ROLE OF PROSTAGLANDIN E₂ IN TGFβ SIGNALING IN PROSTATE CANCER CELLS

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Abstract: Transforming growth factor-β (TGF-β) plays an important role in the progression of prostate cancer. It exhibits both tumor suppressor and tumor promoting activities. Correlations between COX-2 overexpression and enhanced production of PGE₂ have been implicated in cancer progression; however, there are no studies indicating that TGF-β effects in prostate cancer cells involve PGE₂ synthesis. In this study, we investigated TGF-β regulation of COX-1 and COX-2 expression in prostate cancer cells and whether the effects of TGF-β on cell proliferation and migration are mediated by PGE₂. COX-1 protein was ubiquitously expressed in prostate cells; however, COX-2 protein levels were only detected in prostate cancer cells. TGF-β treatment increased COX-2 protein levels and PGE₂ secretion in PC3 cells. Exogenous PGE₂ and PGF₂α had no effects on cell proliferation in LNCaP, DU145, and PC3 cells while PGE₂ and TGF-β induced migration and invasive behavior in PC3 cells. Only EP2 and EP4 receptors were detected at mRNA levels in prostate cells. The EP4-targeting siRNA inhibited PGE₂ and TGF-β-induced migration of PC3 cells. TGF-β and PGE₂ induce activation of PI3K/AKT/mTOR pathway as indicated by increased AKT, p70S6K, and S6 phosphorylation. Rapamycin completely blocked the effects of TGF-β and PGE₂ on phosphorylation of p70S6K and S6 but not on AKT phosphorylation. PGE₂ and TGF-β induced phosphorylation of AKT which was blocked by antagonists of PGE₂ (EP4) receptors (L161982, AH23848) and PI3-kinase inhibitor (LY294002) in PC3 cells. Pretreatment with L161982 or AH23848 blocked the stimulatory effects of PGE₂ and TGF-β on cell migration, while LY294002 or rapamycin completely eliminated PGE₂, TGF-β, and EGF-induced migration in PC3 cells. We conclude that TGF-β increases COX-2 levels and PGE₂ secretion in prostate cancer cells which, in turn, mediate TGF-β effects on cell migration and invasion through the activation of PI3K/AKT/mTOR pathway.