Review

Clinical Cancer Research

Bad to the Bone: The Role of the Insulin-Like Growth Factor Axis in Osseous Metastasis

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Abstract

Bone metastases are a frequent complication of cancer that are associated with considerable morbidity. Current treatments may temporarily palliate the symptoms of bone metastases but often fail to delay their progression. Bones provide a permissive environment because they are characterized by dynamic turnover, secreting factors required for bone maintenance but also stimulating the establishment and growth of metastases. Insulin-like growth factors (IGF) are the most abundant growth factors in bone and are required for normal skeletal development and function. Via activation of the IGF-1 receptors (IGF-1R) and variant insulin receptors, IGFs promote cancer progression, aggressiveness, and treatment resistance. Of specific relevance to bone biology, IGFs contribute to the homing, dormancy, colonization, and expansion of bone metastases. Furthermore, preclinical evidence suggests that tumor cells can be primed to metastasize to bone by a high IGF-1 environment in the primary tumor, suggesting that bone metastases may reflect IGF dependency. Therapeutic targeting of the IGF axis may therefore provide an effective method for treating bone metastases. Indeed, anti–IGF-1R antibodies, IGF-1R tyrosine kinase inhibitors, and anti–IGF-1/2 antibodies have demonstrated antitumor activity in preclinical models of prostate and breast cancer metastases, either alone or in combination with other agents. Several studies suggest that such treatments can inhibit bone metastases without affecting growth of the primary tumor. Although previous trials of anti–IGF-1R drugs have generated negative results in unselected patients, these considerations suggest that future clinical trials of IGF-targeted agents may be warranted in patients with bone metastases.

Introduction

Bone metastases are a frequent complication of cancer, and the skeleton is the site of the most significant tumor burden in many patients with advanced disease (1). Prognosis after the development of bone metastases varies by tumor type, but in most cases, bone metastases lead to considerable morbidity, with devastating consequences including intractable bone pain, pathologic fractures, hypercalcemia, and spinal cord compression (2). Existing treatments for bone metastases are not curative, but may slow the progression and provide symptom palliation. Consequently, there is an unmet need for new therapeutic interventions (2).

Over the last few decades, extensive research has identified some of the molecular mechanisms that promote bone metastases, including bone-derived growth factors such as the insulin-like growth factors (IGF; ref. 3). Research suggests that IGFs play a fundamental role in bone development, remodeling, and repair, and contribute to key hallmarks of primary cancers, via alteration of stem-cell renewal/differentiation, epithelial–mesenchymal transition (EMT), and treatment resistance (4). In this review, we discuss the clinical significance of bone metastases, review the normal physiologic role of IGFs in bone development and homeostasis, and consider the potential role of the IGF axis in the metastasis of primary tumors to bone. Finally, we evaluate the available evidence suggesting that targeting this signaling network may lead to potential therapeutic strategies for the prevention and/or treatment of bone metastases.

Prevalence, Clinical Relevance, and Treatment of Bone Metastases

Bone metastases are a common feature of solid tumors, and in one U.S. study, were found to affect almost 7% of patients overall; the highest incidence of bone metastases was in prostate cancer (18%–29%), followed by lung (up to 13%), renal (up to 10%), and breast cancers (up to 8%; ref. 5). In some tumor types such as hepatocellular carcinoma, the incidence of bone metastases is increasing, likely due to improved tumor control at other disease sites (6, 7). Bone metastases can cause severe bone pain, which can be treated with palliative radiotherapy but is often difficult to control (8). Further, by promoting bone resorption, bone metastases can lead to bone fragility and skeletal-related events (SRE), including pathologic fracture, spinal cord compression, and hypercalcemia (1, 9, 10). SREs are typically associated with reduced quality of life and substantially higher healthcare costs (11). Tumors that have metastasized to bone are generally

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incurable (11); survival varies with primary cancer type and is lower if patients have skeletal complications (11). Indeed, in a large population-based cohort study, the median overall survival (OS) for patients with breast cancer with bone metastases was 16 months but only 7 months for patients with bone metastases and an SRE (11).

The main goals of treatment are to palliate bone pain, alleviate and prevent bone complications, maintain quality of life, and slow metastatic progression (12, 13). Symptom palliation can be achieved using analgesia, endocrine therapy, chemotherapy, localized radiation, and surgery. However, the only agents specifically designed to treat bone metastases are bone-targeting agents, including the bisphosphonates zoledronate and pamidronate; the targeted alpha therapy radium-223 dichloride; and the receptor activator of NF-κB ligand (RANKL)–inhibiting antibody denosumab (9, 12). Although radium-223 has been shown to prolong survival and delay time to first symptomatic skeletal event in metastatic prostate cancer, a recent phase III trial was prematurely unblinded because of an increase of fractures and deaths in patients treated with radium-223 in combination with abiraterone and prednisone (14). Bisphosphonates reduce skeletal morbidity in advanced breast cancer and can also decrease the number of bone metastases (15–17). However, 30% to 50% of patients treated with bone-targeting agents develop new bone metastases, skeletal complications, and disease progression, highlighting the need for more effective therapies (6).

The Role of IGF in Normal Bone Development and Remodeling

The IGF system is critical for skeletal growth and maintenance (18). All skeletal cells express IGF-1 and its receptor, IGF-1R, and require IGF-1 for normal development and function (19). IGF-1 and IGF-2 play an important role in regulating growth and development of normal human tissues by promoting cellular proliferation and differentiation via activation of IGF-1R and IGF-1R/insulin receptor (INSR) hybrids (4, 20). In addition, IGF-2 binds to the A isoform of the INSR (INSR-A), a fetal variant of the classical metabolic INSR (INSR-B), which is frequently overexpressed in tumors (4).

