J Musculoskel Neuron Interact 2004; 4(4):375-376

Perspective Article

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Revisiting the seed and soil theory of bone metastasis: New tools, same answer

P.J. Kostenuik

Metabolic Disorders Research, Amgen Inc., Thousand Oaks, CA, USA

Keywords: OPG, Bisphosphonates, Bone Metastasis, Breast Cancer, Bone Resorption

Over a century ago, Dr. Stephen Paget recognized that breast cancers had a predilection for metastasizing to bone[1]. The frequency of this occurrence was greater than would be predicted by obvious variables such as blood flow to bone. He hypothesized that certain tumor cells (seeds) will selectively colonize distant organs (soil) where there is a favorable environment for localization and growth. The skeleton may be a suitable soil for several common malignancies because bone matrix contains high concentrations of numerous growth factors that may stimulate the proliferation of tumor cells[2].

This notion is supported by abundant animal data demonstrating that anti-resorptive agents such as bisphosphonates can reduce skeletal tumor burden in experimental models of bone metastasis[3]. Paget's hypothesis predicts that this therapeutic effect may be related to the well-established ability of bisphosphonates to suppress bone resorption, which would decrease the release of growth factors from bone matrix. However, there is also ample literature from cell culture studies demonstrating that bisphosphonates can have direct cytotoxic effects on tumor cells that are exposed for several days to very high concentrations of bisphosphonates. These concentrations, commonly in the micromolar-millimolar range, are frequently justified based on analyses conducted in neonatal rats that were directly injected with a very high dose of alendronate[4]. Under these conditions, micromolar-millimolar concentrations of alendronate were presumed to exist within the sealed Howship's lacunae beneath osteoclasts. However, it is unlikely that tumor cells within the skeleton of cancer patients are exposed to these concentrations of bisphosphonates. Unlike osteoclasts, tumor cells do not resorb bone directly, nor do they form a tight seal around bisphosphonate-laden bone. However, it is inherently difficult to dissociate the potential effects of suppressed bone resorption versus direct tumor cytotoxicity on bone metastasis using bisphosphonates.

The discovery of osteoprotegerin (OPG) has led to the development of novel tools to further explore the extent to which bone resorption promotes bone metastasis. OPG binds and neutralizes RANKL, the key and dominant mediator of osteoclast differentiation, activation and survival. Animal studies reveal that OPG is capable of rapidly reducing osteoclast numbers and suppressing bone resorption. However, OPG does not appear to have direct inhibitory effects on tumor cells *in vitro*. These properties allow us to directly examine the role of bone resorption on bone metastases. OPG has been tested in several animal models of bone metastasis. OPG treatment dramatically reduces osteoclast numbers and bone resorption in nude mice that were injected (intracardiac) with human MDA-231 breast cancer cells. This anti-resorptive effect was associated with complete suppression of tumor-associated osteolysis and a significant reduction in skeletal tumor burden[5]. In head-to-head studies using the MDA-231 model, OPG suppresses skeletal tumor burden to an extent that was similar to that observed with a very high dose of zoledronic acid (5 mg/kg). OPG also prevents osteolysis and suppresses skeletal tumor burden in normal mice injected intracardiac with C-26 murine colon adenocarcinoma cells[5]. OPG treatment has no influence on the growth of subcutaneously grown C-26 cells but causes dramatic suppression of skeletal tumor burden within bone[6]. This further suggests that the localized reduction of skeletal tumor burden in OPG-treated animals is an indirect consequence of bone resorption suppression.

Together, these data support the seed and soil theory as a viable mechanism by which certain cancer cells preferentially metastasize to bone. Two different classes of anti-resorptive agents (RANKL antagonist or bisphosphonates), with entirely different mechanisms of action, are each capable of suppressing skeletal tumor burden to a similar extent in animal studies. Direct cancer cell killing by bisphosphonates *in*

The author has a corporate appointment and stock ownership in Amgen Inc.

Corresponding author: Paul Kostenuik, Amgen, Inc, One Amgen Center Drive, M/S 15-2-B, Thousand Oaks, CA 91320-1799, USA
E-mail: paulk@amgen.coml

Accepted 4 August 2004

vivo is an unlikely scenario for reducing skeletal tumor burden, based on the low concentrations of bisphosphonate that a cancer cell is likely to be exposed to within the bone marrow environment. The pure anti-resorptive effects of RANKL antagonists suggest that suppression of bone resorption is an adequate and promising approach to controlling tumor-associated osteolysis and perhaps to reduce the growth of cancer cells within bone.

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