Expression or ligand activation of the androgen receptor does not influence the action of signal transduction inhibitors in prostatic cell lines

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Introduction:

Novel therapeutic strategies involving Epidermal Growth Factor receptor (EGFR) and ErbB2/HER2 inhibitors are making their way into clinical trials. In this study, we sought to define a cellular model to explore the molecular basis for the differential sensitivity of prostate cancer (PC) cells to inhibitors of the EGFR family and to inhibitors of the phosphoinositide 3'kinase (PI3K); an important signalling pathway involved in PC development.

Materials and methods:

Androgen sensitive (LNCaP and CWR22Rv1) and androgen insensitive (DU145 and PC3) PC cell lines were treated with the EGFR inhibitor: ZD1839/Iressa (AstraZeneca), the ErbB2 inhibitor: Herceptin/trastuzumab (Roche, Basel, Switzerland) and the PI3K inhibitor (LY294002, Calbiochem). Effects on ErbB, akt and MAPK phosphorylation (P-ErbB, P-Akt and P-MAPK) were assessed by Western blotting while effects on cell proliferation were assessed by cell counting. Flow cytometric analysis of the cell cycle and apoptosis were employed to identify the mechanisms by which these agents affect PC cell growth.

Results:

ZD1839 effectively inhibited EGF-induced P-EGFR, P-ErbB2, P-Akt and P-MAPK in PC cells. Herceptin modestly reduced P-ErbB2 after 24 hours of treatment and had minimal effects on downstream signal transduction pathways. EGF-induced cell proliferation was abolished in all EGF-responsive cells while Herceptin failed to inhibit the growth of any of the PC cell lines. LY294002 specifically inhibited P-Akt without affecting P-ErbB or P-MAPK activation. Sensitivity to this inhibitor was seen in all serum-deprived cells except PC3. In the presence of EGF, DHT or serum, this sensitivity was reduced or lost. Cell cycle arrest was identified as the major mechanism for inhibition by ZD1839 while both apoptosis and cell cycle arrest were observed with LY294002 treatment.

Conclusion:

Sensitivity to signal transduction inhibitors was observed in all PC cell lines regardless of androgen receptor expression or activation but is influenced by the availability of growth factors or androgen.