Progesterone Pre-treatment Potentiates EGF Pathway Signaling in The Breast Cancer Cell Line ZR-75

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Summary

Progesterone in hormone replacement therapy (HRT) preparations increases, while hysterectomy greatly reduces, the incidence of breast cancer. Cross-talk between the progesterone and growth factor signaling pathways occurs at multiple levels and this maybe a key factor in breast cancer survival and progression. To test this hypothesis, we characterized the effect of progesterone pre-treatment on the sensitization of the epidermal growth factor (EGF) signaling pathway to EGF in the breast cancer cell line ZR-75. For the first time in ZR-75 cells and in agreement with previous work using synthetic progestins, we demonstrate that pre-treatment with the natural ligand progesterone increases EGF receptor (EGFR) levels and subsequent ligand-dependent phosphorylation. Downstream we demonstrate that progesterone alone increases erk-1 + 2 phosphorylation, potentiates EGF-phosphorylated erk-1 + 2 and maintains these levels elevated for 24 h; over 20 h longer than in vehicle treated cells. Additionally, progesterone increased the levels of STAT5, another component of the EGF signaling cascade. Progesterone increased EGF mediated transcription of a c-fos promoter reporter and the nuclear localization of the native c-fos protein. Furthermore, progesterone and EGF both alone and in combination, significantly increase cell proliferation. Several results presented herein demonstrate the conformity between the action of the natural ligand progesterone with that of synthetic progestins such as MPA and R5020 and allows the postulation that the progestin/progesterone-dependent increase of EGF signaling provides a survival advantage to burgeoning cancer cells and may contribute to the breast cancer risk associated with endogenous progesterone and with progestin-containing HRT.