A Crucial Role For Osteoclasts In The Microenvironment Of Chondrosarcoma

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Disclosures:

Introduction: Chondrosarcoma (CHS) is an aggressive primary tumor of bone that is resistant to chemotherapy and radiation treatment. Surgery is the mainstay of current therapy, and survival is poor in patients with recurrent and metastatic disease. Cellular and molecular mechanisms of pathogenesis in CHS remain elusive. Recent research has implicated microenvironmental factors in the behavior of chondrosarcoma in bone. We hypothesized that osteoclasts in the microenvironment of CHS play a crucial role in local aggressiveness and growth of the tumor in bone. The Swarm rat chondrosarcoma (SRC) is a transplantable chondrogenic tumor with biological behavior that mimics CHS in bone. A particularly aggressive derivative of the tumor (JWS) was developed at our institution that possesses the ability to destroy bone, invade local tissues, and colonize distant sites. The JWS tumor in rats is a suitable in vivo model to study CHS. The objective of our study was to document the presence and characterize the activity of osteoclasts at the bone tumor interface, to determine the local effect of tumor on bone, and to study the effect of inhibition of osteoclasts on tumor behavior.

Methods: Three groups of rats were utilized in the study. One group received PBS injections into the tail vein weekly for three weeks and then underwent JWS tumor implantation into the right tibia. The contralateral tibia served as an internal control. Another group of rats received weekly tail vein injections of zoledronic acid (ZA), an osteoclast inhibitor, for three weeks before implantation of tumor into the right tibia. The control group received PBS injection and sham surgery consisting of corticotomy and wound closure. X rays were taken weekly, and animals were euthanized at day 21 post-operatively. Bilateral tibiae were analyzed by peripheral quantitative computed tomography (pqCT) and were evaluated histomorphomerically for tumor growth, osteoclast activation, and bone destruction.

Results: Implantation of JWS into tibia induced a massive osteolytic response in local bone. There was a concomitant increase in osteoclast number and size compared with sham tibiae. Osteoclast surface and resorbed surface were statistically greater in the presence of tumor than in sham tibiae. Furthermore, pqCT showed a statistically significant reduction in local bone mineral density in JWS-implanted tibiae than sham tibiae (p=0.008). ZA increased bone mineral density and inhibited bone destruction in the presence of JWS tumor. Osteoclasts appeared rounded and dysfunctional, and resorbed bone surface was reduced compared with PBS-treated tumor-bearing tibiae. Additionally, there was a significant reduction in tumor volume within the intramedullary space of ZA-treated tumor bearing tibiae than those treated with PBS.

Discussion: Data from our in vivo model suggests that osteoclasts are required for local bone destruction induced by CHS and that osteoclasts contribute to the growth of CHS in bone. Modulation of OC activity represents an attractive therapeutic strategy in local control of CHS growth.

Significance: This work demonstrates that factors in the microenvironment of chondrosarcoma may affect tumor behavior. Osteoclasts have long been known to prime the bone niche for metastatic carcinoma. However, this work represents one of few examples demonstrating the vital role that osteoclasts might play in the pathogenesis of a primary sarcoma of bone.

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Figure 1: Zoledronic acid reduces tumor-mediated osteoclast activation and bone erosion.

Histological sections of (A) Control tibia, (B) Chondrosarcoma-bearing tibia, and (C) Chondrosarcoma bearing tibia treated with zoledronic acid, stained for tartrate resistant acid phosphatase to mark osteoclasts red. Note the destruction of bony trabeculae at the tumor-bone interface. This effect is abrogated in the presence of zoledronic acid, and tumor growth was limited to the extramedullary space when osteoclasts were inhibited. b, bone; t, tumor; arrows, osteoclasts.
Figure 2: Osteoclast inhibition prevents chondrosarcoma-induced bone destruction. Peripheral quantitative computed tomography was used to calculate bone mineral density (BMD) of local bone three weeks after tumor implantation in rat tibiae. The right tibia was the surgical tibia, while left tibia was the non-operative internal control. ZA, zoledronic acid; Sham, surgical control without tumor implantation; JWS, rat chondrosarcoma tumor line; asterisk, p=0.008.