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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 17β-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 (ERα). 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. ERα 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 ERα in cells cotreated with E+TCDD. TCDD alone or in combination with E increases formation of ubiquitinated forms of ERα, and both communoprecipitation and mammalian two hybrid assays demonstrate that TCDD induces interaction of the AhR with ERα in the presence or absence of E. In contrast, E does not induce AhR-ERα interactions. Thus, inhibitory AhR-ERα crosstalk is linked to a novel pathway for degradation of ERα in which TCDD initially induces formation of a nuclear AhR complex which coordinately recruits ERα 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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