The majority of patients dying from cancer of the breast or prostate have metastases to the skeleton. The affinity of these and several other solid tumors for this metastatic site is the consequence of the special microenvironment provided by bone. Stephen Paget in 1889 proposed the seed and soil hypothesis: bone provides the fertile soil in which certain cancer cell seeds prefer to grow. We now appreciate that mineralized bone matrix is a rich storehouse of growth factors, which are mobilized by osteoclastic bone resorption. The released growth factors enrich the local microenvironment. A main effect of the factors appears to be alteration of the tumor cell phenotype rather than an increased growth rate. Tumor cells in turn secrete additional factors that act upon bone cells, causing the responses that characterize the osteolytic and osteoblastic metastases. Local interactions between tumor cells and bone form a vicious cycle, which underlies the development of skeletal metastases. The basic mechanisms of cancer metastases to specific sites have been controversial. Cancer cells in vivo continue to mutate. The ability of cancer cells to metastasize is characteristic of advanced disease and could occur only after the gradual accumulation of a necessary set of pro-metastatic mutations. However, recent experiments suggest that a constellation of expressed genes necessary for metastasis to bone pre-exists within the primary breast tumor. Thus, bone-specific metastases are the consequence of a selection process that has occurred during the development of the primary tumor.
of variants from a heterogeneous population of cells within
the primary tumor, plus changes in gene expression induced
by bone factors. Cells of the osteoblastic lineage appear to
be the main targets of tumor-secreted factors. Bone-derived
transforming growth factor-β (TGFβ) is a major factor regu-
lator of tumor cell behavior in bone.

There are no convenient animal models where primary
tumors reproducibly metastasize to bone. Many of the
results described here use an animal model in which human
tumor cells are inoculated into immuno-deficient mice.
Injection into the venous circulation most often results in
tumor cell entrapment within the capillary beds of the lung
or liver. However, careful tumor administration directly into
the left cardiac ventricle can result in 100% incidence of
bone metastases with many tumor cell lines (Table 1).
Osteolytic lesions are detected by X-ray as early as 3 weeks
and can be quantified by image analysis. Osteoblastic lesions
may take up to 6 months to develop in nude mice, and the
lesions cannot be quantified radiographically.

Osteolytic metastases

Destructive bone lesions are characteristic of breast can-
cer. The most prominent cause of bone destruction is
parathyroid hormone-related protein, PTHrP, which is
secreted by many cancer types and, when systemically elev-
ated, is responsible for humoral hypercalcemia of malign-
nancy (HHM). Breast and lung cancer cells that secrete
PTHrP in concentrations insufficient to induce HHM still
cause extensive osteolytic bone destruction in nude mice.
Bone lesions and tumor burden can be significantly
decreased, and survival increased, by treatment with PTHrP-
neutralizing antibody. The antibody has been humanized
and is in clinical trials against HHM and bone metastases.

PTHrP was originally suspected to play a role in osteolytic
metastases based on its known role as a stimulator of hyper-
calcemia, plus its high expression by tumor cells in bone ver-
sus soft tissue sites in patients. These results suggested that
PTHrP expression by the primary tumor might be prognostic
of metastases to bone. This is not the case. In a prospective
study, PTHrP expression by the primary tumor was an inde-
pendent prognostic marker of improved survival and
decreased metastasis to bone. PTHrP is a complex, multi-
functional protein and appears to play independent roles in
primary and metastatic cells. It is likely that the expression of
PTHrP by breast cancer cells in bone is the result of induction
of its gene by factors in bone, such as TGFβ.

PTHrP cannot be the only factor responsible for bone
metastases, and a number of other proteins play either con-
tributory or PTHrP-independent roles. Candidate factors
that may contribute to PTHrP-induced osteolytic lesions are
interleukin (IL)-11, macrophage colony-stimulating factor
(M-CSF), and vascular endothelial growth factor (VEGF). PTHrP-independent factors have also been reported, in-
cluding IL-8, which can directly stimulate the osteoclast.

