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Molecular Heterogeneity of Prostate Cancer Bone Metastasis

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Akademisk avhandling

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Avhandlingen kommer att försvaras på engelska.

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Abstract

Castration-resistant prostate cancer (CRPC) develops after androgen deprivation therapy of advanced PC, often with metastatic growth in bone. Patients with metastatic CRPC have very poor prognosis. Growth of CRPC, in most but not all patients, seems to involve androgen receptor (AR) activity, despite castrate levels of serum testosterone. Multiple mechanisms behind AR activation in castrated patients have been described, such as AR amplification, AR mutations, expression of constitutively active AR variants, and intra-tumoral steroid synthesis. However, other mechanisms beside AR activation are also involved and CRPC patients with tumors circumventing the need for AR stimulation will probably not benefit from AR targeting therapies but will need alternative treatments.

Available treatments for CRPC are chemotherapy, AR antagonists or inhibition of androgen-synthesis. Novel drugs are constantly under development and several new therapies has recently been approved for clinical use. These include, in addition to new AR targeting therapies also immunotherapy, osteoclast inhibitors and bone-targeting radiopharmaceuticals. Due to heterogeneous mechanisms behind CRPC and that newly developed therapies are based on different mechanisms of action, there are reasons to believe that CRPC patients show different therapy responses due to diverse molecular properties of individual tumors. Although there are promising prospects, no biomarkers are used today for patient stratification into different treatments. Another important aspect is that, when effective, any therapy will probably induce tumor responses that subsequently cause further molecular diversities and alternative paths for development of tumor relapse and castration-resistance. Such mechanisms are important to understand in order to develop new treatment strategies.

In this thesis, global gene expression and methylation patterns were studied in bone metastases obtained from PC patients going through metastasis surgery for spinal cord compression. Gene expression patterns were analyzed by multivariate statistics and ontology analysis with the aim to identify subgroups of biological/pathological relevance. Interesting findings from array analysis were verified using qRT-PCR and immunohistochemical analysis. In addition, a xenograft mouse model was used to study the effects of abiraterone (steroidogenesis inhibitor) and cabazitaxel (taxane), and subsequently developed resistance mechanisms in the 22Rv1 PC cell line expressing high levels of AR-V7; a constitutively active AR splice variant associated with a poor prognosis and resistance to AR targeting therapies.

In summary, results showed that the majority of CRPC bone metastases were AR-driven, defined from high levels of AR-regulated gene transcripts, while a smaller sub-group was non-AR-driven (paper I). AR-driven bone metastases had high metabolic activity in combination with downregulated immune responses while non-AR-driven cases had a more pronounced immune response (paper I) and higher bone cell activity (paper II). Paper III identified pronounced hypermethylation in primary prostate tumors probably causing a suppressed anti-tumor immune-response whereas metastases showed a different methylation pattern related to increased AR activity and patient outcome. In paper IV, 22Rv1 xenografts showed poor response to abiraterone and initially excellent response to cabazitaxel, but eventually resistance occurred probably due to an upregulation of the ABCB1 transporter protein. Anti-androgens partly reversed the resistance.

In conclusion, we have identified molecular heterogeneities in clinical bone metastases associated with biological characteristics, which could perhaps be used both for stratifying patients into treatment modalities, and to aid in further development of effective therapies for CRPC.

Keywords
Prostate cancer, CRPC, castration-resistant, androgen receptor, splice variant, abiraterone, cabazitaxel, ABCB1, cholesterol, Mdr1, P-gp, bone metastasis, immune response, metabolism, osteoblast; osteoclast; BMP, methylation

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