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Organochlorine pesticides and breast cancer: Mechanism of action on human breast cancer cells and animal models

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Given the number of women affected by breast cancer, considerable interest has been raised in understanding the relationships between environmental chemicals and disease development. Hexachlorobenzene (HCB) is a widespread organochlorine pesticide detected in mother's milk and lipid foods. HCB is a dioxin-like compound that weakly binds to the aryl hydrocarbon receptor (AhR), a transcription factor that regulates gene expression associated with proliferation, angiogenesis, migration and invasion. We previously demonstrated that HCB acts as an endocrine disruptor in rat mammary gland and an inducer of cell proliferation. Our studies using negative estrogen receptor alpha (-ERα) MDA-MB-231 human breast cancer cells showed that HCB increases cell migration and invasion and enhances tumor growth stimulating lung and liver metastasis in mice breast cancer models. Increasing evidence indicates that transforming growth factor-β1 (TGF-β1) can contribute to tumor maintenance and progression. In a recent investigation, we found that HCB increases TGF-β1 protein levels and activation, as well as Smad3, JNK and p38 phosphorylation in MDA-MB-231. Real time-qPCR results indicated that HCB reduces AhR mRNA expression through TGF-β1 signaling but enhances TGF-β1 mRNA levels involving AhR. HCB enhances cell migration and invasion through the Smad, JNK and p38 pathways. These results demonstrate that HCB modulates the crosstalk between AhR and TGF-β1 and consequently exacerbates a pro-migratory phenotype in this cell line. Finally, HCB induces the angiogenic switch and increases vascular endothelial growth factor (VEGF) expression in a xenograft model with MDA-MB-231. Human microvascular endothelial cells exposed to HCB showed an increase in cyclooxygenase-2 (COX-2), VEGF and AhR expression. HCB induces cell migration and neovasculogenesis in an AhR, COX-2 and VEGF receptor 2-dependent manner. Altogether, the results showed that HCB is able to modulate several breast cancer-related processes *in vitro* and *in vivo* and suggest that HCB may be a risk factor for human breast cancer progression.

Biography

Andrea Randi has her expertise in evaluation of pesticides mechanisms of action that act as endocrine disruptors, specifically those ligand compounds of the aryl hydrocarbon receptors (AhR). In her laboratory, she is developing two main lines of work, one related to the induced effects by these compounds in the mammary gland and another in the uterus. In mammary gland, her interest is to investigate the different processes of breast cancer progression, such as proliferation, angiogenesis, migration, invasion and metastasis, analyzing the signaling pathways related with growth factor receptors, AhR and estrogen receptors. On the other hand, in the uterus, she is engaged in analyzing the effects on the development of endometriosis, evaluating the growth of endometriotic lesions, proliferation, migration, invasion and angiogenesis.

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