

Public Abstract

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Title:CHARACTERIZATION OF SF-hERRb REPRESSION OF HUMAN ESTROGEN RECEPTOR ALPHA AND ESTROGEN RECEPTOR-BETA TRANSCRIPTIONAL ACTIVITIES

Discovery of new ways to modulate estrogen actions through estrogen receptor is always exciting because of the importance of estrogen and ERs in many human diseases. In this dissertation, we report our discovery of the cross-talk between SF-hERRb and hERs and the mechanism of this cross-talk. We found that SF-hERRb is able to repress the transcriptional activities of hERa and hERb in various cell lines. This inhibitory effect of SF-hERRb is not through alterations of estradiol binding to hERs. SF-hERRb does not inhibit hERs through direct Estrogen Response Element (ERE) competition. SF-hERRb induces no alterations in hERs protein concentrations. SF-hERRb inhibition of hERs is not through competition/sequestration for PGC-1a, though PGC-1a can be involved. The A/B domain of hERa and the A/B and D domains of SF-hERRb are required for this inhibition. We determined that SF-hERRb forms complexes with hERa/hERb. In addition, DY131, a hERRbeta/hERRgamma specific agonist can inhibit hER and SF-hERRb positive human breast cancer MCF-7 cell growth. These findings provide us novel approaches to regulate hERs activities which may lead to discovery of new therapeutic targets for ER-dependent diseases.