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Findings point to molecular 'Achilles heel' for half of breast cancer tumors

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Researchers at Lombardi Comprehensive Cancer Center at Georgetown University Medical Center have shown why a protein known as cyclin D1 may be the Achilles heel for breast tumors that are estrogen receptor positive (ER+) – which is the most common type of breast cancer.

In the December 10th online edition of the journal *Oncogene*, investigators say the findings support testing an experimental class of drugs that aim to inhibit the cyclin D1 protein in women with ER+ breast cancers. These agents are currently being tested in this disease as well as in many other types of cancer, the researchers say, and the study provides additional molecular support for their use in breast cancer.

“Everyone knows that cyclin D1 is a huge player in breast cancer, but no one has shown what happens when cyclin D1 is absent at the same time that the estrogen receptor is being over-expressed on tumors. Now we know the answers, and we hope these insights help further our understanding and treatment of breast cancer,” said the study’s lead author, Maria Silvina Frech, Ph.D., who is currently a postdoctoral researcher at the National Cancer Institute but who worked on the study at Georgetown.

“These findings give insight into how drugs that indirectly inhibit cyclin D1 function, either those in testing or ones to be developed, might help a significant number of women with breast cancer,” said Priscilla Furth, M.D., a professor at the Lombardi Comprehensive Cancer Center who is the study’s senior investigator.

Cyclin D1 belongs to a family of cyclin genes whose proteins regulate cyclin-dependent kinases (CDKs), which in turn control cell division. CDKs are the main facilitators of cell proliferation cycle. Over-production of the Cyclin D1 protein or amplification (extra copies) of the gene have been observed in a number of cancers, and this study continued a body of research in Furth's lab that has examined the relationship between ER+ breast cancer and cyclin D1.

In 2005 Furth and Frech published a study that demonstrated that over expression of ER[alpha] (the main estrogen receptor subtype that mediates cell growth and is the major player in ER+ breast cancer) in mice resulted in the development of the earliest form of breast cancer, ductal carcinoma in situ (DCIS). They then found that cyclin D1 was over expressed in these lesions but not in the surrounding normal tissue. "Once the cancer process begins, cyclin D1 starts being over-expressed," Frech said. "This was an exciting finding, but it was not clear what the precise role cyclin D1 plays in ER+ cancer."

To find out what the protein was doing in these breast tumors, Frech, Furth, Kathleen Torre, B.S., from Georgetown and Gertraud W Robinson, Ph.D. from NIDDK, NIH, decided to take a genetics approach to the problem. They created an animal model that both over-expressed ER[alpha] and lacked cyclin D1.

They thought they would see a decreased incidence in DCIS in the animals, but what they actually found was that they completely lacked the mammary gland tissue that normally encases breast milk ducts. "This was very surprising. Most of the cells that usually make up the gland were absent, replaced by other structural tissue that shouldn't be there," she said.

It was also puzzling, Frech said, because puberty-induced mammary gland development in female mice that simply lack cyclin D1 is

essentially normal. It made no sense to researchers that coupling over expression of ER[alpha] with the absence of cyclin D1 would have a complete lack of mammary glands. “This was striking, very unusual,” she said.

The solution was also very challenging, said Frech, whose three years of work on the project earned her a Ph.D. They eventually found that when cyclin D1 is deleted, levels of another major cyclin family member – cyclin E – are increased. And over-production of cyclin E, in the developing gland of these ER[alpha] over expressing mice led to DNA damage and cell death. The question that remains unanswered is whether this situation would hold true in advanced cancers treated with agents that inhibit cyclin D1 function, she said.

They also discovered that while cyclin D1 was not necessary for maintenance of normal breast cells, it was essential for the proliferation of abnormal mammary gland cells – and this differential use of cyclin D1 seems to be unique to early breast cancer. “That supports the idea that reducing cyclin D1 in breast cancer cells would not harm normal cells,” she said. There are experimental agents now being tested in clinical trials that shut down cyclin D1 function by targeting CDKs, Frech said. For example, flavopiridol is a potent CDK inhibitor currently undergoing clinical trials for a variety of tumors including breast cancer. Clinical activity is encouraging when used in combination with other molecular targeted agents, she said.

Source: Georgetown University Medical Center