Genistein, a specific inhibitor of tyrosine-specific protein kinases.

Akiyama T, **Ishida J**, **Nakagawa S**, **Ogawara H**, **Watanabe S**, **Itoh N**, **Shibuya M**, **Fukami Y**.

Tyrosine-specific protein kinase activity of the epidermal growth factor (EGF) receptor, pp60v-src and pp110gag-fes was inhibited in vitro by an isoflavone genistein. The inhibition was competitive with respect to ATP and noncompetitive to a phosphate acceptor, histone H2B. By contrast, genistein scarcely inhibited the enzyme activities of serine- and threonine-specific protein kinases such as cAMP-dependent protein kinase, phosphorylase kinase, and the Ca2+/phospholipid-dependent enzyme protein kinase C. When the effect of genistein on the phosphorylation of the EGF receptor was examined in cultured A431 cells, EGF-stimulated serine, threonine, and tyrosine phosphorylation was decreased. Phosphoamino acid analysis of total cell proteins revealed that genistein inhibited the EGF-stimulated increase in phosphotyrosine level in A431 cells.

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Genistein affects HER2 protein concentration, activation, and promoter regulation in BT-474 human breast cancer cells.

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The HER2 proto-oncogene, a member of the epidermal growth factor receptor family, is overexpressed in 20-30% of breast cancers. Genistein, the main soy isoflavone, interacts with estrogen receptors (ER) and it is also a potent tyrosine kinase inhibitor. Previously, our laboratory found that genistein delayed mammary tumor onset in transgenic mice that overexpress HER2 gene. Our goal was to define the mechanism through which genistein affects mammary tumorigenesis in HER2 overexpressing mice. We hypothesized that genistein inhibits HER2 activation and expression through ER-dependent and ER-independent mechanisms. Genistein inhibited total HER2 protein expression and tyrosine phosphorylation in BT-474, an ERalpha (-) and ERbeta (+) human breast cancer cell line, however, E2 had no effect. Taken together, these data suggest that genistein has an ER-independent inhibitory effect, presumably, through tyrosine kinase inhibition activity.

Genistein at 1.0 microM mimicked E2 and down-regulated HER2 protein phosphorylation when BT-474 was co-transfected with ERalpha, but not ERbeta. Although E2 and overexpression of HER2 can promote mammary tumorigenesis, an inverse relationship between ER expression and HER2 overexpression has been found in human breast cancer. We cloned a 500-bp promoter region upstream of the HER2 transcription initiation site. Co-transfection with ERalpha, but not with ERbeta, down-regulated HER2 promoter reporter in BT-474. At concentrations > or =1 microM, genistein inhibited HER2 promoter reporter in the absence of ERalpha. In conclusion, genistein at > or =1 microM inhibited HER2 protein expression, phosphorylation, and promoter activity through an ER-independent mechanism. In the presence of ERalpha, genistein mimicked E2 and inhibited HER2 protein phosphorylation. These data support genistein's chemo-prevention and potential chemo-therapeutic roles in breast cancer.

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Abstract

Objective our previous studies have demonstrated that HER-2/neu gene expression in human breast cancer MCF-7 cells promotes angiogenesis in MCF-7 cells xenograft tumors, and genistein inhibits angiogenesis in MCF-7 cells with HER-2/neu expression xenograft tumors. Here, the effects of genistein on the expression of vascular endothelial growth factor (VEGF) in MCR-7 cells with HER-2/neu expression were further studied for exploring the molecular mechanism of anti-angiogenesis in HER-2/neu-overexpressing breast cancer by genistein.

Methods HER-2/neu-overexpressing MCF-7 cells (MCF-7/HER-2) were established by transfecting HER-2/neu gene into HER-2/neu negative expression breast cancer MCF-7 cells. Immunocytochemical staining, western blot and reverse transcription-polymerase chain reaction (RT-PCR) were adopted to measure the expression of VEGF in MCF-7/HER-2 cells treated by genistein for 24, 48 and 72h.

Results HER-2/neu expression up-regulated VEGF mRNA and protein in MCF-7 cells, genistein decreased VEGF mRNA and protein level in MCF-7/HER-2 cells in a time-dependent manner.

Conclusion These results suggest that VEGF plays an important role in HER-2/neu gene expression promoted antiogenesis in breast cancer and genistein induced down-regulation of the expression of VEGF may be one of the molecular mechanisms of its anti-angiogenesis in HER-2/neu-overexpressing breast cancer.

