Invasive and Metastatic Properties of Advanced Prostate Cancer

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

I. Jennbacken K., Vallbo C., Wang W., Damber JE.
Expression of vascular endothelial growth factor C (VEGF-C) and VEGF receptor-3 in human prostate cancer is associated with regional lymph node metastasis. *The Prostate. 2005 Oct 1;65(2):110-116*

II. Jennbacken K., Gustavsson H., Welén K., Vallbo C., Damber JE.
Prostate cancer progression into androgen independency is associated with alterations in cell adhesion and invasivity. *The Prostate. 2006 Nov 1;66(15):1631-1640*

III. Jennbacken K., Gustavsson H., Tešan T., Horn M., Vallbo C., Welén K., Damber JE.
The prostatic environment suppresses growth of androgen-independent prostate cancer xenografts: An effect influenced by testosterone. *The Prostate 2009. In press*

IV. Jennbacken K., Tešan T., Wang W., Gustavsson H., Damber JE., Welén K.
N-cadherin increases after androgen deprivation and is associated with metastasis in prostate cancer. *In manuscript*

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ABSTRACT

Prostate cancer is initially androgen-dependent (AD) and therefore androgen deprivation therapy (ADT) is generally used to treat advanced prostate cancer. However, the long-term treatment effects are insufficient and over time an androgen-independent (AI) tumor relapses, which is generally highly aggressive and metastatic. Treatment regimens in the AI stage are only palliative and median patient survival is less than a year. Therefore, new treatment concepts are urgently needed. The purpose of this thesis was to investigate molecular and cellular characteristics of advanced prostate cancer. The specific focus was on characteristics related to invasivity and metastatic ability in the AI stage. An experimental model system comprising of an AD and an AI prostate cancer cell line was used for *in vitro* studies in cell culture and *in vivo* studies in immunodeficient mice. In addition, samples from prostate cancer patients were included in the studies and evaluated by immunohistochemical analyses. Studies performed using the experimental model showed that transition into androgen-independency was associated with several prometastatic alterations, including increased migration and tumor cell invasivity into blood vessels. Further, the AI tumors displayed elevated levels of N-cadherin, matrix metalloproteinase 9 (MMP-9) and membrane type-1(MT1)-MMP and decreased expression of the tumor suppressor E-cadherin compared to the AD tumors. Further studies demonstrated that intraprostatic AI tumors were suppressed when grown in intact mice compared to castrated mice, probably by androgen-regulated factors secreted from the prostatic stromal cells. In addition, the proinvasive factor N-cadherin was increased by androgen deprivation in experimental AI tumors and in samples from human prostate cancer. Similarly, N-cadherin was increased in specimens from AI prostate tumors compared to early non-treated tumors and was associated with Gleason score and metastasis. Finally, the results show that the lymphangiogenic factor vascular endothelial growth factor C (VEGF-C) and its receptor VEGFR-3 were elevated in primary tumors from patients with regional lymph node metastases compared to patients without lymph node metastases. In summary, this thesis shows that androgen deprivation and the subsequent development of AI tumors are associated with several prometastatic alterations in the prostate cancer cells. The results also suggest that AI tumors do not thrive in the prostatic environment and supports previous observations of frequent progression of AI prostate cancer as metastases in patients. Moreover, the results indicate a possible role for VEGF-C and N-cadherin in promoting dissemination of tumor cells to distant sites. Thus, N-cadherin and VEGF-C might be potential therapeutic targets for future anti-metastatic treatment for advanced prostate cancer.

Key words: Prostate cancer; Androgen-independent; Castration-resistant; Metastasis, Invasion; Lymphangiogenesis; Cell adhesion; N-cadherin; VEGF-C; MRI

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