Poster #17

Xenoestrogen Action in Breast Cancer: Impact on ER-dependent Transcription and Mitogenesis

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The incidence of breast cancer in post-menopausal women continues to rise. This parallels increasing exposure to xenoestrogens known to activate the estrogen receptor (ER) in the absence of estradiol. Delineating the impact of these agents on breast cancer growth and treatment is of significant importance. We examined the effect of two xenoestrogens (bisphenol-A and coumestrol) on ER activation and ER-dependent mitogenesis. We show that the ability of these agents to induce mitogenesis is restricted to conditions of estrogen depletion and these agents fail to cooperate with estradiol to induce growth. These observations are consistent with the impact of each agent on ER activation, wherein the xenoestrogens activate the receptor in the absence of estradiol but fail to cooperate with estradiol. Xenoestrogen-mediated ER activation is blocked by tamoxifen, indicating that exposure to these agents should not disrupt such therapeutic intervention. The response of tumor-derived ER alleles to xenoestrogens was examined. ER-D351Y demonstrated an enhanced response to bisphenol-A versus coumestrol and a differential response to tamoxifen in the presence of these agents. Lastly, we examined the impact of co-activator overexpression (such as occurs in tumor progression) on xenoestrogen response. Bisphenol-A and coumestrol exhibited differential responses to co-activators with regard to ER activation. However, when using mitogenesis as an endpoint, co-activators failed to provide significant growth advantage with different ligand, highlighting the disparity between co-activator function with regard to ER activation and ER-dependent mitogenesis. Combined, these data confirm that xenoestrogens impact ER activity and ER-dependent proliferation in breast cancer cells, but the influence of these agents is restricted to conditions of estrogen depletion, selective mutation of the ER, and overexpression of selected co-activators.

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