Loss of PTEN Permits CXCR4-mediated Metastasis through the ERK1/2 Pathway in Prostate Cancer Cells

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**Short Title:** PTEN inhibits CXCR4-mediated tumorigenesis

**Abstract**

The progression of human prostate cancer is a result of metastasis from the primary tumor to vital organs. Metastasis is a complex process that involves invasion, intravasation, extravasation, and metastatic colonization. To date, the biology underlying the various mechanisms of metastasis has not been fully elucidated. Therefore, novel and effective treatments are required to target the metastatic spread of advanced prostate cancer. Loss of the tumor suppressor Phosphatase and Tensin homolog deleted in chromosome 10 (PTEN) is frequently observed in advanced prostate cancer cells, which results in the promotion of metastatic events, such as cell survival, invasion and migration. PTEN has dual phosphatase activity, which negatively regulates PI3K/AKT signaling and subsequent downstream cellular functions, such as cell cycle, invasion, migration and angiogenesis. Ligand activation of the chemokine CXC receptor 4 (CXCR4) results in the induction of various signaling pathways, including PI3K/AKT, and has been implicated in all events of prostate metastasis. Considering the converging pathways involved, we suggest that PTEN regulates CXCR4 signaling and functions in normal prostate tissues. Previous studies have demonstrated that reconstituted PTEN in lymphocytes down-regulated CXCR4-mediated chemotaxis towards its ligand CXCL12. Additionally, progenitor PTEN-deficient smooth muscle cells (SMC) increased migration towards CXCL12 producing SMC, suggesting that an alteration in PTEN expression negatively regulated CXCR4-mediated events. Based on these observations, we hypothesize that loss of PTEN in prostate cancer promotes CXCR4-mediated events. We have demonstrated that siRNA knock-down of PTEN increased CXCR4-mediated migration of Du145 cells, which exhibits poor migratory behavior. To determine the signaling pathway involved in promoting CXCR4-mediated migration, we transfected PC3 cells with PTEN expressing constructs and analyzed for the basal expression of p-AKT and p-ERK1/2 by western blot analysis. We observed that PTEN inhibited the basal phosphorylation of AKT but not ERK1/2. Conversely, upon ligand activation of CXCR4, PTEN inhibited the phosphorylation of ERK1/2 but not AKT. Furthermore, we show that CXCR4-mediated migration of PC3 cells was through the ERK1/2 pathway, as confirmed by PD98059 treatments. In summary, our results suggest that the absence of PTEN permits CXCR4-mediated migration in Du145 cells. Furthermore, the reconstitution of PTEN in PC3 cells regulated CXCR4-mediated phosphorylation of ERK1/2 but not AKT. In future studies, will determine whether antagonizing the CXCR4 pathway in PTEN-deficient, androgen-independent tissues will reduce growth and migration of tumors *in vivo*. Data obtained from these studies will help us to understand the relationship between loss of PTEN and advanced tumor development through CXCR4 in prostate cancer cells.