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**Review Article**

# Cancer in Bone

Toshiyuki Yoneda

*Department of Biochemistry, Osaka University Graduate School of Dentistry*
*(Chief: Professor Toshiyuki Yoneda)*

**Abstract**: Bone is one of the most preferential metastatic target sites for cancers such as breast, prostate and lung cancers. Although the precise molecular mechanism underlying this preference needs to be elucidated, bone appears to possess unique biological microenvironments that allow circulating cancer cells to home, proliferate and survive. As a consequence of cancer expansion, cellular and molecular homeostasis of bone microenvironments is disturbed and bone is destroyed, leading to the development of bone metastases. Thus, understanding of the crosstalk between cancer cells and bone is critical to design mechanism-based effective and specific therapeutic interventions for bone metastases.

**Key words**: Bone Metastasis, Breast Cancer, Osteoclasts, Bone-stored Growth Factors, Bone Pain

## Breast Cancer Metastasis to Bone

Cancer shows characteristic organ preference for spreading to distant sites[1]. Breast, prostate and lung cancers have strong predilection for disseminating to bone[2]. Coleman and Ruben[3] reported that the frequency of bone metastases (83%) was much higher than lung (27%) and liver (27%) metastases in breast cancer patients. Although the precise molecular mechanism underlying the preferential breast cancer metastasis to bone is yet to be elucidated, bone likely provides the environments that allow circulating breast cancer cells to preferentially arrest, colonize and survive in bone as proposed in the "Seed and Soil" theory by Paget[4]. Based on this theory, it is proposed that breast cancer cells can communicate with bone microenvironments through exchanges of biological information, whereas non-target organs may not allow breast cancer cells to exchange biological information (Fig. 1). Accordingly, determination of the biological properties of both bone microenvironments and breast cancer cells at cellular and molecular levels is important to obtain insights into the mechanism underlying preferential breast cancer metastasis to bone.

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**Requests for reprints**: Toshiyuki Yoneda, Department of Biochemistry, Osaka University Graduate School of Dentistry, 1–8 Yamada-oka, Suita, Osaka 565–0891, Japan, Phone: +81–6–6879–2886, Fax: +81–6879–2890, E-mail: tyoneda@dent.osaka-u.ac.jp

## Bone Microenvironment

### 1. Hard Calcified Tissue

Since bone is primarily composed of hard mineralized matrices, destruction of the mineralized tissue is required for metastasizing breast cancer cells to develop bone metastases. Accumulating lines of evidence suggest that osteoclasts rather than cancer cells destroy bone in the pathophysiology of bone metastases[5,6]. Therefore, formation and activation of osteoclasts in conjunction with cancer colonization are critical to the development of bone metastases. Involvement of bone-resorbing osteoclasts in addition to cancer cells in the pathophysiology is a unique feature of bone metastases.

### 2. Bone-stored Growth Factors

Mineralized bone matrices store various growth factors including IGFs, TGF$\beta$, FGF-1 and FGF-2, PDGFs and BMPs[7]. Since bone continually remodels through osteoclastic bone resorption coupled with osteoblastic bone formation, these growth factors are released in the bone marrow cavity.

