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Review

# Pathogenesis of bone metastasis

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ABSTRACT

Bone metastases are more frequently seen as a complication of cancer than primary bone tumors. For example, it can be seen in as many as 70% of advanced stage breast and prostate cancer cases. Metastatic bone disease is generally categorized as osteoblastic, and osteolytic disease. However most of the cancer types demonstrate a wide spectrum between these two extremes. Paracrine interaction between parathyroid hormone–related protein (PTHrP) which increases the rate of bone osteolysis, and transforming growth factor-β (TGF-β) plays a role in osteolytic metastasis. Increased local bone PTHrP concentration increases expression of receptor activator of nuclear factor kappa-B ligand (RANKL) with resultant activation of osteoclastogenesis. Endothelin − 1 (ET-1), and dickkopf homolog -1 (DKK-1) produced by tumor involve in osteoblastic metastasis. DKK-1 is the central regulator of osteoblastic activity, and osteoblastic bone metastasis. For the elaboration of treatment strategies against frequently seen complication, that is, bone metastases, targets involving in pathogenesis of these complications should be taken into consideration.


## 1. Introduction

Bone metastases are very frequently seen complications of cancer, more frequently seen than primary bone tumors.[1] It ranks third among organ metastases after hepatic, and pulmonary metastases.[2] For example, in 70% of patients with advanced stage breast, and prostate cancers bone metastases can be seen.[3] In addition, it can appear in 15–30% of lung, colon, stomach, bladder, uterus, rectum, thyroid, and kidney cancers. Its incidence is not known exactly. However in the USA every year approximately 350,000 patients with bone metastases are losing their lives.[4] Planning treatment strategies against bone metastases, and development of innovative treatment agents require sound knowledge of the metastatic disease.

Mechanisms involving in detachment of a solid tumor cell from a primary tumor to invade other remote structures have been more clearly understood day by day. Metastatic bone disease is generally divided into 2 categories as osteoblastic and osteolytic disease. However, most of the cancer types display a wide spectrum between these two extremes, and mixed lesions emerge. In prostate cancer, carcinoid, and other endocrine tumors. Generally osteoblastic lesions are seen, osteolytic lesions are more frequently observed in breast, lung, and kidney tumors.[5]

Characteristics of both the tumor, and the skeletal system determine the metastatic potential of a specific tumor to bone. Bone metastasis which is a multistage process becomes manifest at late stages of tumor progression. When the tumor cells enter into circulation, they pass through dilated sinusoidal channels, migrate onto the endosteal surface of the bone, and disseminate through all vascular system including red bone marrow. Metastatic process is generally completed in 3 phases.[6]

1 − Break away of cancer cells from the primary tumor.
2 − Adhesion to, and invasion into a distant organ.
3 − Settlement in bone microenvironment.

## 2. Break away of cancer cells from the primary tumor

Malignant potential of cancer cells is dependent on their capability (1) to pass over basement membrane, and extracellular matrix, (2) to break away from the primary tumor, (3) to invade surrounding tissues with resultant entry into lymphatic system. Animal models of bone metastases support the role played by matrix metalloproteinases. Matrix metalloproteinases belong to a family of at least 28 zinc-dependent proteinases which degrade extracellular matrix proteins.[7] Increased expressions of matrix metalloproteinases have been observed in many cancer types including breast, and prostate cancers, and enhanced levels of metalloproteinases have been associated with poor prognosis.[8,9]

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Common evidence derived from recent studies suggest that platelets encourage formation of metastases. Since predisposition of cancer patients to thrombosis is known for a long time, such an increase in the risk of thrombosis may be related to direct, and mutual interaction between cancer cells, and platelets. Platelets may act as protective "cloaks" for circulating tumor cells against attacks of the immune system, and increase their capability of adhering to impaired vascular epithelium.[10]

## 3. Cancer cells in search for a target, and their adhesion

Stromal cell-derived factor 1 alpha (SDF1 α or n CXCL12) is found in tissues localized in areas with widespread metastatic lesions including bone marrow.[11,12] This ligand demonstrates its affinity to chemokine receptor type 4 (CXCR4) which is expressed in higher amounts in especially breast, and prostate cancers. In vitro blockage of SDF1a/CXCR4 interaction has been demonstrated to inhibit migration of prostate cancer cells from bone marrow into endothelial cells, and decrease metastatic load in bone metastases in experimental animal models with prostate cancer.[12] Another adhesion molecule αvβ3 integrin incorporates RGD (Arg-Gly-Asp) peptide sequence found in various extracellular matrix proteins which is important for the arrival of tumor cells to the target, and potential invasion of endosteum of bone tissue.[13,14] In an animal model of bone metastases, αvβ3 integrin antagonists prevented metastasis of cancer cells into bone tissue.[15] This finding reinforces the notion of metastatic niche configured by bone marrow, and assumption suggesting bone that stromal cells trigger progression of metastatic cancer.

