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

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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: ER\textsubscript{α} and ER\textsubscript{β}. 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 \textit{in vivo}. Transcriptional regulation of estrogen-responsive genes was also compared in mouse mammary epithelium \textit{in vivo} and in the human mammary MCF7 cell line transduced with a repressible ER\textsubscript{β}. Selective activation of ER\textsubscript{β} with the agonist diarylpropionitrile (DPN) \textit{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\textsubscript{β} (\textit{β}ERKO). As expected, 17β-estradiol or selective activation of ER\textsubscript{α} with pyrazole triol (PPT) induced the expression of estrogen-response genes including progesterone receptor, amphiregulin and trefoil factor 1. DPN and ER\textsubscript{β} failed to induce the expression of these genes. Interestingly, the ER\textsubscript{β} agonist DPN selectively induced the expression of genes that repress proliferation including TGF\textsubscript{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\textsubscript{α} and ER\textsubscript{β} have distinct roles in gene regulation. In addition, the ability of DPN and ER\textsubscript{β} to potentiate surveillance pathways while limiting proliferation suggests that ER\textsubscript{β} agonists may have therapeutic and chemopreventive value in breast cancer.