IGF-1 stimulates the growth of human breast cancer

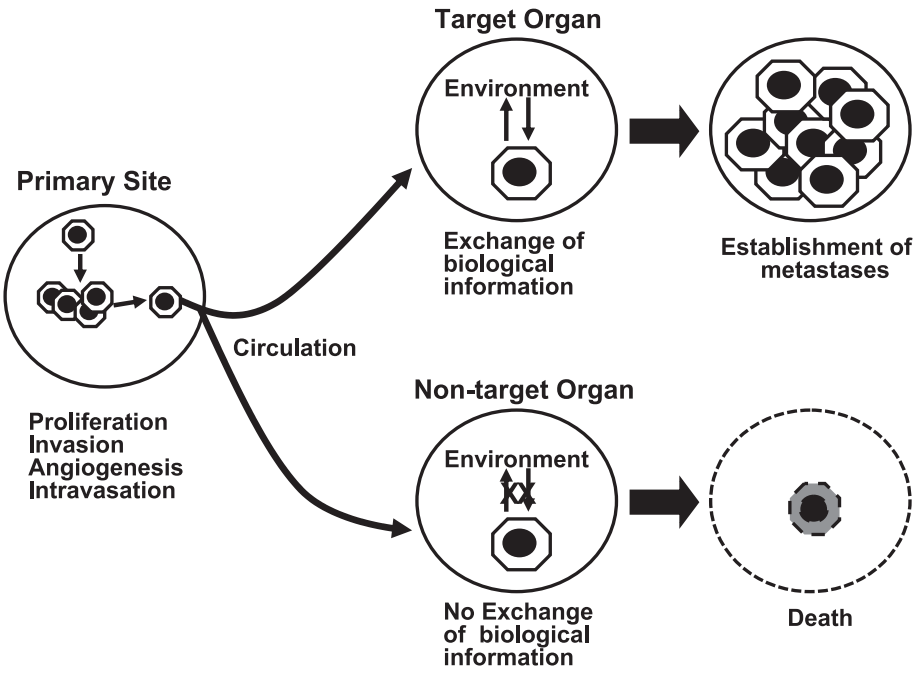


**Fig. 1** Organ-selective Metastasis
Cancer cells proliferate, invade into surrounding tissues and cause tumor-associated angiogenesis. Angiogenesis not only stimulates cancer cell proliferation but also increases cancer cell entry into the circulation (intravasation). Circulating cancer cells egress blood vessels (extravasation) upon arrival in target organs and arrest there. Cancer cells that can communicate with target organ environments through exchanges of mutual biological information can establish metastases. In non-target organs, cancer cells are not allowed to communicate with local environments and consequently are induced to die.

cells through the activation of cascades of cytoplasmic signaling molecules including IRS-1, PI-3 kinase, Akt and NF-$\kappa$B. Overexpression of dominant-negative IGF type I receptors, a dominant-negative AKT or a mutant I$\kappa$B$\alpha$ that inhibits NF-$\kappa$B activation, significantly reduces bone metastases with decreased mitosis and increased apoptosis. Thus, bone-derived IGF-1 promotes the development of bone metastases through stimulation of cell growth and reduction of apoptosis in breast cancer cells (Fig. 2).

TGF$\beta$ is also stored in large amounts in bone[7] and released following osteoclastic bone resorption. TGF$\beta$ markedly promotes the production of parathyroid hormone-related protein (PTH-rP). PTH-rP is a cytokine which is produced by metastatic cancer cells and plays a key role in bone metastases[8,9]. Introduction of a cDNA of TGF$\beta$ type II receptor lacking a cytoplasmic domain (T$\beta$RII$\Delta$cyt) that exhibits dominant-negative effects into breast cancer cells caused no increase in PTH-rP production in response to TGF$\beta$ and fewer and smaller osteolytic lesions than mice which received parental or empty vector-transfected cells[10]. These results suggest that bone-derived TGF$\beta$ promotes bone metastases through the up-regulation of PTH-rP production in breast cancer cells. Elevated levels of PTH-rP in turn enhance osteoclastic bone resorption, causing increased release of bone-stored growth factors.

More recently, we reported that TGF$\beta$ stimulates COX-2 expression in breast cancer cells[11], causing increased $PGE_2$ production in breast cancer cells.

### 3. Bone-stored Minerals

Osteoclastic bone resorption releases free calcium ($Ca^{2+}$) and phosphate as a consequence of dissolution of bone minerals. Some breast cancer cells express calcium-sensing receptors through which extracellular $Ca^{2+}$ stimulates PTH-rP production[12], suggesting that bone-derived $Ca^{2+}$ modulates the phenotype of breast cancer cells metastasized in bone.

Phosphate ($PO_4$) is a major component of bone mineral. $PO_4$ is implicated in the cell proliferation and differentiation through regulating the synthesis of nucleic ac-