Bone development and remodeling are driven by the coordinated activity of osteoclasts and osteoblasts, which regulate bone resorption and formation, respectively (21, 22). Osteoblast proliferation is promoted by IGFs, transforming growth factor β (TGFβ), fibroblast growth factors (FGF), and platelet-derived growth factor (PDGF), and osteoclast apoptosis by TGFβ (1). Of these, IGF-1 and IGF-2 are the most abundant growth factors in bone (18, 23) and have been shown to directly influence both osteoclasts and osteoblasts (24). In particular, the IGF signaling pathway is thought to play a critical role in regulating osteoblast function (25). IGF-1 also helps maintain the normal interaction between osteoblasts and osteoclasts to support osteoclastogenesis (26), and *in vitro* data suggest that IGF-1 stimulates osteoclastic bone resorption by supporting the generation, differentiation, and activation of osteoclasts (26–29). IGF-2 also promotes differentiation and function of primary human osteoblasts and osteoclasts but is less potent than IGF-1 (27, 28).

The liver is the major source of circulating IGF-1, producing approximately 75% of plasma IGF-1 (30). IGF-1 is also produced locally by bone cells such as osteoblasts, chondrocytes, osteoclasts, and osteocytes, thereby functioning as an autocrine/paracrine effector to regulate bone turnover (19, 21, 24, 30, 31). In addition, an inactive form of IGF-1 is stored within the bone matrix, and is activated and released during osteoclast-mediated bone resorption (18). Data from human biopsies suggest that bone volume is positively associated with the IGF-1 content of bone matrix, but not IGF-2 content or serum IGF-1 (32). Notably, IGF-2 is nine times more abundant in adult human bone than IGF-1, unlike in mice, where IGF-1 content is higher postnatally (23).

Biology of Bone Metastases

Bones undergo constant and dynamic cell growth and turnover, and so provide a permissive environment for proliferation of tumor cells (1). A growth factor–rich environment contributes to the tropism of primary tumor cells for bone or bone marrow (22). For bone metastasis to occur, circulating cancer cells must arrest in the bone marrow cavity before migrating into the marrow stroma where they generate their own blood supply (1). Consistent with the seed and soil hypothesis proposed by Paget in 1889 (33), primary tumor cells (seeds) prime the bone microenvironment (soil) for metastasis by secreting factors that stimulate osteoblast activity and bone formation, thus enriching the bone microenvironment with osteoblast-derived growth factors that support the local growth of tumor cells (34). Consequently, both tumor cells and bone cells produce factors that promote malignant growth (13).

Interaction between tumor cells and the bone microenvironment occurs via sequential stages: tumor-cell homing, dormancy, colonization, and expansion (6). Tumor cells preferentially home and adhere to bone marrow endothelium, enabling their invasion into the bone marrow microenvironment via extravasation. Metastatic tumor cells then compete for occupancy of the hematopoietic stem cell (HSC) niche in bone marrow. Tumor cells may subsequently remain dormant in the HSC niche, or begin growth and colonization. Metastatic colonization may be delayed for years, resulting in relapse many years after diagnosis of the primary tumor (11, 13, 35, 36). Upon recovery from dormancy, tumor cells colonize bone and induce differentiation, recruitment, and activation of osteoclasts and/or osteoblasts (6, 37). Secretion of proosteoclastogenic factors such as TNFα, interleukin-8, and parathyroid hormone (PTH) leads to osteoclast-mediated bone resorption and further release of bone matrix–stored growth factors including IGFs, TGFβ, FGFs, and bone morphogenetic proteins (BMP). This sets up a vicious cycle of bone colonization and metastasis, known as the expansion stage (6, 22, 36). Such osteolytic bone metastases are frequently associated with breast and lung tumors (36). Conversely, the release of bone morphogenetic proteins such as TGFβ and FGF, in addition to the IGFs, enhances osteoblast differentiation and activity; the resulting osteoblastic bone metastases are commonly seen in prostate cancer (36, 38). Regardless of the mechanism, this reciprocal cross-talk between tumor and bone cells creates an environment ripe for metastatic growth (6, 37).

Although not all the key players in the development of bone metastases are yet known, multiple molecules and signaling pathways appear to be important for metastasis. Indeed, in addition to the IGF pathway, NF-κB, matrix metalloproteases, and the Wnt, stromal cell–derived factor 1 (CXCL12)/C-X-C chemokine receptor type 4 (CXCR4) and PI3K/AKT signaling axes

may also play key roles in the development and progression of bone metastases (39–46).

The Role of the IGF Axis in Bone Metastases

Altered IGF axis signaling is thought to contribute to the pathogenesis of primary bone tumors including Ewing sarcoma (47) and osteosarcoma, with evidence of IGF axis activation due to downregulation of IGF-binding proteins observed in osteosarcomas as compared with osteoblasts and mesenchymal stem cells (48). Another osteosarcoma study identified recurrent mutations of IGF axis genes that were predicted to result in the activation of IGF-1R signaling in 7%, and *IGF1R* gene amplification in 14% of tumors (49).

