Poster #25

The Effects of DDT and its Metabolites on AP-1 Activity: ER Dependent and Independent Mechanisms

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Endocrine disruptors represent a class of both natural and man-made compounds that exhibit hormone activity. Organochlorines, such as the pesticide DDT and its metabolites, have been shown to bind to and activate estrogen receptors (ERs), thereby producing estrogen-like effects. Although ERs function predominantly through activation of transcription via estrogen responsive elements (EREs), both ERs, α and β, can interact with various transcription factors such as AP-1 and NFκB as well as activating early signaling events such as MAPK. Therefore the biological effects of these environmental estrogens may not be mediated through traditional ER activity alone. Here we examine the ability of DDT and its metabolites to activate AP-1 mediated gene transactivation in both an ER dependent and independent manner. Using two human endometrial carcinoma Ishikawa cell variants, one that is estrogen responsive (Ish+) and another that is estrogen unresponsive (Ish-), results compare stabley transfected AP-1 luciferase cell lines to identify the mechanisms involved. o,p' DDT, p,p' DDT, and o,p' DDD were the most potent activators of AP-1 activity. DDT metabolite activation of AP-1 varied to different degrees depending upon the metabolite treatment and cell variant tested. AP-1 activity, although stimulated in both Ish+ and Ish- cells by the DDTs, was more pronounced in the estrogen unresponsive Ish- cells. This suggests that although DDT and its metabolites may activate the AP-1 transcription factor via the ER, other mechanisms exist that potentate their ability to stimulate an AP-1 response. Together this adds another level of complexity to how compounds once thought to solely affect hormone responses can act upon the cell.