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Targeted Therapeutic Strategies for Prostate Cancer Treatment Using Novel Lipid Kinase Inhibitors in Combination with Current Drugs

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Hörsal 933, Unod B9, Norrlands universitetssjukhus, fredagen den 8 maj, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Prof. Dr. Lukas Kenner
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Abstract
Prostate cancer (PCa) is one of the most common cancer types and the fifth cancer-related cause of death among Western world men. The sex steroid hormone, androgen and androgen receptor (AR) play important roles in PCa progression. Herewith, androgen deprivation therapy (ADT) is used as a regimen for PCa, but inevitably leads to development of castration-resistant PCa (CRPC) and distant metastasis. No effective treatment for metastatic PCa currently exists. Furthermore, it remains poorly understood whether and how the steroid hormone signaling in cooperation with multiple pathways that control proliferation, survival and invasion of cancer cells may contribute to metastatic dissemination and growth.

The aims of my PhD thesis focused on: (i) studying the clinical importance of estrogen- and androgen-related signaling pathways in promoting homing and metastatic growth of PCa cells in bone, (ii) gaining deeper understanding of the underlying mechanisms that facilitate PCa metastasis and treatment resistance, with focus on phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1α), estrogen- and androgen receptor signaling, (iii) testing and characterizing the therapeutic potential of PIP5K1α inhibitor in combination with anti-estrogen or anti-androgen agents to improve treatment and overcome treatment resistance in CRPC.

In my thesis work we have shown that key biomarker genes exhibited unique expression profiles and signatures in PCa subtypes within large patient cohorts. Alterations in androgen- and estrogen-related biomarkers and PIP5K1α/Akt pathways were associated with poor patient outcome. We further discovered that CRPC cells and cancer stem-like cells utilized estrogen-associated factors including aromatase and estrogen receptor alpha (ERα), as well as cyclin A1, a key cell cycle regulator, to gain proliferative advantage, and to survive and metastasize to distant organs. We found that the interaction between PIP5K1α and AR splice variant AR-V7 contributed to enzalutamide resistance. In series of in vivo treatment experiments using tumor xenograft mice, we demonstrated that ISA-2011B alone or in combination with enzalutamide had great therapeutic potential to suppress growth of tumors that had elevated levels of PI3K/Akt and AR-V7, and that were resistant to enzalutamide monotherapy. We further showed that combination treatment using tamoxifen together with ISA-2011B selectively blocked elevated ERα/cyclin D1 and PIP5K1α/Akt, leading to tumor regression and had superior inhibitory effect over monotherapy in xenograft mice.

My studies therefore suggest that steroid hormone receptors, PIP5K1α signaling cascade and multiple cellular pathways cooperatively promote PCa progression. Taken together, the reported findings are the first to suggest a new therapeutic potential to inhibit or utilize the mechanisms related to ERα and PIP5K1α/Akt network, and provide a new therapeutic strategy to treat castration-resistant ER-positive subtype of tumors with metastatic potential.

Keywords
Prostate cancer, bone metastasis, castration-resistant, treatment, precision therapy, PIP5K1A, steroid hormone receptors, cancer stem cells,

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