The IGFs can also encourage metastasis by promoting anchorage-independent growth, motility, and invasion (50, 51). In particular, IGF-1R signaling via INSR substrate 2 (IRS-2) has been implicated in mediating invasion and metastasis versus proliferation (51, 52). Interestingly, IGF-1R inhibition via dominant negative IGF-1R, or an IGF-1R–blocking antibody inhibits metastasis without affecting primary tumor growth (53, 54).

IGFs have been implicated in each of the key stages of bone metastasis: homing, dormancy, colonization, and expansion (6). In triple-negative breast cancer, stromal cancer–associated fibroblasts were identified as the source of IGF-1 and CXCL12, which were shown to prime cells to home to the CXCL12- and IGF-1–rich bone microenvironment, in a process dependent on CXCR4 and IGF-1R expression by cancer cells (55). IGF-1 also enhances homing of myeloma cells to bone marrow, and acts as a chemo-attractant that increases adherence to the extracellular matrix via activation of beta integrin and PI3K/AKT (56). IGF-1R upregulation was shown to promote adherence of neuroblastoma cells to human bone marrow endothelial cells, and transendothelial migration was decreased by IGF-1R inhibition (57).

IGF-1 and IGF-2 have been shown to mediate tumor cell dormancy in bone in models of pancreatic cancer and osteosarcoma (58, 59). In a murine pancreatic cancer model, the activation of IGF-1/AKT signaling was a common survival mechanism in dormant cancer cells that had survived ablation of the oncogenic drivers KRAS and MYC (58). In clinical osteosarcomas and a mouse model of MYC-driven osteosarcoma, IGF-2 expression increased following chemotherapy, and prolonged IGF-2 exposure induced a dormancy-like state, characterized by attenuated responsiveness of the IGF axis to IGF-2, with low levels of AKT–mTOR activity, cell-cycle arrest, and autophagy (59).

Finally, IGF-1 and -2 appear to play important roles in bone colonization and expansion by metastasizing tumor cells. In one study, bone-derived IGFs stimulated metastasis of breast cancer to bone by increasing cancer cell proliferation and survival, via AKT activation and recruitment of NF-κB (60). Further, culture medium from cells stimulated to undergo bone resorption was found to contain high concentrations of IGF-1; notably, the anchorage-independent growth of human breast cancer cells cultured in this medium was inhibited by the IGF-1R–neutralizing antibody αIR3, but not by antibodies against TGFβ, FGF-1 or -2, or PDGF-BB (60). Reflecting cross-talk between the IGF axis and hypoxia signaling, IGF-1 released during RANKL-induced bone resorption was shown to cooperate with tumor cell–derived hypoxia-inducible factors (HIF) in the hypoxic bone microenvironment, to promote bone marrow colonization and establishment of osteoblastic bone metastases in a murine osteosarcoma model (61). Similarly, growth of human breast cancer cells in a human adult bone model was facilitated by active osteoclasts induced by RANKL, and IGFs released following bone resorption (62). The IGF axis may also be involved in bone invasion in oral squamous cell carcinoma, with the depletion of IGF-2 mRNA-binding protein-3 inhibiting regional bone destruction in a xenograft mouse model (63).

Could the IGF Axis Be Targeted for the Treatment of Bone Metastases?

Given the apparent involvement of the IGF axis in the generation and growth of bone metastases, targeting key molecules involved in this pathway represents a rational approach to help prevent and/or manage bone metastases. Indeed, considerable preclinical evidence supports this hypothesis, with most available evidence coming from models of metastatic prostate and breast cancer.

Several preclinical studies have investigated the effects of antibodies or tyrosine kinase inhibitors (TKI) directed at IGF-1R, the results of which suggest that IGF axis inhibition can at least partially prevent the establishment and progression of bone tumors (Table 1). Furthermore, whole-genome expression analysis of bone metastasis biopsies from patients with prostate cancer suggested an inverse relationship between IGF-1R expression and immune cell function, (64) suggesting that IGF-1R inhibition has the potential to stimulate an antitumor response from endogenous immune cells, a concept that is also supported by models of other tumor types (65–68).

Therapeutic targeting of the ligands IGF-1 and IGF-2 has been investigated in preclinical models of prostate and breast cancer metastasis (Table 1). KM1468, an anti–IGF-1/2 antibody, suppressed metastatic development and progression of prostate cancer cells into implanted human adult bone (69). Using the same model, the specific anti–IGF-2 antibody m610 significantly reduced the growth of prostate cancer cells after injection into human bone implanted in the mammary fat pad, but not when the same cells were injected without human bone. These data support the importance of IGF-2 in promoting the progression of bone metastases, and reinforce the relevance of paracrine IGF signaling in bone metastases (23). Similarly, KM1468 reduced the growth of human breast cancer cells in human adult bone implanted into mice but had no effect on growth of the same cells subcutaneously injected in the absence of bone (62). These data are consistent with reports that IGF-1R inhibition can inhibit metastases without affecting the primary tumor (53, 54). Likewise, the transfection of human breast cancer cells with dominant-negative IGF-1R markedly inhibited the development of osteolytic bone metastases, whereas lung metastases were largely unaffected (60). Such findings suggest that IGF inhibition may have more impact in the bone microenvironment (where IGFs play an important role in the normal homeostatic functioning of the tissue) than in the primary tumor.

