands exposed to low doses of ionizing radiation, the surrounding tissue has been programmed to send signals to the cells that would suppress genomic mutations and cause cell apoptosis. But as the exposure intensifies, the defense program becomes "corrupted" and the wrong signals get transmitted.

"We hypothesize that under certain conditions, radiation exposure prevents normal cell interactions, which in turn predisposes susceptible cells to genomic instability that can result in mutations," Barcellos-Hoff says.



These two images of a special line of breast cells compare nonirradiated cells on the left to irradiated cells on the right. Cell nuclei are dyed red, and E-cadherin, an important cell-to-cell adhesion molecule, is dyed green. The nonirradiated cells adhere together in a tightly organized clump, known as an acini, while the irradiated cells, lacking adhesion, are

disorganized. Berkeley researchers propose that extracellular communication disrupted by the irradiation is the cause.

In their study with cells transplanted into irradiated mammary glands, Barcellos-Hoff and senior research associate Shraddha Ravani exposed specially created epithelium-free glands (mouse epithelium develops postnatally and is readily removed from the gland) to low-level radiation doses (4 grays, or 400 rads). Upon observing the persistent carcinogenic effects on the transplanted cells, they established that the radiation damage to the tissue was generating signals that altered how the cells' genomes were expressed. This resulted in the creation of a new cell phenotype with physical characteristics that were cued by the extracellular signals to act cancerous. Breast cells acquiring the new phenotypes passed these characteristics onto their daughter cells.

"Genomes are like the keys on a piano, in that the same keys can be used to play a wide variety of music," says Barcellos-Hoff. "In our studies, the ionizing radiation elicited changes in how the genomes of the transplanted cells were being expressed by changing the extracellular signals they were receiving."

Barcellos-Hoff and her colleagues now want to identify the altered signals that are being sent from the irradiated tissue to the cells and determine the mechanism by which these signals are destabilizing breast cell genomes. To do so they are using a model of organized human breast cells developed by Bissell.

In her AAAS talk Barcellos-Hoff also discussed the preliminary findings of a study on which she is working in collaboration with Bissell and radiation oncologist Catherine Park. The team has found that irradiated human breast cells also show persistent phenotypic changes that affect their ability to interact with other cells. Such behavior is typical of cancer cells.

Berkeley Lab is a U.S. Department of Energy national laboratory located in Berkeley, California. It conducts unclassified scientific research and is managed by the University of California.