THE RECEPTOR FOR ENVIRONMENTAL POLY AROMATIC HYDROCARBONS MEDIATES HUMAN BREAST CANCER PROGRESSION

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Abstract: Breast cancer is the most common invasive carcinoma in women and the leading cause of death in US women. Epidemiological studies have provided evidence for increased risk of breast cancer associated with exposure to environmental pollutants such as polychlorinated biphenyls (PCB), polycyclic aromatic hydrocarbons (PAH) and dioxins in genetically susceptible women. These chemicals exert their carcinogenic effects through binding to an intracellular receptor, the aryl hydrocarbon receptor (AhR), which is a ligand-activated transcription factor. Studies from our laboratory reported dramatically elevated levels of AhR proteins in human breast carcinoma (HBC) cell lines from advanced malignancy (MDA231, MDA468, MDA435s, MCF7), while less levels were expressed in HBC derived from early stages of malignancy (T47D, MDA436) and in immortalized and primary human mammary epithelial cells. Immunocytochemical staining and subcellular fractionation analyses confirmed that AhR in the HBC is predominantly nuclear without ligand treatment. This AhR nuclear accumulation in untreated HBC was coupled by substantial basal expression of CYP1A1 mRNA, reflecting the receptor transactivation. Collectively, our studies have reported a novel finding of elevated levels of activated AhR in human breast carcinomas in direct correlation to their malignancy, suggesting a role for AhR in breast cancer progression independent of PAH, and identify the receptor as a candidate prognostic factor. In further studies we addressed whether over expression of AhR alone is sufficient to induce carcinogenic transformation in human mammary epithelial cells (HMEC). Retroviral expression vectors were used to develop a series of stable cell lines expressing varying levels of AhR protein in an immortalized normal HMEC with relatively low endogenous AhR expression. The resulted increase in AhR expression and activity correlated with the development of malignant phenotypes, including undergoing epithelial-to-mesenchymal transition. Clones over expressing AhR by 3-fold manifested a 50% decrease in population doubling time compared to vector-control cells. Cell cycle analysis revealed that this enhancement in proliferation was mainly due to an increase in the percentage of cells transiting from G0/G1 to S- and G2/M phases. Over expression of AhR enhanced the motility of HMEC and increased their migration. Importantly, these cells acquired the ability to invade matrigel matrix, where more than 80% of plated cells invaded the matrix and crossed the membranes within 24 h, whereas none of parental or the vector control HMEC was able to invade matrigel. These data provide the first evidence for a direct role of AhR in the progression of breast carcinoma. The results suggest a novel therapeutic target that could be considered for treatment and prevention of progression of this disease. Our findings may validate the AhR as a new predictive clinical marker and a unique target for the design of novel selective inhibitors for therapeutic intervention of metastatic breast cancer. More importantly, the AhR expression might identify a subset of patients who could benefit from therapy targeting this receptor.