Genistein is a major component of soybean isoflavone and has preventive effect against breast cancer. In breast cancer, the over-expression of HER-2 contributes to malignant transformation of the cancer cells. The present study was undertaken to estimate if genistein could act as a useful anti-cancer agent against

a breast cancer cell overexpressing HER-2 in combination with a conventional chemotherapy agent, adriamycin (ADR). Genistein enhanced cytotoxic effect of ADR at low doses less than IC50 against the human breast cancer cell. The enhancing effect was mainly dependent on the elevation of necrotic-like cell death but not apoptotic cell death. In conjugation with this event, remarkable inactivation of HER-2 and Akt in the breast cancer cell was caused by the combination of genistein and ADR. These results suggest that genistein enhances necrotic-like cell death of the breast cancer cells through the inactivation of HER-2 receptor and Akt in combination with ADR.

Breast Cancer Treatment Can Be Undermined By The Dietary Supplement Genistein

Main Category: Breast Cancer
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Women taking aromatase inhibitors to treat breast cancer or prevent its recurrence should think twice before also taking a soy-based dietary supplement, researchers report.

Genistein, a soy isoflavone that mimics the effects of estrogen in the body, can negate the effectiveness of aromatase inhibitors, which are designed to reduce the levels of estrogens that can promote tumor growth in some types of breast cancer.

The new study, which included researchers from the University of Illinois, Virginia Polytechnic and State University and the National Center for Toxicological Research, appears in the journal *Carcinogenesis.*

Aromatase inhibitors are a mainstay of breast cancer treatment in post-menopausal women. These drugs work by interfering with the enzyme aromatase, which catalyzes a crucial step in converting precursor molecules to estradiol, the main estrogen in the body.

About two-thirds of all cases of breast cancer diagnosed in the U.S. are estrogen dependent or estrogen sensitive, which means that the tumors grow more rapidly in the presence of estrogen.

Most women diagnosed with breast cancer are post-menopausal, so their ovaries are no longer producing normal levels of estrogen. Other tissues, however, produce a steroid hormone,

androstenedione (AD), which - with the help of aromatases - is converted to testosterone and estrogens. The estrogens produced from AD can stimulate the growth of some types of breast cancer tumors.

The researchers conducted several trials in a mouse model of estrogen-dependent post-menopausal breast cancer. First, they gave the mice AD, which was converted to estrogen and created a high estrogen environment.

This helped the researchers determine the maximum growth rate of the breast cancer tumors.

Next, they added Letrozole, an aromatase inhibitor widely prescribed to post-menopausal women with estrogen-dependent breast cancer. This treatment (Letrozole) effectively blocked the effects of AD and the breast cancer tumors stopped growing.

But when they added genistein (a plant estrogen or "phytoestrogen" present in many dietary supplements) to the mix, the researchers observed a dose-dependent reduction in the effectiveness of the breast cancer drug. Specifically, the tumors began to grow again. They grew fastest at the highest dietary doses of genistein.

"To think that a dietary supplement could actually reverse the effects of a very effective drug is contrary to much of the perceived benefits of soy isoflavones, and unsettling," said William Helferich a professor of food science and human nutrition at Illinois and principal investigator on the study. "You have women who are taking these supplements to ameliorate post-menopausal symptoms and assuming that they are as safe as consuming a calcium pill or a B vitamin."

Many women take genistein supplements to control hot flashes and other symptoms of menopause. The researchers found that the doses commonly available in dietary supplements were potent enough to negate the effectiveness of aromatase inhibitors.

"These compounds have complex biological activities that are not fully understood," Helferich said. "Dietary supplements containing soy-based phytoestrogens provide high enough dosages that it could be a significant issue to breast cancer patients and survivors."

Plant estrogens from soy are not the only ones of concern, Helferich said. In a recent study, he and his colleagues found that certain mixtures of estrogenic botanical components and extracts marketed as supplements to assist "female libido enhancement" and sold without a prescription appeared to spur breast cancer tumor growth at low doses, while having no effect on tumors at high doses.

That study appeared last year in *Food and Chemical Toxicology.*

"We are just starting to understand the complex effects of the dietary supplements that contain phytoestrogens," Helferich said. "There is an ongoing human experiment in which the outcome is unknown. These findings raise serious concerns about the potential interaction of the estrogenic dietary supplements with current breast cancer therapies."

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Source: Diana Yates
University of Illinois at Urbana-Champaign