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Role of Acid Microenvironment in Cancer-induced Bone Pain

T. Yoneda*
Department of Biochemistry, Osaka University Graduate School of Dentistry, 1-8 Yamadaoka, Suita, Osaka 565-0871, Japan
*Contact author: tyoneda@dent.osaka-u.ac.jp

Bone pain is one of the major complications in bone metastases. The widely-known clinical observations that specific inhibitors of osteoclastic bone resorption such as bisphosphonates (BPs) effectively reduce bone pain suggest a potential role of osteoclasts that play a central role in bone metastases. Osteoclasts dissolve bone minerals by releasing protons through the vacuolar type proton pump (V-H+-ATPase). Proton is a well-known cause of pain. Proton directly activates the acid-sensing nociceptors such as TRPV1 that converts pain signals into electrochemical signals and transduces them to CNS. Here, we studied the role of TRPV1 in the induction of bone pain associated with cancer colonization in bone using an animal model of bone cancer pain we established. TRPV1 was expressed on the calcitonin gene-related protein-positive sensory neurons in bone. Cancer-inoculated bones showed hyperalgesia and increased hind-limb lifting (flinching) compared with control bones, suggesting cancer colonization increased bone pain. The BP zoledronic acid and a specific inhibitor of the V-H+-ATPase FR167356 significantly reduced the hyperalgesia and flinching, suggesting a critical role of protons released by osteoclasts. Ipsilateral dorsal root ganglion (DRG) showed increased Erk phosphorylation (pErk). In contrast, there were no differences in hyperalgesia and flinching between cancer-inoculated and control bones in TRPV1-/- mice. Acid (pH 5.5) increased pErk in WT DRG in organ culture. IRTX, a specific inhibitor of TRPV1, reduced pErk. However, acid failed to increase pErk in TRPV1-/- DRG. These results suggest TRPV1 is responsible for elevated pErk. In conclusion, our results suggest that the activation of TRPV1 on the sensory neurons innervating bone by protons that are released by bone-resorbing osteoclasts plays a critical role in cancer-induced bone pain.

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Targeting MMP13 in Human Breast Cancer Metastasis to Bone

M Shah¹, T Blick¹, D Huang¹, C Pinto¹, J Trinh¹, LA Reiter³, JR Hardink³, M Waltham¹,², EW Thompson¹,²,*¹

¹St. Vincent’s Institute & ²University of Melbourne Department of Surgery, St. Vincent's Hospital, Melbourne, Australia; ³Pfizer Global Research and Development, Groton Laboratories, Groton, CT, USA.
*Contact author: rik@medsvt.unimelb.edu.au

Matrix metalloproteinases (MMPs) play important roles in cancer growth, invasion and metastasis, but to date have eluded therapeutic address in cancer. MMP-inhibition trials have been confounded by the emergence of cancer-inhibitory roles for some MMPs, and also the dose-limiting toxicity musculoskeletal syndrome (MSS). We reasoned that certain specific MMPs may not have such cancer inhibitory roles such that specific targeting of these may afford therapeutic benefit. Our initial approach was to survey the MMPs produced by, and in response to, a series of human breast cancer xenografts. We found that MMP13 is dramatically upregulated in the stroma of xenografted human breast cancer cell lines in the primary site and in bone metastases developing after intracardiac inoculation (1). We hypothesise that MMP13 may represent an important MMP target if it can be targeted specifically.

To test this, we investigated the ability of a MMP-13-selective inhibitor (cmpd-1), to inhibit the osteolytic potential of human breast cancer cells in vivo. Treatment with cmpd-1 for up to 55 days inhibited the occurrence of osteolytic lesions in the intracardiac mouse model and suppressed the growth of primary MDA-MB-231 human breast cancer cells tumours in the mfp. Although the specific mechanism for MSS has not been reported, MMP13-selective inhibitors such as cmpd-1 lack any evidence of MSS in animal models (2) and thus MMP13 appears not involved. Thus, MMP13 may represent an important specific MMP target. Further genetic studies with MMP13-deficient mice and MMP13-specific shRNA are ongoing to validate this possibility.