It should be noted that although the findings from these studies are encouraging, the IGF system of mice is substantially different from that in humans; thus, in contrast to mouse bone cells, human bone cells produce less IGF-1 than IGF-2 (23, 70). Thus, the roles of the IGFs and the effects of their inhibition may also differ between species. Indeed, because IGF-2 also induces proliferative/antiapoptotic signaling via INSR-A (4), the contribution

Table 1. *In vitro* and *in vivo* studies investigating inhibition of the IGF/IGF-1R axis for bone metastases and osteosarcoma

Tumor type	Inhibitor	Target	Model	Results	Reference
PC – bone metastases	NVP-AEW541 (TKI) ± castration	IGF-1R	Rat PC cell line (Dunning) injected into tibial bone of immune-competent rats. NVP-AEW541 given 4 weeks later, then by castration/sham castration	Tumor cell proliferation significantly reduced independently of the growth site (inside or outside bone marrow cavity); maximum decrease (24%) within the bone marrow cavity when combined with castration	64
PC – bone metastases	NVP-AEW541 (TKI) ± simvastatin	IGF-1R	Human PC cells (PC-3 and 22Rv1) cocultured with neonatal mouse calvarial bones (to simulate the bone microenvironment)	Significant increase in apoptotic cells; most pronounced when combined with simvastatin	89
BC – bone metastases	486STOP (dominant-negative IGF-1R)	IGF (competitive inhibition of binding to IGF-1R)	Mice inoculated with human BC cells (MDA-MB-231) stably transfected with 486STOP	Reduction in bone metastases in 486STOP-transfected cells versus controls	60, 61, 64
BC – bone metastases	KM1468 (anti-human mAb)	IGF-1, IGF-2	Human BC cells (MCF-7) injected into human adult bone implanted into mice; mice treated for 4 weeks with KM1468 immediately after injection of BC cells	Tumor area of MCF-7 cells in the implanted bone decreased to about 30% of the tumor area in controls. No effect on the growth of subcutaneously injected MCF-7 cells	62
PC – bone metastases	KM1468 (anti-human mAb)	IGF-1, IGF-2	Human PC cells (MDA PCa 2b) injected into human adult bone implanted into mice; KM1468 given for 4 weeks immediately before or 4 weeks after injection of PC cells	KM1468 markedly suppressed the development of new bone tumors and progression of established tumor foci	69
PC – bone metastases	m610 (anti-human mAb)	IGF-2	Human PC cells (MDA PCa 2b) injected into human adult bone implanted into mice; m610 given for 4 weeks immediately after injection of PC cells	m610 significantly, but not completely, suppressed the growth of bone tumors via suppression of tumor cell proliferation. No inhibition in PC cells not implanted in bone	23
Osteosarcoma	R1507 (anti-IGF-1R mAb), cetuximab (anti-EGFR mAb), XGFR (bispecific IGF-1R/EGFR Ab)	IGF-1R ± EGFR	Human osteosarcoma cells injected into mouse tibia; mice then treated with R1507, cetuximab, R1507 + cetuximab, or XGFR for 3 weeks	Primary tumor growth significantly inhibited by cetuximab and XGFR; R1507 had no effect, alone or in combination with cetuximab. Mice treated with XGFR, but not other agents, had significantly fewer lung metastases than controls	68

Abbreviations: Ab, antibody; BC, breast cancer; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; PC, prostate cancer.

of IGF-1R–mediated signaling may be less important in humans than in mice.

Clinical Studies of IGF Axis Inhibition and Implications for Future Studies

To date, no clinical trials have specifically examined the impact of IGF inhibition on the development and/or progression of bone metastases. Previous studies of monoclonal antibodies and TKIs targeting IGF-1R in patients with a range of solid tumors have yielded mixed, mostly negative, results, both as monotherapy and when combined with established therapies (see Supplementary Table S1 for details). Objective responses have been low and mainly limited to studies in osteosarcoma, Ewing sarcoma, and other soft tissue sarcomas (71–75). The failure of IGF-1R–inhibitory drugs to impact tumor growth in unselected patients may be attributable to compensatory activation of other signaling pathways, including those involving the epidermal growth factor receptor (EGFR; ref. 76) and Wnt (77), and by the lack of a validated biomarker for patient selection (4). Further, IGF-1R inhibitors are commonly associated with hyperglycemia, due to coinhibition of INSR-B (71, 72, 78–85), which may preclude their use at therapeutic doses; consequently, most agents targeting IGF-1R are no longer in clinical development.

Despite these limitations, there remains considerable interest in the therapeutic targeting of the IGF axis, particularly in view of the recent development of IGF ligand–neutralizing antibodies. The issue of dose-limiting hyperglycemia may have been overcome by the development of such antibodies, which do not interfere with glucose metabolism (86, 87). These agents inhibit proliferative/antiapoptotic signaling via both IGF-1R and INSR-A, without interference with the metabolic INSR-B isoform (4). Given the disappointing clinical results with the IGF-1R–targeted agents, it is possible that IGF-1R is activated and critically involved in oncogenic signaling pathways in only a minority of patients (88). However, the evidence summarized herein supports a clear role of the IGF axis in bone metastasis development, which suggests that the presence of bone metastases could potentially indicate involvement of an IGF-dependent process.

