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## Regulation of Aryl Hydrocarbon Receptor Expression in Breast Carcinoma Cells

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Both xenobiotic and endogenous estrogens have been implicated as risk factors in breast cancer development. Our goal is to determine the role of estrogen and how it regulates the expression of the aryl hydrocarbon receptor (AhR) in cancer pathogenesis. The AhR is a ligand-activated transcription factor that, when activated, controls expression of cytochromes P450 1A1 (CYP1A1) and 1B1 (CYP1B1), enzymes that catalyze the metabolic activation of polycyclic aromatic hydrocarbons to ultimate carcinogens and the metabolism of estrogens to catechol estrogens. One theory of estrogen-dependent carcinogenicity is that initiation occurs when CYP1A1 and CYP1B1 metabolize 17beta-estradiol (E2), which may give rise to genotoxic estrogen quinones. We hypothesize that estrogen exposure upregulates AhR expression in breast tumor cells, which in turn, induces bioactivating enzymes CYP1A1 and CYP1B1, resulting in a higher risk of DNA adduct formation and initiation of carcinogenesis.

Our research plan involves: (1) identification of regulatory promoter elements at which transcription factors interact and may be responsible for regulation of AhR expression by estrogen; (2) determining whether estrogen exposure affects posttranscriptional AhR mRNA stability in MCF-7 breast carcinoma cells; and (3) determining the effects of estrogen exposure on AhR expression in other estrogen receptor positive breast carcinoma cell lines. Currently, we have found several putative regulatory elements in the AhR promoter which may be important for regulation of AhR gene transcription. We will further study the protein:DNA interactions of these promoter elements, as well as focus on estrogenic effects on AhR mRNA stability.