

Editorial

Molecularly Targeted Therapies in Breast Cancer Bone Metastases

Breast cancer is prone to metastasize to bone: around 70-80% of patients with advanced disease exhibit bone metastases. Once metastatic cells are in the bone marrow, they do not, on their own, destroy bone. Instead, they alter the functions of bone-resorbing (osteoclasts) and bone-forming (osteoblasts) cells [1]. For example, breast cancer cells secrete many factors that stimulate the activity of osteoclasts [interleukins IL-6, IL-8 and IL-11, parathyroid hormone related peptide (PTHrP)] and inhibit that of osteoblasts [Noggin, dickkopf-1 (DKK-1)], leading to the formation of osteolytic lesions [1]. Conversely, cancer cells may release endothelin-1, which stimulates bone formation and inhibits bone resorption, leading to the formation of osteoblastic lesions [1]. Overall, these skeletal lesions (whether they are lytic or blastic) can be fatal or may rapidly impede the quality of life of patients by causing pathological fractures, hypercalcemia, nerve compression and loss of mobility. Most of these patients will also experience substantial, life-altering cancer-induced bone pain. Yet, current treatments are only palliative and do not provide life-prolonging benefit to patients with advanced cancers. There is therefore a need to better understand molecular mechanisms associated with cancer-induced bone diseases in order to improve existing therapies and/or develop new targeted therapies.

The realization that normal cells in the bone microenvironment support the development of skeletal lesions has led to the use of bisphosphonates, as inhibitors of osteoclast-mediated bone resorption, in the treatment of patients with bone metastases. Indirect and direct anti-tumor effects of bisphosphonates have been also reported in a number of preclinical studies [2]. In this issue of *Current Pharmaceutical Design*, Holen and Coleman [3] summarize the main studies that have investigated the anti-tumor effects of bisphosphonates, alone or in combination with other anti-cancer agents, in animal models of breast cancer bone metastasis. The authors also give an overview of the use of bisphosphonates in the treatment of breast cancer, including adjuvant bisphosphonate treatment which may have benefits on disease recurrence when combined with standard endocrine therapy. Finally, the authors show that there are some potential limitations to the use of bisphosphonates, suggesting that additional drugs targeting osteoclasts are needed.

The RANK/RANKL signaling pathway is the primary mediator of osteoclast-mediated bone resorption [4]. RANKL, when bound to RANK on the surface of osteoclast precursors, promotes osteoclastogenesis. There is also a growing body of evidence that bone resorption, governed by RANK/RANKL, plays a critical role in the expansion of tumor cells in bone [4]. The RANK/RANKL signaling pathway is therefore an attractive therapeutic target. In the present issue, Buckle *et al.* [5] discuss the evidence for the RANK/RANKL system in normal osteoclast biology, its abnormal regulation in the cancer setting and the possible involvement of bone marrow-derived RANKL as a chemo-attractant for RANK-expressing tumour cells. In addition, the authors review the effect of blocking the RANK/RANKL pathway in both experimental models and in the clinic [5].

Beside the possible involvement of RANKL as a potentiator of primary tumor cell migration to secondary sites within the skeleton, there is now evidence that chemokines and their receptors are playing a key role in organ-specific cancer metastasis [6]. For example, several chemokine receptors (CXCR3, CXCR4, CCR4, CCR5, and CCR7) expressed by tumor cells are associated with metastases in breast cancer [6-8], among which CXCR4 seems to be a major metastasis-regulator receptor [6]. Here, Hirbe *et al.* [9] review the current data regarding the role of CXCR4 and its ligand, SDF-1/CXCL-12, in the development of bone metastases. The authors also discuss the potential advantages and risks at targeting this chemokine axis for the prevention of tumor cell spread to bone. Interestingly, it has been very recently shown that CXCL-12 is not only implicated in the homing of breast cancer cells in the bone marrow but also in their survival [10]. CXCL-12, by binding to CXCR4, activates the nonreceptor tyrosine kinase Src which, in turn, stimulates the AKT cell survival pathway in breast cancer cells [10]. Given that several agents that target Src have become available for clinical testing [11], one could envision using Src inhibitors (and/or CXCR4 antagonists ?) as a means to block tumor growth at an early stage in the course of the metastatic disease.

