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Team discovers new inhibitors of estrogen-dependent breast cancer cells

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Researchers have discovered a new family of agents that inhibit the growth of estrogen-dependent breast cancer cells. The finding, described today at a meeting of the Endocrine Society, has opened an avenue of research into new drugs to combat estrogen-dependent breast cancers.

"This cell-based study is exciting because it suggests these compounds are likely to be effective in tumors that remain dependent on estrogen for growth but are resistant to current therapies," said principal investigator David J. Shapiro, a professor of biochemistry in the School of Molecular and Cellular Biology at the University of Illinois.

Although multiple factors contribute to the development of breast cancer, estrogens play a key role in the growth of many tumors. More than 80 percent of breast cancer tumors in women over age 45 are activated by estrogen by way of a protein called an estrogen receptor. When estrogen binds to the receptor, this "estrogen-receptor complex" latches on to DNA and prompts it to transcribe the RNA blueprints for new proteins that promote cell growth, migration and division.

Current therapies for estrogen-receptor-positive (ER-positive) breast cancers include the use of drugs, such as tamoxifen, that interfere with estrogen's ability to bind to the estrogen receptor. Over time, however, ER-positive breast cancer tumors become resistant to tamoxifen. In some resistant tumors, tamoxifen even begins to act like estrogen and actually stimulates tumor growth.

"Tamoxifen is useful in that it is very effective at blocking recurrence of breast cancer in patients for whom the entire tumor is removed," Shapiro said. "But for patients who still have existing tumors, eventually those tumors will become resistant."

Shapiro's team sought to target other steps in the pathway of estrogen action. Using a technique they developed that can quickly determine whether the target DNA is – or is not – bound by the estrogen-receptor complex, the team was able to screen a long list of potential therapeutic compounds to see if they inhibited the binding of the complex to the DNA. They then tested these agents in ER-positive breast cancer cells.

The team identified several compounds that reduce the binding of estrogen-receptor complex to the regulatory regions of genes that are normally activated by this complex. These agents effectively retarded production of the proteins that promote the growth and proliferation of ER-positive breast cancer cells.

"These small molecules specifically block growth of estrogen-dependent breast cancer cells with little or no effect on other cells," Shapiro said. "This work sets the stage for further development and testing of these inhibitors."

Source: University of Illinois at Urbana-Champaign