Summary

Bones are the sites of dynamic cell turnover that provide a supportive environment for the establishment and growth of tumor metastases (1). Bone metastases are a frequent

complication in patients with advanced cancer and a significant cause of morbidity (5, 8). The IGF axis plays an important role in bone development and remodeling (18), and is implicated in metastasis of primary tumors to bone. Preclinical data demonstrate that inhibition of IGF axis signaling can suppress metastasis and tumor cell proliferation in bone (23, 60, 62, 64). Most evidence related to the value of targeting IGF comes from the models of breast and prostate cancer bone metastases, probably because these cancers are commonly associated with metastatic spread to the bone (5). Preliminary evidence suggests that IGF inhibition may also be relevant to the treatment of bone metastases from other primary tumors, such as oral squamous cell carcinoma (63). As yet, there is no clinical evidence to support the use of IGF-targeted therapies as specific treatments for bone metastasis, and there are differences in IGF production between human and rodent bone cells (70) that may impact clinical relevance. Nevertheless, given the known involvement of the IGF axis in bone metastasis (6, 60, 61), and initial preclinical data supporting the utility of IGF blockade in this context (23, 60, 62, 64), we suggest that exploration of the potential benefits of IGF inhibition may be warranted in patients with bone metastases, particularly for breast and prostate cancers.

Disclosure of Potential Conflicts of Interest

V.M. Macaulay is a consultant/advisory board member for Boehringer Ingelheim. A.V. Lee is Senior Advisor, Translational Sciences at UPMC Enterprises. T. Bogenrieder holds ownership interest (including patents) in Roche, Seattle Genetics, Celgene, Gilead, and Immunogen. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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References

1. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002;2:584–93.
2. Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, et al. Bone metastases: an overview. Oncol Rev 2017;11:321.
3. Casimiro S, Ferreira AR, Mansinho A, Alho I, Costa L. Molecular mechanisms of bone metastasis: which targets came from the bench to the bedside? Int J Mol Sci 2016;17:1415.
4. Simpson A, Petnga W, Macaulay VM, Weyer-Czernilofsky U, Bogenrieder T. Insulin-like growth factor (IGF) pathway targeting in cancer: role of the IGF axis and opportunities for future combination studies. Target Oncol 2017;12:571–97.
5. Hernandez RK, Wade SW, Reich A, Pirolli M, Liede A, Lyman GH. Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States. BMC Cancer 2018;18:44.
6. Weilbaecher KN, Guise TA, McCauley LK. Cancer to bone: a fatal attraction. Nat Rev Cancer 2011;11:411–25.
7. Fukutomi M, Yokota M, Chuman H, Harada H, Zaitsu Y, Funakoshi A, et al. Increased incidence of bone metastases in hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2001;13:1083–8.
8. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27:165–76.
9. Hernandez RK, Adhia A, Wade SW, O'Connor E, Arellano J, Francis K, et al. Prevalence of bone metastases and bone-targeting agent use among solid tumor patients in the United States. Clin Epidemiol 2015;7:335–45.
10. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243s–49s.
11. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group. Bone health in cancer patients: ESMO clinical practice guidelines. Ann Oncol 2014;25:iii124–37.
12. Zheng H, Li W, Kang Y. Tumor-stroma interactions in bone metastasis: molecular mechanisms and therapeutic implications. Cold Spring Harb Symp Quant Biol 2016;81:151–61.
13. Steeg PS. Targeting metastasis. Nat Rev Cancer 2016;16:201–18.
14. Parker C, Heidenreich A, Nilsson S, Shore N. Current approaches to incorporation of radium-223 in clinical practice. Prostate Cancer Prostatic Dis 2018;21:37–47.
15. Fromigue O, Kheddoumi N, Body JJ. Bisphosphonates antagonise bone growth factors' effects on human breast cancer cells survival. Br J Cancer 2003;89:178–84.
16. Tang X, Zhang Q, Shi S, Yen Y, Li X, Zhang Y, et al. Bisphosphonates suppress insulin-like growth factor 1-induced angiogenesis via the HIF-1alpha/VEGF signaling pathways in human breast cancer cells. Int J Cancer 2010;126:90–103.
17. Rizzoli R, Body JJ, Brandi ML, Cannata-Andia J, Chappard D, El Maghraoui A, et al. Cancer-associated bone disease. Osteoporos Int 2013;24:2929–53.
18. Kawai M, Rosen CJ. The insulin-like growth factor system in bone: basic and clinical implications. Endocrinol Metab Clin North Am 2012;41:323–33.
19. Bikle DD, Wang Y. Insulin-like growth factor-I and bone. IBMS BoneKEy 2011;8:328–41.
20. Chitnis MM, Yuen JS, Protheroe AS, Pollak M, Macaulay VM. The type 1 insulin-like growth factor receptor pathway. Clin Cancer Res 2008;14:6364–70.
21. Sheng MH, Lau KH, Baylink DJ. Role of osteocyte-derived insulin-like growth factor I in developmental growth, modeling, remodeling, and regeneration of the bone. J Bone Metab 2014;21:41–54.
22. Roodman GD. Mechanisms of bone metastasis. N Engl J Med 2004;350:1655–64.
23. Kimura T, Kuwata T, Ashimine S, Yamazaki M, Yamauchi C, Nagai K, et al. Targeting of bone-derived insulin-like growth factor-II by a human neutralizing antibody suppresses the growth of prostate cancer cells in a human bone environment. Clin Cancer Res 2010;16:121–9.
24. Crane JL, Cao X. Function of matrix IGF-1 in coupling bone resorption and formation. J Mol Med 2014;92:107–15.
25. Govoni KE. Insulin-like growth factor-I molecular pathways in osteoblasts: potential targets for pharmacological manipulation. Curr Mol Pharmacol 2012;5:143–52.
26. Wang Y, Nishida S, Elalieh HZ, Long RK, Halloran BP, Bikle DD. Role of IGF-I signaling in regulating osteoclastogenesis. J Bone Miner Res 2006;21:1350–8.
27. Bosetti M, Sabbatini M, Nicoli E, Fusaro L, Cannas M. Effects and differentiation activity of IGF-I, IGF-II, insulin and preptin on human primary bone cells. Growth Factors 2013;31:57–65.
28. Xian L, Wu X, Pang L, Lou M, Rosen CJ, Qiu T, et al. Matrix IGF-1 maintains bone mass by activation of mTOR in mesenchymal stem cells. Nat Med 2012;18:1095–101.
29. Mochizuki H, Hakeda Y, Wakatsuki N, Usui N, Akashi S, Sato T, et al. Insulin-like growth factor-I supports formation and activation of osteoclasts. Endocrinology 1992;131:1075–80.

