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Original Article

Specific bone region localization of osteolytic versus osteoblastic lesions in a patient-derived xenograft model of bone metastatic prostate cancer

Takeshi Hirata [a], Seung Chol Park [b], Michelle T. Muldong [c,d,e], Christina N. Wu [c,f], Tomonori Yamaguchi [g], Amy Strasner [c,d,e], Omer Raheem [d,e], Hiromi Kumon [a], Robert L. Sah [h], Nicholas A. Cacalano [i], Catriona H.M. Jamieson [c,f], Christopher J. Kane [c,d,e], Koichi Masuda [g], Anna A. Kulidjian [c,g], Christina A.M. Jamieson [c,d,e,*]

[a] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[b] *Department of Urology, Wonkwang University School of Medicine and Hospital, Iksan, South Korea*
[c] *Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA*
[d] *Department of Urology, University of California, San Diego, La Jolla, CA, USA*
[e] *Department of Surgery, University of California, San Diego, La Jolla, CA, USA*
[f] *Department of Medicine, University of California, San Diego, La Jolla, CA, USA*
[g] *Department of Orthopaedic Surgery, School of Medicine, University of California, San Diego, La Jolla, CA, USA*
[h] *Department of Bioengineering, University of California, San Diego, La Jolla, CA, USA*
[i] *Department of Radiation Oncology, University of California at Los Angeles, Los Angeles, CA, USA*

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Abstract *Objective:* Bone metastasis occurs in up to 90% of men with advanced prostate cancer and leads to fractures, severe pain and therapy-resistance. Bone metastases induce a spectrum of types of bone lesions which can respond differently to therapy even within individual prostate cancer patients. Thus, the special environment of the bone makes the disease more complicated and incurable. A model in which bone lesions are reproducibly induced that

* Corresponding author. Department of Urology, Department of Surgery, Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA.
E-mail address: camjamieson@ucsd.edu (C.A.M. Jamieson).
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Bone microenvironment; Microstructural CT; Osteolytic lesions; Osteoblastic lesions

mirrors the complexity seen in patients would be invaluable for pre-clinical testing of novel treatments. The microstructural changes in the femurs of mice implanted with PCSD1, a new patient-derived xenograft from a surgical prostate cancer bone metastasis specimen, were determined.
Methods: Quantitative micro-computed tomography (micro-CT) and histological analyses were performed to evaluate the effects of direct injection of PCSD1 cells or media alone (Control) into the right femurs of *Rag*$2^{-/-}\gamma c^{-/-}$ male mice.
Results: Bone lesions formed only in femurs of mice injected with PCSD1 cells. Bone volume (BV) was significantly decreased at the proximal and distal ends of the femurs ($p < 0.01$) whereas BV ($p < 0.05$) and bone shaft diameter ($p < 0.01$) were significantly increased along the femur shaft.
Conclusion: PCSD1 cells reproducibly induced bone loss leading to osteolytic lesions at the ends of the femur, and, in contrast, induced aberrant bone formation leading to osteoblastic lesions along the femur shaft. Therefore, the interaction of PCSD1 cells with different bone region-specific microenvironments specified the type of bone lesion. Our approach can be used to determine if different bone regions support more therapy resistant tumor growth, thus, requiring novel treatments.

1. Introduction

Prostate cancer is the most common solid cancer in men and the second leading cause of cancer of death in men [1]. The majority of prostate cancer patients with metastatic disease will develop bone metastases. Patients with bone metastases are at risk of skeletal related events, including spinal cord compression, pathological fracture, and severe bone pain leading to surgery and/or radiation to alleviate bone pain, and prevent or repair pathologic fractures. In a recent large US study, 10% of prostate cancer patients with newly diagnosed bone metastasis already had skeletal related events (SREs) [2]. During follow-up, the cumulative incidence of SREs in these patients increased: 21.5% at 6 months, 30.4% at 12 months, 41.9% at 24 months, and 48.9% at 36 months [2]. Therefore, bone metastases contribute substantially to patients' mortality and morbidity.

Bone metastases in most men with prostate cancer are a mix of osteoblastic and osteolytic lesions [3]. The mechanisms by which prostate cancer tumor cells induce osteoblastic lesions which are characterized by new bone formation, or osteolytic lesions which are characterized by increased bone resorption leading to thinning bone are unclear. It is hypothesized that osteoblastic lesions are formed by intense osteoblastic activity, preceded by osteoclastic bone resorption in patients with prostate cancer [3]. However, it is possible that prostate tumor cells can induce metastatic bone lesions that do not involve osteoclastic activity [4]. The relative contribution of extrinsic factors from specific bone microenvironments versus factors intrinsic to the tumor cells themselves to the type of bone lesion formed is not understood. The reciprocal interaction of the tumor cells and bone microenvironment also gives rise to a pathologically altered tumor microenvironment which can drive further malignant tumor progression [5].

The type of cancer cells themselves plays a crucial role in determining the type of bone reaction both in patients and mouse models transplanted with human tumor cells. Most of the group of cancers that often metastasize to bone such as breast, lung and kidney cancer invariably induce osteolytic lesions [2,4]. Prostate cancer, on the other hand, has a higher proportion of osteoblastic and mixed lesions compared to purely osteolytic lesions [1–5]. The complexity of the types of osseous lesions induced by bone metastatic prostate cancer in patients was comprehensively analyzed in the recent work of Vargas and co-workers in which the types of bone metastatic lesions in castration resistant prostate cancer patients were evaluated using computed tomography (CT), FDG-PET and FDHT-PET [6]. They showed a range of at least six bone lesion types classified along a spectrum from dense osteoblastic to mixed osteoblastic-osteolytic to purely osteolytic in nature even within a single patient. Patients with the highest number of bone lesions and whose lesions had the highest ^{18}F-DHT (dihydrotestosterone, DHT) uptake had the shortest overall survival [6]. Different types of osseous lesions were also investigated in the study of bone metastasis samples obtained in a rapid autopsy study from patients who had died of metastatic castrate resistant disease [7–9]. Histomorphometric analysis revealed significant heterogeneity comprising a wide range of osteolytic to osteoblastic osseous responses within individual patients [8]. The mechanisms and clinical implications of the types of prostate cancer bone metastasis lesions found even within an individual patient need to be determined. Elucidating the mechanisms underlying bone metastatic lesion formation may lead to the development of new treatments for bone metastatic prostate cancer [10].

The complexity of prostate cancer bone lesions makes them extremely challenging to study and, therefore, to develop effective treatments in patients [6,10]. Thus, there is a significant need for accurate models to investigate prostate cancer interaction with the bone microenvironment. In experimental models of cancer bone metastasis, prostate cancer cells or xenografts harvested from human rapid autopsy programs show differential osteoblastic versus osteolytic reactions in the mouse