May 8th, 12:30 PM - 1:30 PM

Estrogen receptor beta selectively restricts proliferation and favors surveillance in mammary epithelial cells

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Et al.

Title: Estrogen receptor beta selectively restricts proliferation and favors surveillance in mammary epithelial cells

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Abstract:

Estrogen (17β-estradiol) has paradoxical effects in both promoting and preventing breast cancer as estrogen activates proliferation, but also promotes p53-mediated surveillance pathways. Estrogen mediates its effects in target tissues through the activation of estrogen receptor subtypes: ERα and ERβ. To examine the capability of these receptors in mediating surveillance as opposed to proliferation, selective estrogen receptor agonists were compared with 17β-estradiol for induction of proliferation and radiation induced apoptosis *in vivo*. Transcriptional regulation of estrogen-responsive genes was also compared in mouse mammary epithelium *in vivo* and in the human mammary MCF7 cell line transduced with a repressible ERβ. Selective activation of ERβ with the agonist diarylpropionitrile (DPN) *in vivo* enhances p53-mediated apoptosis in the mouse mammary epithelium without stimulating proliferation. In addition, radiation-induced apoptosis is significantly reduced in mice lacking ERβ (βERKO). As expected, 17β-estradiol or selective activation of ERα with pyrazole triol (PPT) induced the expression of estrogen-response genes including progesterone receptor, amphiregulin and trefoil factor 1. DPN and ERβ failed to induce the expression of these genes. Interestingly, the ERβ agonist DPN selectively induced the expression of genes that repress proliferation including TGFβ2 while inhibiting proliferative canonical wnt signaling via beta-catenin by inducing WNT5a and AXIN2. DPN was also more potent in stimulating the expression of EGR1, a modulator of p53 activity. These results suggest that ERα and ERβ have distinct roles in gene regulation. In addition, the ability of DPN and ERβ to potentiate surveillance pathways while limiting proliferation suggests that ERβ agonists may have therapeutic and chemopreventive value in breast cancer.