and movement-evoked pain behaviors, as well as spinal neurochemical changes reflecting both peripheral and central sensitization. While this and other work suggests that tumor-induced bone resorption plays a role in driving bone cancer pain, other mechanisms, such as the release of pronociceptive compounds (e.g., prostaglandins) by tumor and/or inflammatory cells may also be involved.

Several tumor types including sarcomas and breast, prostate, and lung carcinomas grow in or preferentially metastasize to the skeleton where they proliferate and induce significant bone remodeling, bone destruction and cancer pain. Many of these tumors, as well as sensory and spinal cord neurons, express the isoenzyme cyclooxygenase-2 (COX-2) which is involved in the synthesis of prostaglandins. To begin to define the role prostaglandins play in driving bone cancer and bone cancer pain, we used an in vivo model where murine osteolytic sarcoma cells, which were stably transfected with green fluorescent protein (GFP), were injected and confined to the intramedullary space of the femur of male C3HHeJ mice. Following tumor implantation, mice develop ongoing and movement-evoked bone cancer pain-related behaviors, extensive tumor-induced bone resorption, infiltration of the marrow space by tumor cells, and stereotypic alterations in the spinal cord reflective of a persistent pain state. Thus, following injection of tumor cells, bone destruction is first evident at day 6 and pain-related behaviors are maximal at day 14.

To explore the involvement of COX-2-generated prostaglandins in driving bone cancer and bone cancer pain, a selective COX-2 inhibitor was administered either acutely (NS-398, Sigma, St. Louis, Missouri; 100mg/kg, i.p.) on day 14 or chronically in chow (MF tricyclic, Merck & Co., Kirkland, Quebec; 0.015%, p.o.) from day 6 to day 14 following tumor implantation. Mice were then assessed for behavioral, radiological, immunohistochemical, fluorescent, and histologic indices of bone cancer. Acute administration...
of a selective COX-2 inhibitor attenuated both ongoing and movement-evoked bone cancer pain but did not affect tumor burden or tumor induced bone destruction. In contrast, chronic inhibition of COX-2 significantly reduced ongoing and movement-evoked pain behaviors and reduced tumor burden, osteoclastogenesis and bone destruction by over 50%. The present results suggest that chronic administration of COX-2 blocks prostaglandin synthesis at multiple sites and given their relatively low side effect profile, selective COX-2 inhibitors may have significant clinical utility in the management of bone cancer and bone cancer pain.

References