30. Bikle DD, Tahimic C, Chang W, Wang Y, Philippou A, Barton ER. Role of IGF-I signaling in muscle bone interactions. Bone 2015;80:79–88.
31. Tahimic CG, Wang Y, Bikle DD. Anabolic effects of IGF-1 signaling on the skeleton. Front Endocrinol 2013;4:6.
32. Seck T, Scheppach B, Scharla S, Diel I, Blum WF, Bismar H, et al. Concentration of insulin-like growth factor (IGF)-I and -II in iliac crest bone matrix from pre- and postmenopausal women: relationship to age, menopause, bone turnover, bone volume, and circulating IGFs. J Clin Endocrinol Metab 1998;83:2331–7.
33. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889;133:571–73.
34. Logothetis CJ, Lin SH. Osteoblasts in prostate cancer metastasis to bone. Nat Rev Cancer 2005;5:21–8.
35. Zhang XH, Wang Q, Gerald W, Hudis CA, Norton L, Smid M, et al. Latent bone metastasis in breast cancer tied to Src-dependent survival signals. Cancer Cell 2009;16:67–78.
36. D'Oronzo S, Brown J, Coleman R. The role of biomarkers in the management of bone-homing malignancies. J Bone Oncol 2017;9:1–9.
37. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, et al. Pre-metastatic niches: organ-specific homes for metastases. Nat Rev Cancer 2017;17:302–17.
38. Sohail A, Sherin L, Butt SI, Javed S, Li Z, Iqbal S, et al. Role of key players in paradigm shifts of prostate cancer bone metastasis. Cancer Manag Res 2018;10:1619–26.
39. Tong HB, Zou CL, Qin SY, Meng J, Keller ET, Zhang J, et al. Prostate cancer tends to metastasize in the bone-mimicking microenvironment via activating NF-kappaB signaling. J Biomed Res 2018;32:343–53.
40. Jin R, Sterling JA, Edwards JR, DeGraff DJ, Lee C, Park SI, et al. Activation of NF-kappa B signaling promotes growth of prostate cancer cells in bone. PLoS One 2013;8:e60983.
41. Chen X, Pei Z, Peng H, Zheng Z. Exploring the molecular mechanism associated with breast cancer bone metastasis using bioinformatic analysis and microarray genetic interaction network. Medicine 2018; 97:e12032.
42. Tseng JC, Lin CY, Su LC, Fu HH, Yang SD, Chuu CP. CAPE suppresses migration and invasion of prostate cancer cells via activation of non-canonical Wnt signaling. Oncotarget 2016;7:38010–24.
43. Campbell JP, Karolak MR, Ma Y, Perrien DS, Masood-Campbell SK, Penner NL, et al. Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. PLoS Biol 2012;10: e1001363.
44. Tauro M, Lynch CC. Cutting to the chase: how matrix metalloproteinase-2 activity controls breast-cancer-to-bone metastasis. Cancers 2018; 10:E185.
45. Sun YX, Wang J, Shelburne CE, Lopatin DE, Chinnaiyan AM, Rubin MA, et al. Expression of CXCR4 and CXCL12 (SDF-1) in human prostate cancers (PCa) *in vivo*. J Cell Biochem 2003;89:462–73.
46. Jinnah AH, Zacks BC, Gwam CU, Kerr BA. Emerging and established models of bone metastasis. Cancers 2018;10:E176.
47. Gorlick R, Janeway K, Lessnick S, Randall RL, Marina N. Children's Oncology Group's 2013 blueprint for research: bone tumors. Pediatr Blood Cancer 2013;60:1009–15.
48. Yang R, Piperdi S, Zhang Y, Zhu Z, Neophytou N, Hoang BH, et al. Transcriptional profiling identifies the signaling axes of IGF and transforming growth factor-b as involved in the pathogenesis of osteosarcoma. Clin Orthop Relat Res 2016;474:178–89.
49. Behjati S, Tarpey PS, Haase K, Ye H, Young MD, Alexandrov LB, et al. Recurrent mutation of IGF signalling genes and distinct patterns of genomic rearrangement in osteosarcoma. Nat Commun 2017;8:15936.
50. Samani AA, Yakar S, LeRoith D, Brodt P. The role of the IGF system in cancer growth and metastasis: overview and recent insights. Endocr Rev 2007;28: 20–47.
51. Brook N, Brook E, Dharmarajan A, Dass CR, Chan A. Breast cancer bone metastases: pathogenesis and therapeutic targets. Int J Biochem Cell Biol 2018;96:63–78.
52. Chan BT, Lee AV. Insulin receptor substrates (IRSs) and breast tumorigenesis. J Mammary Gland Biol Neoplasia 2008;13:415–22.
53. Sachdev D, Hartell JS, Lee AV, Zhang X, Yee D. A dominant negative type I insulin-like growth factor receptor inhibits metastasis of human cancer cells. J Biol Chem 2004;279:5017–24.
54. Sachdev D, Zhang X, Matise I, Gaillard-Kelly M, Yee D. The type I insulin-like growth factor receptor regulates cancer metastasis independently of primary tumor growth by promoting invasion and survival. Oncogene 2010;29:251–62.