Once cancer cells have reached and invaded the bone marrow, they start to grow and form small clumps of cancer cells called micrometastases. Invasion of the bone marrow cavity by cancer cells requires the coordinated action of integrins and proteases. Their functions in cancer and (bone) metastasis formation have been very recently reviewed [12,13] and, therefore, will not be discussed here. Invading cancer cells that form micrometastases need also to adapt to the bone microenvironment (a process called osteomimetism), in order to survive and acquire the ability to grow into a clinically detectable bone metastasis [1]. For example, breast cancer cells that metastasize to bone specifically express transcription factors (Runx2, MSX2), extracellular matrix proteins (osteonectin, osteocalcin, ...), proteases (cathepsin K), and other bone-related factors [connexin 43, cadherin-11, bone morphogenetic proteins (BMPs)] that, under physiological conditions, regulate osteoblast differentiation and osteoclast activity [1]. In this issue, Buijs *et al.* [14] review the biological functions of BMPs, which can be produced by cancer cells, and they discuss their role during the progression of bone metastases. The authors also discuss the possibility that BMP7 could serve as therapeutic molecule, interfering with transforming growth factor- β (TGF- β) signaling. In skeletal tissue, TGF- β is indeed a major bone-derived factor responsible for driving a feed-forward vicious cycle of breast cancer growth in bone. It regulates the expression of many factors (integrin $\alpha\beta$ 3, CXCR4, IL-6, IL-8, IL-11, metalloproteinase MMP-1, endothelin-1, etc...) that are involved in bone metastasis formation. Here, Juárez and Guise [15] summarize the current knowledge of TGF- β in bone metastases, the use of TGF- β inhibitors and its potential for clinical use and consequences.

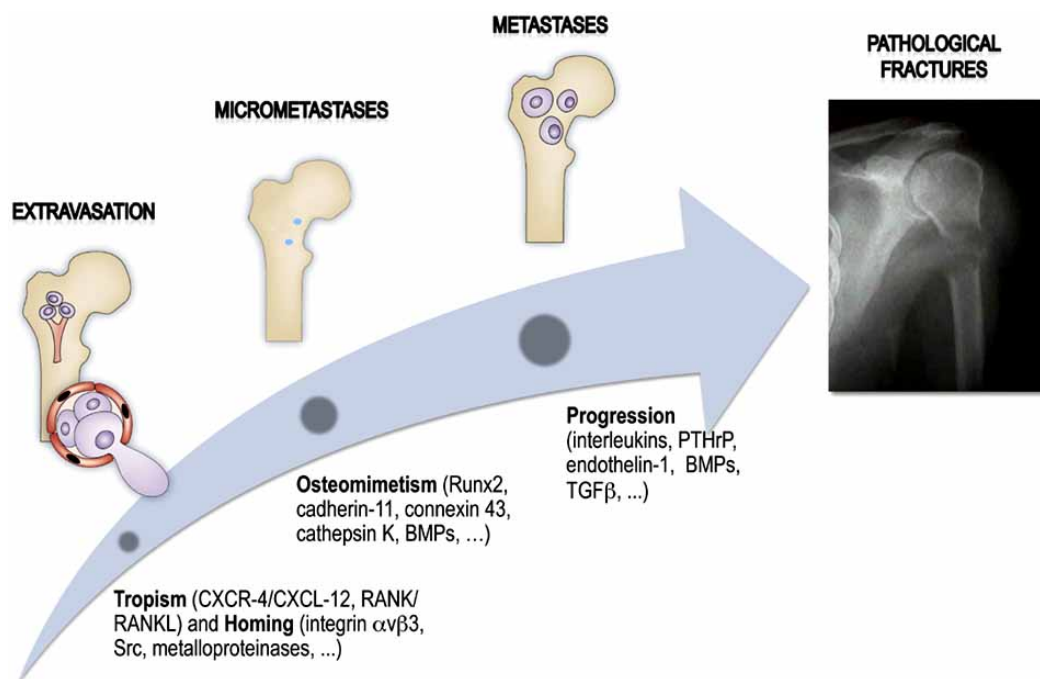


Fig. (1). Molecular mechanisms associated with the development and progression of breast cancer bone metastases, causing pathological fractures.

In summary, findings presented in this issue of *Current Pharmaceutical Design* highlight several molecular components acting at early and late stages during the development and progression of bone metastases (Fig. 1). These components stand as attractive new targets for cancer therapeutics. They could be used in combination with bisphosphonates to efficiently block the development of skeletal lesions in women with breast cancer.

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Philippe Clézardin, PhD, DSc

INSERM, Research Unit U664,
University of Lyon-1, Faculty of Medicine Laennec,
rue Guillaume Paradin,
69372 Lyon cedex 08,
France
Tel.: +33 4 78 78 57 37;
Fax: +33 4 78 77 87 72;
E-mail: philippe.clezardin@inserm.fr