Researchers describe how breast cancer cells acquire drug resistance

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A seven-year quest to understand how breast cancer cells resist treatment with the targeted therapy lapatinib has revealed a previously unknown molecular network that regulates cell death. The discovery provides new avenues to overcome drug resistance, according to researchers at Duke Cancer Institute.

"We've revealed multiple new signaling pathways that regulate cell death," said Sally Kornbluth, PhD, vice dean of Basic Science and professor of Pharmacology and Cancer Biology at Duke University School of Medicine. "And we've shown, at least in one disease, these signaling pathways can go awry in drug resistance. It also suggests you could manipulate these other pathways to overcome drug resistance."

The researchers—co-directed by Kornbluth and Neil Spector, M.D., associate professor of medicine at Duke—identified a protein that effectively shuts down the signals that tell a cell to die, enabling cancer cells to keep growing. That protein, MDM2, is already generating intense interest in the cancer research community because it is a master regulator of the tumor suppressor protein called p53.

Findings are published in the May 7, 2013, issue of the journal *Science Signaling*.

The Duke research team, with assistance from collaborators at the University of Michigan, identified a new role for MDM2 in activating cell death pathways independent of its role in regulating p53, a known

initiator of cell death. More than half of all human tumors contain a mutation or deletion of the gene that controls p53.

The researchers began by studying four different types of breast cancer cells that were able to keep growing despite treatment with lapatinib, a powerful drug that targets two growth pathways commonly disrupted in breast cancer, HER2 and epidermal growth factor receptor. They found that in each case, the drug resistance could be traced to the presence of high levels of MDM2, which was found to be blocking cell death signals independent of whether p53 was activated.

"These results suggest that inhibition of MDM2, at least in the setting of breast cancer, might overcome lapatinib resistance even if p53 is mutated," Kornbluth said.

Spector and his colleagues first reported the activation of estrogen receptor signaling, which led to FDA-approval of lapatinib in combination with letrozole as a first-line treatment for advanced-stage HER2-positive and estrogen receptor-positive breast cancers. Researchers at Duke, including the Spector laboratory, and other investigators have worked to identify various mechanisms of lapatinib resistance.

"The importance of this new MDM2 finding is that it may underlie these proposed mechanisms of resistance and therefore provide a more effective treatment," Spector said.

The findings also suggest that other drugs targeting tyrosine kinases may be vulnerable to resistance using this same mechanism. Gefitinib is a targeted cancer therapy that blocks a tyrosine kinase enzyme to treat non-small cell lung cancers caused by mutations in the epidermal growth factor receptor.

"This study raises the possibility that resistance to other tyrosine kinase inhibitor drugs, such as gefitinib-resistant lung cancer, could involve MDM2," Kornbluth said. "We are now going to investigate whether MDM2 has anything to do with gefitinib resistance."

The lead author of the paper, Manabu Kurokawa, is now an assistant professor at Dartmouth University. Other authors of the paper include Jiyeon Kim, Joseph Geradts, Kenkyo Mastuura, Wenle Xia, Thomas J. Ribar, Ricardo Henao, Neil L. Spector, Mark W. Dewhirst, and Joseph E. Lucas of Duke; Wun-Jae Kim of Chungbuk National University Hospital; and Shaomeng Wang, Liu Liu, and Xu Ran of the University of Michigan.

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The authors have filed a patent application based on this work. Shaomeng Wang owns stocks and is a consultant for Ascenta, and is a co-inventor on MI-219 and related MDM2 inhibitors. Ascenta has licensed MI-219 and related MDM2 inhibitors from the University of Michigan to Sanofi for clinical development.

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