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The Microenvironment Matters: Estrogen Deficiency Fuels Cancer Bone Metastases

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Summary

Factors released during osteoclastic bone resorption enhance disseminated breast cancer cell progression by stimulating invasiveness, growth and a bone-resorptive phenotype in cancer cells. Post-menopausal bone loss may accelerate progression of breast cancer growth in bone, explaining the anti-cancer benefit of the bone-specific anti-resorptive agent zoledronic acid in the post-menopausal setting.

Commentary

In this issue of *Clinical Cancer Research*, Ottewell and colleagues [1] report that progression of metastatic breast cancer in bone was mediated by osteoclastic bone resorption in a pre-clinical model of surgical menopause (ovariectomy; OVX). In these studies, anti-tumor activity of the anti-resorptive agent zoledronic acid (ZOL) was detected only in a post-menopausal estrogen deficient setting when osteoclastic bone resorption was increased.

Bone has long been recognized as a unique metastatic microenvironment due to growth factors stored in mineralized bone matrix, vascularity and an enrichment of cytokines capable of stimulating tumor cell invasiveness, growth and a bone-resorptive phenotype in cancer cells [2]. The bone microenvironment is further complicated by the fact that its cells are acutely sensitive to changes in endocrine status. Pre- and post-menopausal bone niches may differ greatly as host environments for disseminated cancer cells due to increased osteoclastic bone resorption that occurs in the setting of estrogen deficiency and ovarian failure as women reach menopause. This postulate is supported by recent clinical reports demonstrating differential anti-cancer effects of bone-targeted anti-resorptive bisphosphonate therapy in breast cancer patients depending on menopausal status. In the AZURE, ZO-FAST and ABCSG-12 trials, ZOL consistently improved disease-free survival in breast cancer patients, however, this effect was limited to post-menopausal women [3–5]. Direct anti-cancer effects of ZOL have been pursued with little evidence that physiologically relevant doses can directly elicit cancer cell apoptosis [6]. Although direct anti-tumor effects

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of bisphosphonates have been shown in vitro [7], the anti-cancer activity of ZOL has been attributed to indirect effects via inhibition of osteoclastic bone resorption. Ottewell and colleagues provide the first pre-clinical data to explain the anti-tumor effect of ZOL in an estrogen deficient post-menopausal state characterized by significant bone loss. These data are analogous to the clinical setting in which ZOL shows anti-cancer benefit [3–5] and align with established concepts that tumor progression in the bone compartment is largely driven by cues from the microenvironment, and specifically, by osteoclastic bone resorption.

Declining ovarian sex steroid production and a concomitant increase in inflammatory tone associated with menopause alters the bone microenvironment in ways that may promote cancer cell homing, tumor growth and an osteolytic phenotype in cancer cells (Fig. 1). Under normal physiological conditions, estrogen 1) acts directly on bone cells to regulate the lifespan of both osteoclasts and osteoblast and 2) inhibits T-cell production of inflammatory cytokines, which can drive osteoclast activation and bone resorption [8]. In the absence of estrogen, osteoclastic bone resorption outpaces formation via increased osteoblast expression of RANKL, which binds to its cognate receptor RANK on the osteoclast and stimulates osteoclastogenesis [8]. Reduced expression of the soluble decoy receptor for RANKL, OPG, is also associated with estrogen deprivation and contributes to excessive bone resorption [8]. Women can lose up to a quarter of their trabecular bone mass in a mere of five-seven year span following menopause [9]; this acute phase of bone loss is followed by a gradual and continued decline in bone mass for the remainder of post-menopausal life [9].

Increased bone resorption has been demonstrated in pre-clinical models to fuel cancer progression in bone [10] presumably via release of growth factors from the mineralized bone matrix, including transforming growth factor (TGF)-β, insulin-like growth factor (IGF), fibroblast growth factors (FGF), platelet-derived growth factor (PDGF), which stimulate tumor growth and expression of osteolytic factors that perpetuate a feed-forward bone destructive cycle [2]. Furthermore, osteoclast-derived proteolytic enzymes can promote angiogenesis, cancer cell invasiveness and engraftment at metastatic sites [11], further contributing to the potential pathways by which osteoclastic bone resorption may promote tumor progression in bone and colonization of dormant disseminated tumor cells. As predicted, Ottewell and colleagues report that gene expression of factors associated with osteoclastic bone resorption, including RANKL, Cathepsin-K and MMP9, were increased in OVX bone, but not in ZOL-treated OVX bone. Blockade of bone destruction by ZOL thus prevents numerous downstream events that are triggered by a heightened state of bone resorption (Fig. 1). In this way, anti-resorptives have the potential to drastically curb cancer cell progression in the post-menopausal setting. Pre-menopausal breast cancer patients undergoing anti-estrogen therapy treatment that leads to artificial menopause and increased bone resorption using aromatase inhibitors or LH-releasing hormone agonists also stand to benefit from ZOL therapy, as reported clinically in the ZO-FAST and ABCSG-12 trials, respectively [4–5].

