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Midkine in Advanced Prostate Cancer

- Biological Impact and Biomarker Potential

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av **Anna Nordin**

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I. **Nordin, A**., Wang, W., Welén, K., Damber, JE. Midkine is associated with neuroendocrine differentiation in castration-resistant prostate cancer.
Prostate. 2013; 73 (6): 657-67.

II. **Nordin, A**., Damber, JE., Welén, K. The role of Midkine in high-grade prostate cancer cells before and after steroid deprivation.
Manuscript.

III. **Nordin, A**., Wang, W., Ahlgren, G., Josefssson, A., Welén, K., Damber, JE. Midkine as a progression biomarker in advanced prostate cancer.
Manuscript

IV. **Nordin, A**., Welén, K., Damber, JE. Long-term steroid deprivation transforms prostate cancer cells to anaplastic castration resistant cells.
Manuscript.

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Midkine in Advanced Prostate Cancer

Biological Impact and Biomarker Potential

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ABSTARCT

Prostate cancer (PC) is generally an androgen-driven disease, why androgen deprivation therapy (ADT) is the cornerstone for treatment of advanced and metastatic hormone-naïve PC (HNPC). ADT generally offers a good initial response, but normally fails with time, and the disease relapses into lethal castration-resistant PC (CRPC). Neuroendocrine differentiation (NED) is a transdifferentiation process that results in the accumulation of neuroendocrine (NE)-like tumor cells. NED is increased in CRPC and in response to ADT, and may represent a therapy-driven escape mechanism. Midkine (MDK) is a pleiotropic growth factor that is highly expressed during human embryogenesis, but is also induced in many pathological conditions, as in most human carcinomas, including PC. In recent years, MDK has received increased attention as a tumor biomarker in different human carcinomas.

In addition to a lack of curative treatments for advanced PC, there is a lack of reliable prognostic and predictive biomarkers. There is a need to find new biomarkers and to better understand the mechanisms behind castration-induced transformation into CRPC, including NED and acquired resistance.

The purpose of this thesis was to evaluate the role and impact of MDK in PC, with a focus on the CR stage and castration induced transformations, including NED. In this work we found MDK to be highly expressed both in advanced HNPC and in progressed CRPC and that MDK is associated with NED in CRPC. MDK was found to be influenced by castration and is presumed to be functionally associated with the androgen receptor. MDK was associated with a profound biological role in androgen-sensitive PC cells *in vitro* and was found to promote PC cell survival during the initial phase of steroid deprivation. Lastly, MDK was demonstrated to represent a powerful prognostic biomarker in both advanced HNPC and at relapse into CRPC. NED, in response to steroid deprivation, was observed as a transient phase of adaptation before transition into castration resistance, and was furthermore inducible also in the CR-state in response to AR-targeting.

In conclusion, this thesis identifies MDK as an important tumor biomarker in PC, with the potential to improve clinical decisions in treatment of patients with both advanced HNPC and CRPC. Furthermore, the functional importance of MDK in tumor evolution was partly elucidated.

Keywords: Castration resistant prostate cancer, neuroendocrine differentiation, Midkine, steroid deprivation

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