Kang et al. compared less- and more-metastatic variants
of a breast cancer cell line by gene expression profiling. They identified mRNAs whose expression strongly correlated
with increased bone metastasis. Five of the mRNAs encoded
IL-11, matrix metalloproteinase (MMP)-1 osteopontin, con-
nective tissue growth factor (CTGF), and CXCR-4. MMP-1 is
an interstitial collagenase made by osteoblasts. It cleaves col-
lagen at a site resistant to osteoclastic enzyme hydrolysis and
may be rate-limiting in normal bone resorption. Osteopontin
plays a complex role in metastasis, including modulation of anti-tumor immune responses and is differenti-
ally regulated in tumor cells metastatic to bone versus
other sites. CTGF is a potent osteoblast-stimulatory fac-
tor, as well as being expressed by tumor cells. CXCR-4 is
the receptor for the chemokine SDF-1 and functions in the
attraction of breast cancer cells to specific metastatic sites
including, but not limited to, bone. Kang et al. found that
the pro-metastatic gene set was coordinately increased in
cells that pre-existed in the original cell population. The
authors attempted to convert low-metastatic MDA-MB-231
breast cancer cell line clones into ones highly metastatic to
bone by overexpressing each of the five individual factors.
They found that conversion of the cells to a phenotype of
aggressive metastasis to bone required co-transduction of
combinations of four of the five factors. The results strongly
support a multi-factorial mechanism underlying organ-spe-
cific metastases.

Many osteolytic factors act via osteoblasts and stimulate
osteoclastic bone resorption indirectly, rather than acting
directly on cells of the osteoclast lineage. This has been
shown for PTHrP, which induces osteoblastic expression of
RANK ligand. IL-11 can act similarly, while M-CSF and
VEGF serve as co-factors for the RANK ligand-stimulated
differentiation of hemopoietic precursors into active osteoclasts.

Osteoblastic metastases

Metastases with net formation of disorganized new bone
are characteristic of prostate cancer and also occur in 15% of
breast cancer bone metastases. The tumor-induced
lesions are characterized by formation of new but abnormal
disorganized new bone, and they are accompanied by
increased bone resorption. A number of candidate factors
made by tumor cells could stimulate osteoblasts, but
progress has lagged in the area until recently. Endothelin-1
(ET-1), a 21-amino acid vasoactive peptide, is a potent stim-
ulator of new bone formation. It is secreted by tumor cells
and can cause osteoblastic metastases in the nude mouse
model. Metastases are effectively blocked with a selective
antagonist of the endothelin A receptor. This orally
active antagonist is in clinical trials in men with advanced
metastatic prostate cancer. The vicious cycle model pre-
dicts that osteoblasts, osteoclasts and tumor cells cooperate
to cause the pathology of bone metastases. The endothelin
receptor antagonist blocks the activation of osteoblasts by
tumor-produced ET-1. It also decreases osteoclastic bone
resorption, as indicated by decreases in markers of resorp-
<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Bone Metastases</th>
<th>PTHrP</th>
<th>IL-6[^f]</th>
<th>IL-11[^f]</th>
<th>VEGF</th>
<th>Other Osteolytic Factors</th>
<th>ET-1</th>
<th>AM</th>
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<td>ZR-75-1</td>
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<td>0</td>
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<td>MCF-7</td>
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<td>3.3±0.2</td>
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<td>MDA-</td>
<td>OL</td>
<td>0.54±0.1</td>
<td>360</td>
<td>240±3</td>
<td>1258±34</td>
<td>IL-8[^c]</td>
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<td>+</td>
<td>CTGF[^d]</td>
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<td>OL</td>
<td>64±2</td>
<td>117±2</td>
<td>0</td>
<td>1233±14</td>
<td></td>
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<td>SBC-5G</td>
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<tr>
<td>A549</td>
<td>OL</td>
<td>+[^h]</td>
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<tr>
<td>HARAI</td>
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Table 1. Cancer Cell Lines and Phenotypes of Bone Metastases. PTHrP in pM/10^5 cells/48 hr by Nichols Institute 2-site IRMA. ET-1, IL-6, IL-11, VEGF in pg/ml/10^5 cells/48 hr by R&D Systems immunoassays. OB = osteoblastic, OL = osteolytic, M = mixed, N = none, when cells are inoculated into the arterial circulation of nude mice via the left cardiac ventricle. Most data from Yin et al.[^27]. ^AAM = adrenomedullin (Miller et al.[^40]. ^PDGF = platelet-derived growth factor B chain (Yi et al.[^97]; ^IL-8 = interleukin-8 (Bendre et al.[^15]; ^CTGF = connective tissue growth factor (Kang et al.[^5]; ^AM = adrenomedullin (Abasolo et al.[^41]; ^Gallwitz et al.[^31]; ^Miki et al.[^92]; ^Hastings et al.[^42]; ^I(Iguchi et al.[^9]; ^J(Chiao et al.[^90]; ^Fmol/mg protein (Rocchi et al.[^9]; ^pg/mg protein (Dall’Era et al.[^94]; ^M Arbitrary mRNA units (Scott et al.[^95]. Remaining data, indicated by pluses, are unpublished from the authors’ laboratory. Note that some of these cells (MCF-7 and MDA-MB-231, for examples), vary in PTHrP production depending on source of the cell line. A number of cell lines, scored N here, cause bone responses when injected directly into the marrow cavity of the tibia or femur[^96]. Most of the cell lines are of human origin.
tion seen in the patient trials. Conversely, bisphosphonates effectively reduce skeletal-related events in prostate cancer. These observations support an important role for the vicious cycle in patients.