Effects of ZOL on pre- and post-menopausal ER-positive breast cancer progression were not addressed in these studies due to poor engraftment of the ER-positive breast cancer cell line, MCF-7. Despite this caveat, use of the ER-negative human MDA-MB-231 breast cancer line

is advantageous because changes in tumor growth can be attributed exclusively to alterations in the bone microenvironment independent of the confounding effect of estrogen-mediated tumor growth.

The study by Ottewell and colleagues is important because it addresses the longstanding query of whether alterations in the bone microenvironment can alter tumor growth in bone. Such studies are difficult to perform in mice and in humans. Menopausal status in clinical trials is often self-reported and definitions of pre-menopause and post-menopause can vary across studies. Pre-clinical modeling of ovarian failure by OVX eliminates that variability as cessation of ovarian hormone production can be precisely timed and the subsequent osteoclast-driven bone loss can be measured prospectively. However, this model lacks a peri-menopausal phase characterized by increased FSH and decreased inhibin concentrations in state of relative estrogen sufficiency [12]. As such, events in the mouse model may not reflect the window of the peri-menopausal state and would require further study. Additionally, estrogenic activity is not completely blocked with surgical menopause or OVX due to peripheral aromatization of androgens. Total estrogen depletion would require administration of an aromatase inhibitor in the setting of OVX and will likely lead to more profound bone loss and tumor progression relative to OVX alone in cancer-bearing mice. Nonetheless, despite these caveats, the message from this study is clear: the microenvironment matters and can influence tumor growth in bone. These microenvironment changes due to estrogen deficiency can be reversed by blocking osteoclastic bone resorption and have important therapeutic and preventive implications for our post-menopausal women with breast cancer.

These important findings raise further questions: 1) Could other clinical entities or cancer treatments that increase osteoclastic bone resorption, such as radiation, glucocorticoids, or aromatase inhibitors, influence cancer progression in bone? Can these effects be prevented? 2) What are the mediators released from actively resorbed bone that contribute to tumor progression in bone? IGFs and TGF-β are candidates as both are released as a consequence of osteoclastic bone resorption and can promote tumor growth and invasion. Further pre-clinical studies such as those performed by Ottewell and colleagues can address the growing importance of the microenvironment and the clinical implications for our patients with breast cancer.

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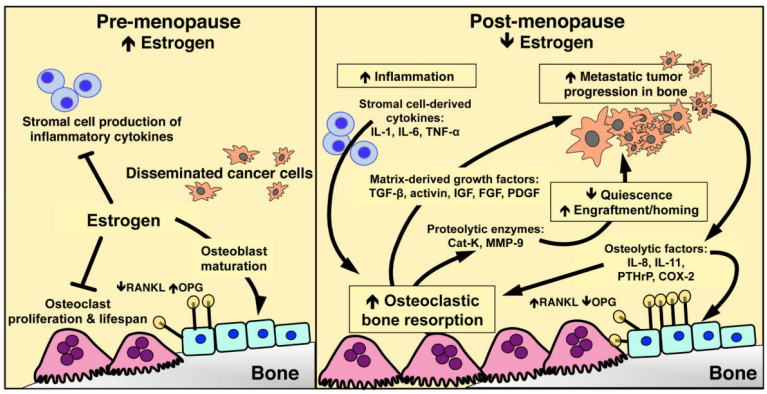

Figure 1.

Molecular mechanisms by which post-menopausal bone loss may prime the bone microenvironment for progression of breast cancer in bone. In the premenopausal state (left panel), estrogen suppresses excessive osteoclast activity. After menopause (right panel), loss of estrogenic regulation of osteoclast and osteoblast cell lifespan, increased RANKL expression, decreased OPG expression, and increased stromal cell production of inflammatory cytokines lead to excessive osteoclastic bone resorption and net bone loss. Matrix-derived growth factors are released into the bone microenvironment where they stimulate tumor cell invasiveness, growth and a bone-resorptive phenotype in cancer cells. Osteoclast-derived proteolytic enzymes aid in the colonization of disseminated tumor cells by promoting angiogenesis, cancer cell invasiveness and engraftment at metastatic sites. Blockade of post-menopausal bone loss by use of an anti-resorptive agent such as zoledronic acid likely has potent downstream anti-tumor effects at sites of bone metastases.