

Abstract

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S179D prolactin increases vitamin D receptor and p21 through up-regulation of short 1b prolactin receptor in human prostate cancer cells.

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OBJECTIVE: In this study, we further investigated the mechanisms by which pseudophosphorylated prolactin (S179D PRL) inhibits the growth of human prostate cancer cells.

RESULTS: When treated with S179D PRL for 3 days, LnCAP cells responded by increasing expression of the vitamin D receptor (VDR) and the cell cycle regulatory molecule, p21, whereas PC3 and DU145 cells did not. After 5 days of treatment, both PC3 and DU145 cells responded. Untreated LnCAP cells express the short 1b form (SF1b) of the human prolactin receptor, but DU145 and PC3 cells express only low amounts of this receptor until elevated by treatment with S179D PRL. DU145 and PC3 cells become sensitive to the negative effects of S179D PRL on cell number after induction of the SF1b. Transfection of either SF1b or SF1a into PC3 or DU145 cells made them sensitive to S179D PRL in the 3-day time frame, a finding that was not duplicated by transfection with the long form of the receptor. Treatment of LnCAP cells with S179D PRL increased long-term activation of extracellular signal-regulated kinase 1/2 (ERK1/2). This did not occur in PC3 and DU145 cells until transfection with SF1a/SF1b. Blockade of ERK signaling eliminated S179D PRL-stimulated expression of the VDR and p21 in LnCAP cells and transfected PC3 and DU145 cells.

CONCLUSION: We conclude that initiation of alternative splicing to produce SF1b, and subsequent altered signaling, contribute to the growth inhibitory mechanisms of S179D PRL. This is the first indication of a role for short prolactin receptors in the regulation of cell proliferation.

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