Androgen-Independent Prostate Cancer – studies on angiogenesis and ADAMTS1

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Heléne Gustavsson

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Avhandlingen baseras på följande delarbeten:

I. Gustavsson H., Welén K. and Damber JE.
Transition of an androgen-dependent human prostate cancer cell line into an androgen-independent subline is associated with increased angiogenesis.
The Prostate 2005 Mar 1;62(4):364-373

II. Gustavsson H., Jennbacken K., Welén K. and Damber JE.
Altered expression of genes regulating angiogenesis in experimental androgen-independent prostate cancer. *The Prostate 2008 Feb 1;68(2):161-170*

III. Gustavsson H., Wang W., Jennbacken K., Welén K. and Damber JE.
ADAMTS1, a putative anti-angiogenic factor, is decreased in human prostate cancer.
BJU International 2009, In press

IV. Gustavsson H., Tešan T., Jennbacken K., Kuno K., Damber JE. and Welén K.
ADAMTS1 is involved in the regulation of blood vessel morphology, TSP1 levels and tumor growth in experimental prostate cancer. *In manuscript*

UNIVERSITY OF GOTHENBURG

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Heléne Gustavsson

Department of Urology, Lundberg Laboratory for Cancer Research, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sweden

ABSTRACT

Androgen deprivation therapy (ADT) is the standard treatment for advanced prostate cancer since prostate tumors initially are dependent on androgens for growth. However, most tumors will eventually relapse and grow in a highly aggressive and androgen-independent (AI) manner. AI prostate cancer is associated with poor prognosis and new treatment modalities are therefore urgently needed. Anti-angiogenic therapy could be one strategy to suppress tumor growth, but this requires an increased understanding about the regulation of angiogenesis in AI prostate cancer. The aim of this thesis was therefore to increase the knowledge about AI prostate cancer, with special focus on angiogenesis. First, an experimental model system that allows comparative studies of androgen-dependent (AD) and AI prostate cancer was established. An AD human prostate cancer cell line was cultured under selective pressure in androgen depleted medium, which resulted in an AI subline. Characterization of the newly established AI cell line revealed that transition into androgen-independency was associated with a more rapid tumor take, decreased PSA levels, increased microvessel density (MVD) and altered blood vessel morphology. To identify factors that could be of importance for the increased angiogenesis observed in AI tumors, a gene expression analysis was performed. The results demonstrated that transition into androgen-independency was accompanied with altered expression of a number of genes associated with angiogenesis, including ADAM metallopeptidase with thrombospondin type 1 motif, 1 (ADAMTS1). ADAMTS1 is a potent anti-angiogenic factor that was found to be significantly downregulated in AI cancer cells and its expression correlated negatively with MVD in the tumor xenografts. Furthermore, immunohistochemical studies of tumor tissue from prostate cancer patients demonstrated significantly lower levels of ADAMTS1 in cancer areas than in benign glands. In addition, low levels of ADAMTS1 were associated with metastatic disease and higher MVD in AI tumors. In order to further elucidate the role of ADAMTS1 in prostate cancer progression and tumor angiogenesis, the expression of ADAMTS1 was modified by transfection in the experimental model system. The results revealed that altered expression of ADAMTS1 markedly affected the blood vessel morphology but not the number of blood vessels in the tumor xenografts. Modified expression of ADAMTS1 also affected the levels of the anti-angiogenic protein TSP1, whose expression was inversely related to ADAMTS1. Moreover, upregulation of ADAMTS1 resulted in a markedly delayed growth of AI tumors, while the opposite was observed in AD tumors. In summary, the results show that transition into androgen-independency is associated with increased angiogenesis and altogether the data from this thesis suggest that ADAMTS1 is an important factor in prostate cancer biology that is lost during disease progression and that is associated with decreased angiogenesis, tumor growth and metastasis in AI prostate cancer.

Key words: Prostate cancer, Androgen-independent, Castration resistant, Hormone refractory, Angiogenesis, Microvessel density, ADAMTS1, LNCaP, VEGF, TSP1

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