CHEMOSENSITIZATION OF RESISTANT BREAST AND PROSTATE CANCER CELLS BY SELECTIVE ARYL HYDROCARBON RECEPTOR MODULATORS (SAHRMS).


Recent reports indicate that SAhRMs such as 3, 3’-diindolylmethane (DIM) inhibit α-estrogen receptor (ER) expression and estrogen signaling in human breast cancer cells and inhibit androgen receptor (AR) signaling in human prostate cancer cells. DIM is an AhR agonist derived from Brassica vegetables and has been shown to have antiproliferative and proapoptotic effects in breast and prostate cancer cells. α-naphthoflavone (ANF) belongs to the family of flavonoids and is an AhR antagonist.

In Breast cancer cell lines interaction of AhR with BRCA1 has also been shown to enhance the latter’s transcriptional activity. Also, tamoxifen resistance has been attributed to decreased BRCA1 levels. However, the effects of AhR and its agonists and antagonists, and their modulatory effect on BRCA1 in resistant human breast cancer cells have not been investigated.

We have tested the hypothesis that DIM chemosensitizes breast cancer cells to 4-OH tamoxifen (TAM).

This hypothesis driven study was tested in the following manner –
(a) MTT cell viability assay was utilized to determine the cytotoxic effect of DIM and TAM against MCF-7 and MCF-7/dox, and the IC$_{50}$ values were approximately 90 μM and 20 μM respectively for both cell lines at 72 hr.
(b) Combination studies with DIM and TAM resulted in an increase in cytotoxicity and significant lowering of the IC$_{50}$ concentration to 50 μM and 10 μM for each drug, respectively.
(c) Results from western blot analysis show that there is an increase in BRCA1 and AhR protein levels of MCF-7 and MCF-7 /dox cells treated with DIM versus protein levels from untreated cells.

These data suggest that DIM increases the activity of TAM against both MCF-7 cells and MCF-7/DOX cells.

Prostate cancer is the most common malignancy and the second leading cause of death in men. Bicalutamide (BIC) is a non-steroidal antiandrogen that is used in the treatment of prostate cancer, however, relapses with more aggressive form of prostate cancer have been observed. Hence, other drugs and combinations are being tried. Raloxifene (Ralox) is a Selective Estrogen Receptor Modulator that has been shown to induce apoptosis in androgen dependent and androgen-independent prostate cancer cell lines.

We have tested the hypothesis that DIM chemosensitizes prostate cancer cells to Ralox and BIC.

This hypothesis driven study was tested in the following manner –
(a) MTT cell viability assay was utilized to determine the cytotoxic effect of DIM and Ralox and BIC against prostate cancer cells. The IC$_{50}$ values of Ralox in LnCap, PC3, C42b and DU145 were 11μM, 18μM, 24μM, 27μM respectively. The IC$_{50}$ values of BIC in LnCap, PC3, C42b and DU145 were 22μM, 65μM, 36μM, 36μM respectively. The IC$_{50}$ values of DIM in LnCap, PC3, C42b and DU145 were 21μM, 46μM, 40μM, 47μM respectively.
(b) Combination studies with Ralox (10μM), BIC (20μM) and DIM (20μM) resulted in an increase in cytotoxicity and a 65% reduction in cell survival in LnCap, 55% reduction in cell survival in C42b and PC3 cells.
(c) The IC$_{50}$ values of ANF in LnCap, PC3, C42b and DU145 were 21μM, 52μM, 43μM, 41μM respectively. Combination studies with Ralox (10μM), BIC (20μM) and ANF (20μM) resulted in an increase in cytotoxicity and a 75% reduction in cell survival in LnCap and C42b and a 55% reduction in cell survival in PC3 cells.

These data suggest that DIM and interestingly ANF as well increases the activity of Ralox and BIC against all three prostate cancer cell lines LnCap, C42b and PC3.