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Mechanisms of Inhibitory Ah Receptor-Estrogen Receptor Crosstalk in Breast Cancer Cells

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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and other aryl hydrocarbon (AhR) ligands suppress 17 β -estradiol (E)-induced responses in the rodent uterus and mammary tumors and in human breast cancer cells. Treatment of ZR-75, T47D and MCF-7 human breast cancer cells with TCDD induces proteasome-dependent degradation of endogenous estrogen receptor α (ER α). The proteasome inhibitors MG132, PSI and PSII ablate the proteasome-dependent effects induced by TCDD, whereas the protease inhibitors EST, calpain inhibitor II and chloroquine do not affect this response. ER α levels in the mouse uterus and breast cancer cells were significantly lower after cotreatment with E+TCDD than after treatment with E or TCDD alone, and our results indicate that AhR-mediated inhibition of E-induced transactivation is mainly due to limiting levels of ER α in cells cotreated with E+TCDD. TCDD alone or in combination with E increases formation of ubiquitinated forms of ER α , and both coimmunoprecipitation and mammalian two hybrid assays demonstrate that TCDD induces interaction of the AhR with ER α in the presence or absence of E. In contrast, E does not induce AhR-ER α interactions. Thus, inhibitory AhR-ER α crosstalk is linked to a novel pathway for degradation of ER α in which TCDD initially induces formation of a nuclear AhR complex which coordinately recruits ER α and the proteasome complex resulting in degradation of both receptors. We have also used the AhR as a drug target and the effects of selective AhR modulators (SAhRMs) as anticancer agents will be described.

References

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