Herceptin effective in breast cancer cells with low HER-2 levels

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Northwestern University researchers have discovered that the monoclonal antibody Herceptin (trastuzumab) used in combination with certain cancer chemotherapies effectively treats breast cancer tumors that produce low or undetectable amounts of the HER-2 oncogene but overexpress the growth factor heregulin (HRG), an activator of the HER-2 cancer oncoprotein. Increased levels of HER-2 are associated with poor patient prognosis, enhanced metastasis (cancer spread) and resistance to chemotherapy.

Until now it was believed that trastuzumab combined with cytotoxic drug therapy was effective only in HER-2--positive, or HER-2--overexpressing, breast cancer – which represents about 25 percent of all breast cancers, said Dr. Ruth Lupu, director of Evanston Northwestern Healthcare Breast Cancer Program, who led the study, published in the August 10 issue of the *Journal of Clinical Oncology*.

Lupu is also professor of medicine at Northwestern University Feinberg School of Medicine and a researcher at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The study was conducted as part of the Cancer Center's breast cancer SPORE (Specialized Program of Research Excellence) grant.

In their study Lupu and colleagues Javier A. Menendez and Inderjit Mehmi of the Evanston Northwestern Healthcare Research Institute found that HER-2 must be activated to exert its malignant effects.

HER-2 is capable of being activated by either overexpression (overproduction) or transactivation -- when a protein at one location is activated by the presence of a particular protein at another location.

HRG is an activator of the HER-2 oncogene, promoting breast cancer growth and tumor formation in laboratory models. Dr. Lupu has previously shown that blocking HRG expression inhibits tumor growth and spread of breast cancer cells. HRG is expressed in a significant proportion of human breast cancer biopsies and correlates with poor prognosis.

Lupu and her laboratory group discovered that continuous production of HRG in breast cancer cells that do not overexpress HER-2 causes the receptor to be continuously activated and therefore constantly signals breast cancer cells to grow and proliferate.

Previous clinical studies have shown that trastuzumab used in combination with such cancer chemotherapy drugs as cisplatin, Taxol (paclitaxel), docetaxel, vinorelbine and cyclophosphamide in HER-2--positive breast tumors is more beneficial than the antibody used alone. This effect, termed receptor-enhanced chemosensitivity (REC), was thought to target only HER-2--overexpressing cells but seemingly had no impact on cells expressing low amounts of HER-2 protein.

In the current study, the researchers used breast cancer cells genetically engineered to produce HRG to determine if HRG-induced activation of HER-2 can cause the same biologic responses as HER-2 overexpression with regards to sensitivity to chemotherapeutic drugs, such as cisplatin and paclitaxel.

They found that overexpression of HRG promotes resistance to cisplatin-induced cell death, while co-treatment of the genetically engineered cells with trastuzumab or cisplatin produced a synergistic apoptotic (cell-

killing) effect. They also found that this synergy occurred with trastuzumab and either paclitaxel or vincristine.

"Our data not only confirm that a considerable potentiation of chemotherapy efficacy occurs when combined with trastuzumab but further demonstrate that an REC effect, which has been suggested to specifically target cancer cells bearing HER-2 overexpression and has no effect on cells expressing low levels of HER-2, is equally pronounced in HRG expression and induces activation of HER-2 occurring in the absence of HER-2 overexpression," the authors said.

Results of their study also support the view that trastuzumab blocks the effect of HER-2--driven activation of anti-apoptotic and proliferative cascades in breast cancer cells exhibiting HRG-dependent--activation of HER-2. Conversely, in the absence of HRG, trastuzumab promotes this effect in cells producing low amounts of the HER-2 protein.

Further, the group's findings strongly support the idea that measuring the activity of HER-2 on the surface of breast cancer cells maybe a better – and earlier – marker for breast cancer progression than simply determining the level of HER-2 production in malignant tumor cells. Moreover, profiling tumors for the expression of HRG maybe of tremendous benefit for those patients whose tumors express low levels of HER-2 protein.

Source: Northwestern University