Other factors responsible for osteoblastic metastases remain to be identified. Such factors need to meet two initial criteria: 1) ability to stimulate osteoblastic new bone formation, and 2) expression by cancer cells. The bone morphogenetic proteins (BMPs) are obvious candidates, but a causal role in bone metastases has not been demonstrated. CTGF, identified in the experiments of Kang et al. is another factor that stimulates osteoblasts. It is a normal product of hypertrophic chondrocytes and is the second of three closely related gene products CCN1-3, which are selectively expressed in certain tumor types. It is possible that CCN1 and CCN3 may contribute to bone metastases. CCN3 is expressed by prostate cancers, while CCN1, Cyr61, is expressed by breast and other cancers.

Adrenomedullin (AM) is a 52-amino acid vasoactive peptide with potent bone-stimulatory actions in vitro and in vivo. It is made by many cancers, including breast and prostate. We have recent data that it increases bone metastases in vivo. We tested the A549 human lung adenocarcinoma cell for its ability to form bone metastases when inoculated into the left cardiac ventricle. Animals developed osteolytic metastases after five weeks. These cells express PTHrP, ET-1, and AM. AM secretion was reduced 50% by stable expression of AM siRNA. These cells, made by Dr Alfredo Martinez at the National Cancer Institute, caused fewer metastases and increased survival, compared to empty vector-transfected A549 cells (unpublished results). In experiments the human prostate cancer cell line PC-3 was transfected with an AM expression DNA, resulting in a greater than ten-fold increase in AM secretion. These cells showed slower growth in vitro and as subcutaneous tumors; this response is opposite to that found with many other tumors, where AM is an autocrine growth stimulatory and pro-angiogenic factor. However, when these same PC-3 subclones were inoculated into nude mice, animal survival was less than half that of mice receiving control PC-3 cells. Mice with AM-overexpressing tumors showed accelerated osteolytic lesions and also adjacent areas of osteoblastic new bone formation (unpublished).

Another factor that could play a role in osteoblastic metastases is stanniocalcin, a polypeptide that is produced by cancer cells and can stimulate new bone formation.

Mixed osteolytic/osteoblastic metastases

Mixed lesions are characteristic of both breast and prostate cancers. The effect of combined expression of osteolytic and osteoblastic factors on bone has not been studied, so the net response of bone at the metastatic site is unpredictable. As noted above, osteolytic factors such as PTHrP and IL-11 act on osteoblasts to increase expression of RANK ligand. We tested the effects of introducing the osteoblastic factor, ET-1, into the PTHrP-secreting MDA-MB-231 breast cancer cell line. Instead of converting the bone response from osteolytic to osteoblastic, the bone-destructive effects were enhanced by ET-1. Some of this effect may be caused by autocrine responses of the tumor cells to ET-1. We believe that osteoblastic factors can stimulate osteoblast proliferation, increasing the population of early osteoblasts. The enlarged pool of early osteoblasts responds to osteolytic factors by increased expression of RANK ligand. A similar mechanism may be involved in the metastases caused by A549 and PC-3 cells, described in the preceding paragraph. Both cell lines secrete PTHrP and adrenomedullin, and A549s make ET-1 as well (unpublished). Thus, expression of an osteoblastic factor may not simply convert an osteolytic tumor cell line into one that causes osteoblastic metastases.

