AUTOCRINE INTERLEUKIN–6 DE–SENSITIZES LNCAP CELLS TO ENDOCRINE/PARACRINE INTERLEUKIN–6 SIGNAL BY INCREASING CONSTITUTIVE EXPRESSION OF INHIBITORS OF INTERLEUKIN–6 SIGNALING.

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Introduction and Objectives: In LNCaP cells that secret IL–6 (autocrine) either through IL–6 cDNA transfection (Clin Cancer Res, 2003, 9:370–6) or induced by long–term treatment with exogenous IL–6 (Clin Cancer Res, 2001, 7:2941–8; Prostate, 2007, 67:764–773), IL–6 promotes cell growth and protects LNCaP cells from undergoing apoptosis induced by androgen deprivation therapy. In contrast, LNCaP cells treated with exogenous IL–6 (mimicking endocrine/paracrine effect) undergo cell growth arrest and neuroendocrine differentiation (NED). The objective of this study was to investigate the differences between autocrine and endocrine/paracrine IL–6 signaling pathways in LNCaP cells.

Methods: LN–S17 (LNCaP cells overexpressing IL–6) and control cell line LN–C3 (LNCaP cells not expressing IL–6) were compared in cell growth, NED marker expression, and intracellular signaling molecules by cell culture, Western blot, and real–time quantitative PCR.

Results: LN–C3 cells underwent growth arrest and NED when they were treated with exogenous IL–6 or co–cultured with LN–S17 cells for 4 days, whereas LN–S17 cells continued to proliferate. LN–C3 cells expressed approximately the same amount of IL–6R, gp130, JAK1, JAK2, and Tyk2, compared to LN–S17 cells. JAK3 was not expressed in LNCaP cells. Phospho–JAK2 but not JAK1 or Tyk2 was induced in LN–C3 cells but not in LN–S17 cells upon exogenous IL–6 treatment. Phospho–STAT3 was minimal in LN–S17 cells but was dramatically induced in LN–C3 cells when both cell lines were treated with exogenous IL–6. LN–S17 cells constitutively expressed higher levels of cytokine–inducible SH2–containing protein (CIS) and suppressor of cytokine signaling 7(SOCS7) than LN–C3 cells. The levels of SOCS1–6 proteins were equal in both cell lines.

Conclusions: Autocrine IL–6 de–sensitizes LNCaP cells to endocrine/paracrine IL–6 signal by increasing constitutive expression of CIS and SOCS7.