Title

The Role Of ERα, ERβ And Phytoestrogens From Soy In P53- Mediated Response To Dna Damage In Mammary Epithelium

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Abstract

Estrogenic compounds can stimulate proliferation of the mammary epithelium, but also potentiate the activity of the p53 tumor suppressor protein. These contradictory activities of estrogenic compounds in mammary tissues may be mediated through activation of two estrogen receptor (ER) subtypes, ERα and ERβ. The following experiments were conducted to examine the roles of these receptors in regulating p53 activity in the mammary epithelium *in vivo* and *in vitro* .

Selective agonist for ERα (PPT) and ERβ (DPN) were compared with 17β-estradiol to examine the roles of ERα and ERβ in potentiating p53 activity, radiation-induced apoptosis and proliferation in ovariectomized mice. DPN was sufficient to potentiate p53-dependent apoptosis in the mammary epithelium following irradiation without inducing proliferation. DPN was also 2.5-fold more potent in stimulating expression of *Egr1* , a modulator of p53 activity. Introduction of ERβ into MCF-7 cells increased in the transcriptional activity of p53. As radiation-induced apoptosis was diminished in mice lacking ERβ (BERKO) mice, ERβ appears necessary for optimal activity of p53 in the mammary epithelium. The ability of DPN to maximally stimulate responsiveness of p53 to ionizing radiation in the absence of proliferation suggests that ERβ agonists may be an effective adjuvant therapy.

Phytoestrogens are estrogenic compounds that are abundant in soy-based products, a key component in Asian diet associated with reduced breast cancer incidence in Asian women, and are preferential ligands for ERβ. However, the effects of soy differ greatly depending on the form and doses administered. Therefore, the effects of water-soluble extracts of non-fermented and fermented soy (NFSE and FSE, respectively) were compared. At physiological relevant doses both NFSE and FSE inhibited proliferation of cell lines from normal breast epithelium (76N-TERT) and breast cancers (21MT-1,MDA-MB-231). The FSE also increased the tumor-free survival of mice bearing xenografts of MDA-MB-231 cells. However, these effects of soy extracts were independent of both p53 and ERα. As both p53 and ERα are commonly lost in breast tumors, the pathways by which soy extracts antagonize tumor growth could provide valuable therapeutic

targets for the treatment and prevention of breast tumors.

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