Another puzzling question has been the role of PTHrP in osteoblastic metastases, especially those due to prostate cancers, which nearly always express PTHrP. A partial explanation was provided by the observation that prostate-specific antigen (PSA) is a serine protease, which cleaves PTHrP after phenylalanine residues 22 and 23. The resulting fragment fails to activate the classical PTH/PTHrP receptor. This is not the end of the story. It was later observed that the inactive fragment PTHrP1-16 increased contraction of cardiac myocytes apparently by binding to the endothelin A receptor. Binding was attributed to a 4 amino acid near-identity between the two peptides. We have extended these observations to bone. PTHrP1-23 is a potent stimulator of calvarial new bone formation at concentrations as low as 1nM (unpublished results), although this polypeptide has no detectable affinity for the type 1 PTH receptor. New bone formation was blocked by the endothelin A receptor antagonist, ABT-627. The results suggest that PSA proteolysis of PTHrP, rather than inactivating it, converts the protein from an osteolytic factor to a potent osteoblastic one. These preliminary results are in vitro and require confirmation of their physiological significance in vivo. PTHrP can also be cleaved by the neutral endopeptidases, nephrilysin, which is expressed on the surface of prostate and bone cells, so N-terminal fragments of PTHrP could play a role in normal bone metabolism.

Actions of bone on tumor cells

The effects of bone-derived factors on tumor cells remain understudied. Van der Pluijm et al. elegantly demonstrated that several mRNAs are increased in bone versus non-bone sites of human breast cancer metastases in nude mice. RNA abundances were determined by species-specific RT-PCR. PTHrP, VEGFs and M-CSF were increased specifically in bone, while several mouse markers of host angiogenesis were similarly increased. These experiments did not identify the factor(s) responsible for the bone-specific mRNA induction. Hauschka et al. found that insulin-like growth factors (IGFs) -2, then -1, were the most abundant factors in bone matrix, followed by TGFβ, after which were lower concentrations of...
BMPs, fibroblast growth factors -1 and -2, and platelet-derived growth factor1. Of these, only TGFβ has been shown to play a direct role in stimulating tumor cells. TGFβ is growth-inhibitory in the early stages of tumorigenesis. Advanced cancers lose growth inhibition but retain TGFβ regulation of metastasis-promoting genes54, such as CTGF and IL-11, identified by Kang et al.5, and PTHrP13,55. In the MDA-MB-231 model of breast cancer metastasis to bone, detailed experiments showed that tumor cell expression of PTHrP is the major target of TGFβ and that TGFβ is the most important regulator of PTHrP56. These experiments also showed that dual pathways in the tumor cells, through p38 MAP kinase and through the Smad proteins, transmit TGFβ signaling to the nucleus. Osteoclastic bone resorption specifically activates TGFβ from its stored form in bone matrix57. This step may be another point at which the efficacy of bisphosphonates against bone metastases is exerted51.

It is likely that in patients, tumor cells secrete sets of multiple proteins with actions on bone cells2, and these sets may vary between metastatic sites within individuals. The list of the factors contributing to bone metastases is already large (Table 1) and will continue to grow. The effects of multiple factors and their relative expression levels probably change during the course of growth of a metastatic lesion, and the responses of the host cells at the metastatic site will also change over time. Many of the factors isolated from bone matrix1 have been generically named as growth factors. However, tumor cell proliferation is generally growth factor-independent, and such proliferation is not rate-limiting for the progress of bone metastases. Experiments with inhibitors of bone responses to tumor cells (but which do not directly target the tumor cells) effectively decrease tumor burden8,27,58,59. These results suggest that paracrine interactions between tumor cells and bone cells are central regulators of skeletal metastases, and that the regulation is not via control of cell proliferation.

**The vicious cycle**

Animal models have established that bone metastases involve a vicious cycle between tumor cells and the skeleton (Figure 1). The cycle is driven by four obvious contributors: the tumor cells, bone-forming osteoblasts, bone-destroying osteoclasts, and organic bone matrix. Osteoclast formation and activity is controlled by the osteoblast, adding complexity to the vicious cycle. The mineralized matrix of bone provides a rich store of growth factors, such as insulin-like and transforming growth factors1. These factors are synthesized by osteoblasts and released by osteoclasts. The factors reach high local concentrations in the bone microenvironment and can act on tumor cells to encourage metastatic growth. The products released from resorbing bone attract tumor cells50.

