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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.

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Dunphy KA, Roman-Perez E, Hooshyar R, Hagen MJ, Roberts AL, Guerrero-Zayas MI, Jerry DJ. (2013). Estrogen receptor beta selectively restricts proliferation and favors surveillance in mammary epithelial cells. UMass Center for Clinical and Translational Science Research Retreat. Retrieved from https://escholarship.umassmed.edu/cts_retreat/2013/posters/61

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

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Abstract:

Estrogen (17 β -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: ER α and ER β . To examine the capability of these receptors in mediating surveillance as opposed to proliferation, selective estrogen receptor agonists were compared with 17 β -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 ER β . Selective activation of ER β 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 ER β (β ERKO). As expected, 17 β -estradiol or selective activation of ER α with pyrazole triol (PPT) induced the expression of estrogen-response genes including progesterone receptor, amphiregulin and trefoil factor 1. DPN and ER β failed to induce the expression of these genes. Interestingly, the ER β agonist DPN selectively induced the expression of genes that repress proliferation including TGF β 2 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 ER α and ER β have distinct roles in gene regulation. In addition, the ability of DPN and ER β to potentiate surveillance pathways while limiting proliferation suggests that ER β agonists may have therapeutic and chemopreventive value in breast cancer.