The regulatory role of osteoblasts in castration-resistant growth of prostate cancer

Akademisk avhandling

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ABSTRACT

Bone metastasis of a predominantly osteoblastic (sclerotic) nature is the outcome for the vast majority of patients with castration-resistant prostate cancer (CRPC). Pathologically, osteoblastic tumors are characterized by excessive bone formation resulting in decreased quality of life due to severe pain, fractures, nerve compression, and a suppressed immune system. Despite the success of novel therapeutic approaches, castration-resistant tumors remain the primary unsolved obstacle for patient survival. Therefore, an improved understanding of the molecular mechanisms behind the osteoblastic growth of CRPC is important in the search for novel therapeutic strategies. The aim of this thesis was to investigate the specific role of osteoblasts in the growth of prostate cancer in bone. By establishing and characterizing a novel model of sclerotic CRPC, it was demonstrated that both osteoblasts and prostate cancer cells are potential mediators of bone formation. It was further demonstrated that osteoblasts promote the osteogenic and metastatic progression of CRPC cells and potentiate the cross talk between CRPC and bone cells. Moreover, it was shown that osteoblasts induce and alter steroidogenesis in the CRPC cells by increasing the expression of steroidogenic enzymes in a similar manner to what has previously been described in bone metastases from patients. Further studies revealed that Runx-related transcription factor 2 (Runx2) – which is under the control of osteoblasts – is a putative regulator of de novo steroid synthesis in osteogenic CRPC cells, and this mimics a mechanism of steroid synthesis previously only described in osteoblasts. Finally, a preclinical study with tasquinimod showed that this drug efficiently impaired the establishment of bone metastases in mice by interfering with the osteoblastic pre-metastatic niche and osteoblastic activity, thus emphasizing the role of osteoblasts in the early phases of the metastatic process. In summary, the studies performed in this thesis have characterized the role of osteoblasts in castration-resistant growth of prostate cancer in bone and suggest that osteoblasts could be an attractive target for the development of novel therapeutic approaches. A better understanding of the osteoblast–tumor cell interaction might facilitate the design of treatment strategies targeting the osteoblasts as a way to inhibit the metastatic process and thus bypass the castration resistance of CRPC bone metastases.

Keywords: Castration resistant prostate cancer, bone metastases, osteoblasts