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**Figure 1.** Tumor stimulation of osteoblasts can increase both new bone formation and resorption. Tumor products, such as endothelin-1 and adrenomedullin, stimulate osteoblast (Obl) proliferation. Immature osteoblasts respond to osteolytic cytokines, such as parathyroid hormone and interleukin-11, by expressing RANK ligand (Y). RANK ligand stimulates bone resorption by osteoclasts, which releases growth factors, such as transforming growth factor-β, from mineralized matrix. Mature osteoblasts synthesize growth factors, which are incorporated into bone and also enrich the local microenvironment. Growth factors stimulate tumor cells. Osteoblasts lose RANK ligand expression during maturation. The balance of osteoblast proliferation versus maturation, plus tumor production of factors like PTHrP, determines whether bone metastases are osteoblastic, osteolytic, or mixed. The new bone synthesized in osteoblastic metastases is disorganized and of poor mechanical quantity.
In turn, breast cancers secrete many factors that act on bone cells. It is likely that at sites of osteoblastic metastases, the tumor cells continue to secrete osteolytic factors, such as parathyroid hormone-related protein, which stimulate bone resorption. Therapies targeting the vicious cycle can decrease metastases by lowering the concentrations of growth factors in bone. It is characteristic of skeletal metastases that the properties of the bone are altered, contributing to the clinical pathology seen in patients. As disease progresses, the bone and the bone cells probably become more and more abnormal, under the continuing influence of tumor-secreted factors. It should be borne in mind that the images of metastases seen in animal models represent a much-simplified version of the clinical picture. The animal models are of much shorter duration and involve homogeneous tumor lines, whereas bone metastases in patients are much more heterogeneous, even within individual patients.

Roles of other cells in bone to skeletal metastases

It is an oversimplification to consider only osteoblasts and osteoclasts as the interacting partners of tumor cells in the vicious cycle of cancer bone metastases. Vascular endothelial cells are a major fourth cellular component. Most of the tumor-produced factors discussed above are vasoactive and many are pro-angiogenic, including endothelin, adrenomedullin, IL-8, the CCN proteins, stanniocalcin, as well as VEGF. PTHrP may be anti-angiogenic. These same angiogenic factors are also increased by the hypoxic response in tumor cells, including endothelin, adrenomedullin, the CCN proteins, stanniocalcin. To further complicate the situation, many of these factors are both regulated by and regulators of VEGF, and many are also TGFβ-regulated genes. Thus, there must be an extremely complex cross-talk between endothelial cells, bone cells, and tumor cells at the metastatic site. Making sense of these interactions will require the development of novel and subtle experimental strategies.

Endothelial cells in bone differ from the cells lining blood vessels in other organs, which could contribute to the bone-tropism of certain tumors. Just as tumor-secreted factors can alter the phenotypes of bone cells in the vicinity of metastases, such factors will probably also alter the behavior of endothelial cells. Van der Pluijm et al. observed specific changes in host vascular markers in bone versus non-bone metastatic sites. Di Raimondo et al. similarly detected angiogenic factors at higher concentrations in bone marrow plasma than in the peripheral circulation of patients with multiple myeloma, suggesting the specific induction of angiogenic factor expression within the bone microenvironment of patients with cancer in the skeleton. Tumor cells are also likely to perturb the lineages of cells in bone. Bone marrow is a major site of stem cells, including the stem cells of the bone stromal lineage, and cells in bone such as pericytes could alter their differentiation under the influence of tumor-produced factors. Thus, tumor cells could alter the supply of osteoblastic precursors and also alter the differentiation of hematopoietic precursors into osteoclasts. The animal model that is the focus of this article relies on T-cell deficient nude mice, which ignores the contribution in patients of the immune system to both normal bone cell function, as well as to cell-mediated immune surveillance and killing of tumor cells.

Clinical applications

The bisphosphonates are a class of drugs that resemble pyrophosphate. The replacement of the central oxygen of pyrophosphate by a carbon in the bisphosphonate backbone results in resistance to hydrolysis and confers high affinity for bone mineral, which is the basis for bisphosphonate-radiouclide conjugates as diagnostic bone-scanning agents. The bisphosphonates have high affinity for bone, where they can persist for years. They are released at high concentrations in areas of active bone remodeling and are absorbed by nearby cells. They inhibit cells by several mechanisms, including the stimulation of apoptosis. Bisphosphonates are effective in animal models and the clinic. Whether bisphosphonates have significant effects in vivo on tumor cells or angiogenesis, especially at non-bone sites where their concentrations are low, is controversial.

An inhibitor of intracellular src signaling, when modified by the addition of a pair of phosphate groups, inhibited osteoclastic bone resorption. This approach could add bone specificity to existing chemotherapeutic and adjuvant compounds. Recombinant osteoprotegerin decreased osteolytic destruction and tumor burden in bone, without affecting metastases to soft-tissue sites in an animal model, and decreased cancer bone pain. Recombinant osteoprotegerin entered clinical trials but is likely to be superseded by neutralizing antibodies against RANK ligand.

