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Title: **Regulation of the Hippo-YAP Signaling by Cytokines in Prostate Cancer Cell Lines**

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Abstract

The transcriptional co-activator YAP1 (yes-associated protein 1), a crucial effector of the Hippo pathway in mammals, regulates cell growth, cell motility, cell migration, and carcinogenesis. The STK4/Hippo kinase phosphorylates Ser127 and inactivate YAP1 activity in mammalian cells. Cytokines such as receptor activator of nuclear factor Kappa B (RANKL) regulate the immune system and bone remodeling. Similarly, stroma-cell derived factor 1 alpha (SDF1α) produced by the bone marrow stromal cell, is directly linked to cell migration and metastasis. We hypothesize that RANKL/SDF1α attenuates phospho-Ser127 and enhances YAP nuclear localization. We conducted immunological assays to evaluate the effects of SDF1α or RANKL on YAP1 in the LNCaP prostate cancer cell line. We showed that SDF1α and RANKL modulate phospho-Ser127 and total YAP1 protein in a time-dependent manner, as demonstrated by western blotting. We also showed that SDF1α exposure promoted YAP1 nuclear localization, as revealed by immunofluorescence imaging with confocal microscopy. These findings suggest that cytokines positively regulate YAP1 activity, possibly by counteracting with the STK4/Hippo signaling. The results of this study imply that cytokines secreted by the tumor cell environment promote an invasive cancer cell phenotype by modulating the Hippo-YAP1 pathway.