Prostate cancer and bone cell interactions: implications for metastatic growth and therapy

Annika Nordstrand

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i Hörsal E04, byggnad 6A, fredagen den 17 mars, kl. 09:00. Avhandlingen kommer att förvaras på engelska.

Fakultetsopponent: Docent Päivi Östling
Institutionen för onkologi-patologi, Karolinska institutet, Stockholm.
Abstract
The skeleton is the most common site of prostate cancer bone metastasis, and at present, there are no curable treatments for these patients. To further understand what stimulates tumor cell growth in the bone microenvironment and to find suitable therapies, reliable model systems are needed. For this purpose, we have developed an in vitro co-culture system that can be used to study interactions between tumor cells and murine calvarial bones.

One of the major reasons why prostate cancer cells colonize bone is the abundance of tumor-stimulating factors, such as insulin-like growth factors (IGFs), present in this milieu. Using our co-culture model we found that prostate cancer cells can increase the release of such factors from bone, which can in turn stimulate tumor growth. Since IGF-1 is known to be a strong survival factor for tumor cells, we hypothesized, that concurrent inhibition of IGF-1R signaling can enhance the effects of apoptosis-inducing therapies, such as castration. We used our co-culture model to target human prostate cancer cell lines, PC-3 and 22Rv1, with simvastatin (an inhibitor of the mevalonate pathway and an inducer of apoptosis), in combination with anti-IGF-1R therapy. Tumor cell viability declined with either one of the therapies used alone, and the effect was even more pronounced with the combined treatment. The hypothesis was also tested in rats that had been inoculated with rat prostate cancer cells, Dunning R3327-G, into the tibial bone, and treated with either anti-IGF-1R therapy, castration, or a combination of both therapies. The tumor cells were found to induce an osteoblastic response, both in vivo in rats, and in vitro using the co-culture model. Interestingly, the therapeutic response differed depending on whether tumor cells were located within the bone marrow cavity or if they had leaked out into the knee joint cavity, highlighting the role of the microenvironment on metastatic growth and therapeutic response. Therapies targeting the IGF-1R have been tested in clinical trials, unfortunately with disappointing results. By immunohistochemical evaluation of bone metastases from patients with castration-resistant prostate cancer, we found a large variance in IGF-1R staining within this group of patients. Hence, we postulate that the effects of anti-IGF-1R therapies could be more beneficial in patients with high tumoral IGF-1R-activity than in IGF-1R negative cases.

In a separate study, using whole-genome expression data from bone metastases obtained from prostate cancer patients, we present evidence that a high activity of osteoblasts is coupled to a high activity of osteoclast. Moreover, we found that high bone remodeling activity is inversely related to tumor cell androgen receptor (AR) activity. The results from this study may be of importance when selecting therapy for patients with bone metastatic cancer, especially when bone-targeting therapies are considered, and could aid in the search for novel therapeutic targets.

In summary, we present an in vitro model for studies of the bidirectional interplay between prostate cancer cells and the bone microenvironment. We also demonstrate the importance of IGF-1 in prostate cancer bone metastases and suggest that inhibition of IGF-1R signaling can be used to treat prostate cancer as well as to enhance effects of other treatments such as androgen deprivation therapy. Furthermore, we emphasize the possibility of molecular tumor characterization when designing treatment plans for individual patients, thereby maximizing the therapeutic effects.

Keywords
Prostate cancer, bone metastasis, bone remodeling, IGF-1R, androgen receptor

Language: English
ISBN: 978-91-7601-678-7
ISSN: 0346-6612
Number of pages: 78 + 4 papers