Blocking Parathyroid Hormone 1 Receptor Inhibits Prostate Cancer Metastases

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Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) have 30% of the 5-year survival rate and contribute significantly to prostate cancer-related death. Parathyroid hormone-related protein (PTHrP), secreted by cancer cells, is shown to be a driver for cancer-induced bone metastasis, including mCRPC. However, clinical trials using PTHrP monoclonal antibodies demonstrated only palliative effects. On the other hand, PTHrP affects through the only known receptor, parathyroid hormone 1 receptor (PTH1R), which is a member of the G protein-coupled receptor that consists of up to 35% of all clinical drug targets. Therefore, we will investigate the role of PTH1R in prostate cancer metastasis using genetic and pharmacological approaches.

Methods: To investigate the paracrine effect of PTH1R on advanced prostate cancer metastases, we crossed the floxed PTH1R ($PTH1R^{FloxE2}$) mouse with the Col1α2 CreERT mouse. Following tamoxifen administration, the Cre-positive mouse's mesenchymal cell-specific PTH1R gene is deleted, producing a $PTH1R^{ColCreERT}$ KO mouse. The Cre-negative littermates with the same tamoxifen injections were used as the control $PTH1R^{FloxE2}$ mouse. Pharmacologically, we tested the effect of blocking PTH1R on prostate cancer cell growth and viability.

Results: Human prostate cancer cells, PC3 cells (luciferase labeled), were intracardially injected into both $PTH1R^{FloxE2}$ and $PTH1R^{ColCreERT}$ KO littermates. We found PC3 metastases in various organs, including the liver, kidney, and bones. The overall and organ-specific metastases, such as bone metastases, were significantly inhibited in the $PTH1R^{ColCreERT}$ KO, compared to the $PTH1R^{FloxE2}$ mice, suggesting that blocking the paracrine effects of PTH1R effectively inhibits prostate cancer metastases. In vitro, we used a small molecule inhibitor called XC039 and a commercially available PTH1R peptide antagonist (Asn10, Leu11, D-Trp12)-PTHrP(7-34) amide to block PTH1R. Both antagonist and XC039 can suppress ligand-dependent cAMP production and XC039, but not the peptide antagonist, significantly inhibited prostate cancer cell growth.

Conclusion: These data suggest that inhibiting PTH1R could effectively inhibit prostate cancer metastases.

