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17α-Estradiol Inhibits Osteoblast Stimulation of Prostate Cancer Cell Migration and Invasion through Blockade of TGF-β1/SMAD2 Signal Pathway

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Prostate cancer (PC) is curable if it is diagnosed and treated in localized and regional stage. However, PC outcome is poor once it has distant metastasis. Approximately 70% to 100% of PC deaths have bone metastasis, presumably due to a specific bone microenvironment. In this study, we investigated the role of osteoblast cells in PC cell migration and invasion and revealed the effect and mechanism of 17 alpha-estradiol (αE2) on osteoblast-stimulated PC cell migration and invasion using cell culture analysis. Transwell experiments with PC and osteoblast h.FOB cell co-culture showed that PC cell migration and invasion were specifically promoted by osteoblast cells, but not cells originated from mammary gland, kidney and liver. Moreover, PC cell migration and invasion was specifically stimulated by h.FOB condition media in transwell and wound-healing assay. Multiplex immunoassays revealed that the concentration of TGF-β1 was markedly higher in the h.FOB condition media compared to other cell condition media. Treatment with TGF-β1 produced a time- and dose-dependent induction of PC cell migration and invasion and SMAD2 phosphorylation. Both the h.FOB and TGF-β1 effects were effectively suppressed by a specific TGFβ receptor inhibitor LY2157299 as well as by αE2. Most intriguing this αE2 inhibitory effect was observed at very low nanomolar concentrations and presumably mediated through estrogen receptor. These findings suggest that TGF-β1 is a major factor in mediating h.FOB cell stimulation of PC cell migration and invasion and αE2 is a potential agent to block PC cell bone metastasis, probably through inhibition of TGF-β1/SMAD2 signal pathway.

Keywords: Prostate cancer, Bone metastasis, h.FOB Cells, TGF-β/SMAD, 17α-Estradiol, Cell migration and invasion