A recent study identified 6-thioguanine and 6-thioguanosine as effective inhibitors of PTHrP transcription. These agents have long been used against leukaemias and several inflammatory disorders. They were effective in animal models of humoral hypercalcemia of malignancy and breast cancer bone metastases. Endothelin receptor antagonists are in extensive clinical trials, and their efficacy against osteoblastic metastasis is discussed above. Most of these adjuvant treatments target bone cells, but it may be possible to block the effects on tumors of bone-derived factors such as TGFβ.

Treatment options

Bisphosphonate drugs are currently approved for skeletal metastases due to multiple myeloma and solid tumors of the breast and prostate. In the last case, an anti-resorptive is effective against what are predominantly osteoblastic metastases. In fact, osteoblastic metastases are accompanied by active bone remodeling, and prostate cancer patients with bone metastases have markers of bone resorption higher than those seen in patients with osteolytic disease.

J.M. Chirgwin et al.: Metastatic tumor-bone interactions
Bisphosphonates are also effective in animal models of osteoblastic bone metastases. The results are consistent with the importance of the vicious cycle, outlined above and in Figure 1, to both osteolytic and osteoblastic diseases. The role of a vicious cycle in osteoblastic metastases is also supported by the observation that when patients with advanced metastatic prostate cancer were treated with the endothelin A receptor antagonist ABT-627, atrasentan, markers of bone resorption were decreased. Trials are now underway to test whether combining a bisphosphonate drug with an endothelin receptor antagonist is more effective than the single agent treatments.

Future directions and limitations

Areas of active research include the continuing identification of candidate osteolytic and osteoblastic factors. Many of those already identified require substantial further testing in vivo to determine whether they are valid targets for therapeutic intervention. They include IL-8, IL-11, CTGF, adrenomedullin, stanniocalcin, and CXCR-4. Angiogenesis is of obvious central importance in bone metastases. Many of the factors made by tumor cells are increased by hypoxia and in turn are angiogenic, in addition to having stimulatory actions on bone cells.

The roles of the abundant, bone-derived insulin-like growth factors need to be tested for their contributions to metastases to bone. IGF-2 is the most abundant bioactive factor in the mineralized matrix, but its role in skeletal metastasis, along with those of IGF-1, has been little studied. The effects of these molecules, through activation of the type 1 IGF-1 receptor on tumor cells and bone cells, are likely to be complex and extend beyond stimulation of growth. Actions of secreted IGFs are controlled by the IGF binding proteins. The extremely complex relationship between bone metastases and angiogenesis, discussed above, remains to be clarified.

The animal models, which are the focus of this article, have been limited to a modest number of cultured cell lines (Table 1). This is a strength in terms of defining molecular mechanisms, but it is clearly a weakness for understanding the more diverse and complex situations encountered in the clinic. We believe that this weakness is not effectively addressed by repeating the animal model experiments with more cell lines, even if funding were available for such confirmatory studies. A goal of the animal models is to provide platforms for pre-clinical testing of therapeutic interventions. If the animal models provide useful guidance in improving the care of patients with skeletal metastases, then they will have served their purpose well.

On a broader scale are the clinical consequences of bone metastases, in particular severe bone pain and systemic weight loss (cachexia), ET-1, for example, is nociceptive. Mechanisms of bone pain are specific and under active investigation. It seems likely that bone metastases release unknown factors into the circulation, which stimulate wasting of skeletal muscle. These syndromes are of great consequence to the patients who suffer from cancers of the breast and prostate, which are incurable once they become housed in bone. It is now appreciated that the standard treatments for patients with cancers of the breast and prostate result in bone loss. Not only does this result in skeletal morbidity for the patients, but increased bone turnover could enhance metastases to bone by stimulating the vicious cycle. Patients with treatment-related bone loss should benefit from therapy with bisphosphonate anti-resorptive drugs. Tumor-bone interactions, and the secreted factors which mediate them, offer targets for future therapeutic intervention to ameliorate or perhaps prevent skeletal metastases.

Acknowledgements

Work in the authors’ laboratory was supported by funding from the Gerald D. Arbuck Endowment and the Mellon Institute of the University of Virginia Cancer Center, and research grants from the NIH (R01 CA69158) and the U.S. Army (DAMD17-99-1-9401) to TAG and the Veterans Administration Research Service (Merit Award) and the U.S. Army (DAMD17-98-1-8245 and DAMD17-02-1-0586) to JMC. Mr. Cliff Martin assisted in the preparation of the figure.

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