CHARACTERIZATION OF SF-hERR\(\beta\) REPRESSION OF HUMAN ESTROGEN RECEPTOR ALPHA AND ESTROGEN RECEPTOR-BETA TRANSCRIPTIONAL ACTIVITIES

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ABSTRACT

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-hERR\(\beta\) and hERs and the mechanism of this cross-talk. We found that SF-hERR\(\beta\) is able to repress the transcriptional activities of hER\(\alpha\) and hER\(\beta\) in various cell lines. This inhibitory effect of SF-hERR\(\beta\) is not through alterations of estradiol binding to hERs. SF-hERR\(\beta\) does not inhibit hERs through direct Estrogen Response Element (ERE) competition. SF-hERR\(\beta\) induces no alterations in hERs protein concentrations. SF-hERR\(\beta\) inhibition of hERs is not through competition/sequestration for PGC-1\(\alpha\), though PGC-1\(\alpha\) can be involved. The A/B domain of hER\(\alpha\) and the A/B and D domains of SF-hERR\(\beta\) are required for this inhibition. We determined that SF-hERR\(\beta\) forms complexes with hER\(\alpha\)/hER\(\beta\). In addition, DY131, a hERR\(\beta\)/hERR\(\gamma\) specific agonist can inhibit hER and SF-hERR\(\beta\) 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.