55. Zhang XH, Jin X, Malladi S, Zou Y, Wen YH, Brogi E, et al. Selection of bone metastasis seeds by mesenchymal signals in the primary tumor stroma. Cell 2013;154:1060–73.
56. Vishwamitra D, George SK, Shi P, Kaseb AO, Amin HM. Type I insulin-like growth factor receptor signaling in hematological malignancies. Oncotarget 2017;8:1814–44.
57. van Golen CM, Schwab TS, Kim B, Soules ME, Su Oh S, Fung K, et al. Insulin-like growth factor-I receptor expression regulates neuroblastoma metastasis to bone. Cancer Res 2006;66:6570–8.
58. Rajbhandari N, Lin WC, Wehde BL, Triplett AA, Wagner KU. Autocrine IGF1 signaling mediates pancreatic tumor cell dormancy in the absence of oncogenic drivers. Cell Rep 2017;18:2243–55.
59. Shimizu T, Sugihara E, Yamaguchi-Iwai S, Tamaki S, Koyama Y, Kamel W, et al. IGF2 preserves osteosarcoma cell survival by creating an autophagic state of dormancy that protects cells against chemotherapeutic stress. Cancer Res 2014;74:6531–41.
60. Hiraga T, Myoui A, Hashimoto N, Sasaki A, Hata K, Morita Y, et al. Bone-derived IGF mediates crosstalk between bone and breast cancer cells in bony metastases. Cancer Res 2012;72:4238–49.
61. Kuchimaru T, Hoshino T, Aikawa T, Yasuda H, Kobayashi T, Kadonosono T, et al. Bone resorption facilitates osteoblastic bone metastatic colonization by cooperation of insulin-like growth factor and hypoxia. Cancer Sci 2014;105:553–9.
62. Sangai T, Fujimoto H, Miyamoto S, Maeda H, Nakamura M, Ishii G, et al. Roles of osteoclasts and bone-derived IGFs in the survival and growth of human breast cancer cells in human adult bone implanted into nonobese diabetic/severe combined immunodeficient mice. Clin Exp Metastasis 2008;25:401–10.
63. Hwang YS, Ahn SY, Moon S, Zheng Z, Cha IH, Kim J, et al. Insulin-like growth factor-II mRNA binding protein-3 and podoplanin expression are associated with bone invasion and prognosis in oral squamous cell carcinoma. Arch Oral Biol 2016;69:25–32.
64. Nordstrand A, Bergstrom SH, Thysell E, Bovinder-Ylitalo E, Lerner UH, Widmark A, et al. Inhibition of the insulin-like growth factor-1 receptor potentiates acute effects of castration in a rat model for prostate cancer growth in bone. Clin Exp Metastasis 2017;34:261–71.
65. Liu X, Turbyville T, Fritz A, Whitesell L. Inhibition of insulin-like growth factor I receptor expression in neuroblastoma cells induces the regression of established tumors in mice. Cancer Res 1998;58:5432–8.
66. Schillaci R, Salatino M, Cassataro J, Proietti CJ, Giambartolomei GH, Rivas MA, et al. Immunization with murine breast cancer cells treated with antisense oligodeoxynucleotides to type I insulin-like growth factor receptor induced an antitumoral effect mediated by a CD8+ response involving Fas/Fas ligand cytotoxic pathway. J Immunol 2006;176:3426–37.
67. Durfort T, Tkach M, Meschaninova MI, Rivas MA, Elizalde PV, Venyaminova AG, et al. Small interfering RNA targeted to IGF-IR delays tumor growth and induces proinflammatory cytokines in a mouse breast cancer model. PLoS One 2012;7:e29213.
68. Gvozdenovic A, Boro A, Born W, Muff R, Fuchs B. A bispecific antibody targeting IGF-IR and EGFR has tumor and metastasis suppressive activity in an orthotopic xenograft osteosarcoma mouse model. Am J Cancer Res 2017;7:1435–49.
69. Goya M, Miyamoto S, Nagai K, Ohki Y, Nakamura K, Shitara K, et al. Growth inhibition of human prostate cancer cells in human adult bone implanted into nonobese diabetic/severe combined immunodeficient mice by a ligand-specific antibody to human insulin-like growth factors. Cancer Res 2004;64:6252–8.
70. Avnet S, Sciacca L, Salerno M, Gancitano G, Cassarino MF, Longhi A, et al. Insulin receptor isoform A and insulin-like growth factor II as additional treatment targets in human osteosarcoma. Cancer Res 2009;69:2443–52.
71. Tap WD, Demetri G, Barnette P, Desai J, Kavan P, Tozer R, et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. J Clin Oncol 2012;30:1849–56.
72. Schwartz GK, Tap WD, Qin LX, Livingston MB, Undevia SD, Chmielowski B, et al. Cixutumumab and temsirolimus for patients with bone and soft-