## 4. Settlement of cancer cells on bone microenvironment

### 4.1. Osteolytic bone disease

A paracrine interaction exists between cancer cells, and bone microenvironment, and develops on the basis of Stephen Paget's "soil, and seed" theory. Parathyroid hormone-related protein (PTHrP), and transforming growth factor −β (TGF-β) released from breast cancer cells support this hypothesis of paracrine interaction. This exemplary interaction termed as "soil and seed" hypothesis can be perceived as a model leading to the discovery of other signalization pathways regulating formation of bone metastases. PTHrP is especially produced in metastatic breast cancer, specifically in the bone microenvironment.[16] Locally increased concentration of bone PTHrP also increases RANKL expression, and consequently inhibits OPG (osteoprotegerin) secretion by osteoblasts, and stromal cells. Thus, osteoclast precursors activate osteoclastogenesis mediated by RANK. Activated osteoclasts induce bone resorption as a result of release of some factors embedded in bone matrix such as TGF-β. Release of TGF-β then stimulates breast cancer cells, which initiates a vicious cycle. Production of PTHrP by tumor cells stimulates osteoclastic bone resorption which in turn further accelerates TGF-β release. All of these processes result in increase in tumoral release of PTHrP. Blockade of PTHrP and/orTGF-β production appears to be an ideal strategy in the treatment of bone metastases.[5] For example, TGF-β receptor -1 kinase inhibitor was used in mice carrying SD-208, and MDA-MB-231 sequences, and consequently decrease in osteolytic activity was observed.[17]

Transcription factor RUNX-2 which is known mainly for its role in osteoblastogenesis is expressed from breast cancer cells, and its interaction with transcription factor SMAD (small mothers against decapentaplegic) responds to TGF-β. In mouse model of bone metastasis blocking RUNX-2 activity in breast cancer cells decreases tumor growth, and osteolysis. Neutralization of the effects of PTHrP also yields therapeutic benefits.[18]

Use of monoclonal antibody against PTHrP resulted in significantly fewer number of smaller osteolytic lesions when compared with mouse model of breast cancer-induced bone metastases.[16]

Insulin-like growth factors (IGFs) are also released locally from the periphery of the bone during osteolytic process, and play a role in the proliferation of bone metastasis. Osteoclastic resorption of the bone induces release of ionized forms of calcium, and phosphate in higher concentrations which contribute to the vicious cycle of bone metastasis. Calcium-sensitive receptor (CaSR) which is composed of a pair of G proteins is expressed by breast cancer cells, and responds to even the smallest changes in the concentration of extracellular calcium. CaSR regulates tumoral secretion of PTHrP which is promoted by TGF-β.[19,20]

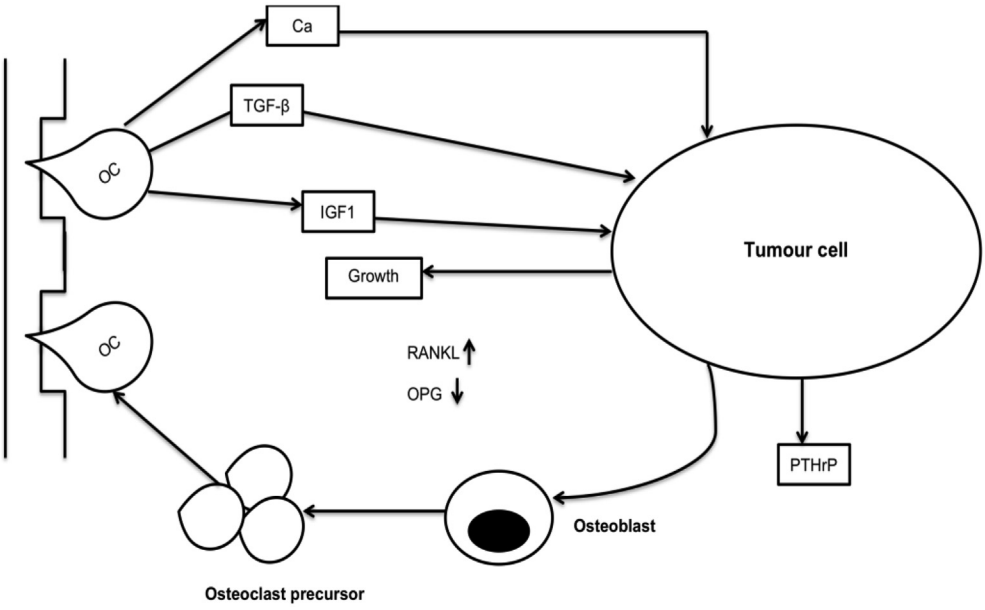


**Fig. 1.** Osteolytic metastases (OC: Osteoclast, PTHrP: parathyroid-hormone-related peptide, RANKL: Receptor activator of nuclear factor-κB ligand, OPG: Osteoprotegrin, TGF-β: transforming growth factor − beta, IGF1: insulin-like growth factor 1.