

Turncoat protein regulates sensitivity of breast cancer cells to drug

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Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

A surprising, paradoxical relationship between a tumor suppressor molecule and an oncogene may be the key to explaining and working around how breast cancer tumor cells become desensitized to a common cancer drug, found researchers at the Perelman School of Medicine at the University of Pennsylvania. The drug, lapatinib, activates the suppressor called FOXO, in HER2+ breast cancer cells, but then FOXO becomes a turncoat molecule, working with an epigenetic regulator that controls gene expression. This drug-triggered relationship induces the expression of the oncogene c-Myc, leading to reduced sensitivity to the cancer drug and eventually relapse. They published their cover article today in *Cancer Cell*.

"We found that an epigenetic [pathway](#) is crucial for growth of HER2+ cells and this epigenetic factor reduces sensitivity of the [cancer cells](#) to lapatinib, a HER2 inhibitor," said senior author Xianxin Hua, MD, PhD, a professor of Cancer Biology. "We need to understand how the body initially responds to these drugs and why there is a relapse and devise a new tool to fix that."

Human epidermal growth factor receptor 2 (HER2) is upregulated in a subset of human breast cancers. The HER2 pathway is mutated in many cancers, which drives tumors, but inhibitors of this pathway, such as lapatinib, have only limited success because [cancer](#) cells quickly adapt.

FOXO was normally thought of as the "good guy" molecule that controls cancerous cell growth, while c-Myc, the cancer-promoting molecule, the "bad guy." However, FOXO becomes the agent that desensitizes cells to cancer drugs, so this "good guy" molecule is converted to a "bad guy," during the treatment of the cancer cells with the anti-cancer drug.

"Now that we know about this triangle among FOXO, c-Myc, and the epigenetic pathway, we can stop c-Myc with an epigenetic inhibitor," Hua said. "Multiple epigenetic regulators participate in the drug-

desensitizing pathway, so they could serve as new targets to improve therapy for this type of cancer."

The findings uncovered an adaptation pathway comprising the normally antagonizing [molecules](#) FOXOs and c-Myc, which are regulated by epigenetic compounds. Unraveling this complex interaction now gives researchers another point in the HER2 cancer pathway to hit.

Provided by University of Pennsylvania School of Medicine

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