tissue sarcoma: a multicentre, open-label, phase 2 trial. Lancet Oncol 2013; 14:371–82.
73. Anderson PM, Bielack SS, Gorlick RG, Skubitz K, Daw NC, Herzog CE, et al. A phase II study of clinical activity of SCH 717454 (robatumumab) in patients with relapsed osteosarcoma and Ewing sarcoma. Pediatr Blood Cancer 2016;63:1761–70.
74. Juergens H, Daw NC, Geoerger B, Ferrari S, Villarroel M, Aerts I, et al. Preliminary efficacy of the anti-insulin-like growth factor type 1 receptor antibody figitumumab in patients with refractory Ewing sarcoma. J Clin Oncol 2011;29:4534–40.
75. Pappo AS, Patel SR, Crowley J, Reinke DK, Kuenkele KP, Chawla SP, et al. R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: results of a phase II Sarcoma Alliance for Research through Collaboration study. J Clin Oncol 2011;29:4541–7.
76. Liu C, Zhang Z, Tang H, Jiang Z, You L, Liao Y. Crosstalk between IGF-1R and other tumor promoting pathways. Curr Pharm Des 2014;20: 2912–21.
77. Rota LM, Albanito L, Shin ME, Goyeneche CL, Shushanov S, Gallagher EJ, et al. IGF1R inhibition in mammary epithelia promotes canonical Wnt signaling and Wnt1-driven tumors. Cancer Res 2014;74:5668–79.
78. Schoffski P, Adkins D, Blay JY, Gil T, Elias AD, Rutkowski P, et al. An open-label, phase 2 study evaluating the efficacy and safety of the anti-IGF-1R antibody cixutumumab in patients with previously treated advanced or metastatic soft-tissue sarcoma or Ewing family of tumours. Eur J Cancer 2013;49:3219–28.
79. Pappo AS, Vassal G, Crowley JJ, Bolejack V, Hogendoorn PC, Chugh R, et al. A phase 2 trial of R1507, a monoclonal antibody to the insulin-like growth factor-1 receptor (IGF-1R), in patients with recurrent or refractory rhabdomyosarcoma, osteosarcoma, synovial sarcoma, and other soft tissue sarcomas: results of a Sarcoma Alliance for Research through Collaboration study. Cancer 2014;120:2448–56.
80. Reidy-Lagunes DL, Vakiani E, Segal MF, Hollywood EM, Tang LH, Solit DB, et al. A phase 2 study of the insulin-like growth factor-1 receptor inhibitor MK-0646 in patients with metastatic, well-differentiated neuroendocrine tumors. Cancer 2012;118:4795–800.
81. Hanna NH, Dahlberg SE, Kolesar JM, Aggarwal C, Hirsch FR, Ramalingam SS, et al. Three-arm, randomized, phase 2 study of carboplatin and paclitaxel in combination with cetuximab, cixutumumab, or both for advanced non-small cell lung cancer (NSCLC) patients who will not receive bevacizumab-based therapy: an Eastern Cooperative Oncology Group (ECOG) study (E4508). Cancer 2015;121:2253–61.
82. Chiappori AA, Otterson GA, Dowlati A, Traynor AM, Horn L, Owonikoko TK, et al. A randomized phase II study of linsitinib (OSI-906) versus topotecan in patients with relapsed small-cell lung cancer. Oncologist 2016;21:1163–4.
83. Schmitz S, Kaminsky-Forrett MC, Henry S, Zanetta S, Geoffrois L, Bompas E, et al. Phase II study of figitumumab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: clinical activity and molecular response (GORTEC 2008-02). Ann Oncol 2012;23: 2153–61.
84. Abou-Alfa GK, Capanu M, O'Reilly EM, Ma J, Chou JF, Gansukh B, et al. A phase II study of cixutumumab (IMC-A12, NSC742460) in advanced hepatocellular carcinoma. J Hepatol 2014;60:319–24.
85. Becerra CR, Salazar R, Garcia-Carbonero R, Thomas AL, Vazquez-Mazon FJ, Cassidy J, et al. Figitumumab in patients with refractory metastatic colorectal cancer previously treated with standard therapies: a nonrandomized, open-label, phase II trial. Cancer Chemother Pharmacol 2014;73:695–702.
86. Friedbichler K, Hofmann MH, Kroez M, Ostermann E, Lamche HR, Koessl C, et al. Pharmacodynamic and antineoplastic activity of BI 836845, a fully human IGF ligand-neutralizing antibody, and mechanistic rationale for combination with rapamycin. Mol Cancer Ther 2014;13:399–409.
87. Haluska P, Menefee M, Plimack ER, Rosenberg J, Northfelt D, LaVallee T, et al. Phase I dose-escalation study of MEDI-573, a bispecific, antiligand monoclonal antibody against IGFI and IGFII, in patients with advanced solid tumors. Clin Cancer Res 2014;20:4747–57.
88. Sclafani F, Kim TY, Cunningham D, Kim TW, Tabernero J, Schmoll HJ, et al. A randomized phase II/III study of dalotuzumab in combination with cetuximab and irinotecan in chemorefractory, KRAS wild-type, metastatic colorectal cancer. J Natl Cancer Inst 2015;107:djv258.
89. Nordstrand A, Lundholm M, Larsson A, Lerner UH, Widmark A, Wikström P. Inhibition of the insulin-like growth factor-1 receptor enhances effects of simvastatin on prostate cancer cells in co-culture with bone. Cancer Microenviron 2013;6:231–40.