Normal gene hinders breast cancer chemotherapy

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Presence of normal p53, a tumor suppressor gene, instead of a mutated version, makes breast cancer chemotherapy with doxorubicin less effective. The preclinical study led by MD Anderson scientists was published today in the journal *Cancer Cell*.

The research, which challenges the existing paradigm, is another step closer to personalized cancer medicine for breast cancer.

"It's really important to understand the genetic defects a tumor cell has before we treat it," said lead author Guillermina Lozano, Ph.D., professor and chair of the Department of Genetics. "What we learned here is the complete opposite of what we expected. We thought tumors would respond better to treatment if the p53 gene were normal. But the opposite was true, and for a really interesting reason."

Lozano said the research in mouse models showed that non-mutated p53 halted cell division, initiating a senescence (cell aging) process that allowed cells to survive. These senescent cells produce factors that stimulate adjacent cells to grow, fueling the relapse. Mutant p53 cells do not arrest and proceed through the cell cycle into cell division with broken chromosomes caused by the chemotherapy.

"That's a signal for the cell to die," she said. "It can't go any farther."

P53 status crucial to predicting response

The tumor suppressor p53 is mutated or inactivated in the majority of cancers, and about one-third of breast cancers have mutations in the gene. It has long been thought that normal p53 results in a better chemotherapy response, but the evidence in breast cancer has been conflicting.

According to the National Cancer Institute, about 227,000 women in the United States are diagnosed with breast cancer each year.

In this study, doxorubicin-treated p53 mutant tumor cells did not stop cell proliferation, leading to abnormal mitoses and cell death, whereas tumors with normal p53 arrested, avoiding mitotic catastrophe.

"There are a lot of data out there on responses of women to doxorubicin and other drugs that break DNA," Lozano said. "The response rates were mixed, and we never understood the difference. Now we understand that we need to know the p53 status to predict a response."

Results consistent in mouse, human models

The scientists first examined the response to doxorubicin in mice with mammary tumors and the role of p53 in the chemotherapy process. When they analyzed the results, they found the mice that responded poorly to treatment had normal p53 genes, while the mice that responded best had mutated p53 genes.

Using human breast tumor cell lines with normal p53, the researchers then replicated the mouse experiment with the same results. When the cells were treated with doxorubicin, which is known commercially as Adriamycin®, they basically stopped. When the p53 gene was removed, the cells continued through the cell cycle and eventual destruction.

Future research to examine relapse

Lozano said the next piece of the research puzzle involves looking at what happens after breast cancer has been treated successfully but comes back.

"A lot of breast cancer tumors relapse," she said. "We want to find out what additional changes these cells acquire that allow them to bypass the cell death mechanism."

Provided by University of Texas M. D. Anderson Cancer Center