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Heterogeneity of tumor cells in the bone microenvironment: Mechanisms and therapeutic targets for bone metastasis of prostate or breast cancer☆

Mitsuru Futakuchi *, Katsumi Fukamachi, Masumi Suzui

Department of Molecular Toxicology, Graduate School of Medical Sciences, Nagoya City University, Nagoya 467-8601, Japan

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ABSTRACT

Bone is the most common target organ of metastasis of prostate and breast cancers. This produces considerable morbidity due to skeletal-related events, SREs, including bone pain, hypercalcemia, pathologic fracture, and compression of the spinal cord. The mechanism of bone metastasis is complex and involves cooperative reciprocal interaction among tumor cells, osteoblasts, osteoclasts, and the mineralized bone matrix. The interaction between the metastatic tumor and bone stromal cells has been commonly referred to as the "vicious cycle". Tumor cells stimulate osteoblasts, which in turn stimulate osteoclasts through the secretion of cytokines such as the TNF family member receptor activator of nuclear κB ligand (RANKL). Activated osteoclasts degrade the bone matrix by producing strong acid and proteinases. Bone degradation by osteoclasts releases TGFβ and other growth factors stored in the bone matrix, that further stimulate tumor cells. Bone modifying agents, targeting osteoclast activity, such as bisphosphonate and RANKL antibodies are considered as the standard of care for reducing SREs of patients with bone metastatic diseases. These agents decrease osteoclast activity and delay worsening of skeletal pain and aggravation of bone metastatic diseases. While the management of SREs by these agents may improve patients' lives, this treatment does not address the specific issues of the patients with bone metastasis such as tumor dormancy, drug resistance, or improvement of survival. Here, we review the mechanisms of bone metastasis formation, tumor heterogeneity in the bone microenvironment, and conventional therapy for bone metastatic diseases and discuss the potential development of new therapies targeting tumor heterogeneity in the bone microenvironment.

Contents

1. Introduction

Tumor metastasis is multiple processes, that involves involve invasion, embolization, survival in the circulation, arrest in a distant capillary bed, extravasation, and re-growth in the microenvironment of the secondary organ [1] (Fig. 1). Metastatic tumor cells are required to

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* Corresponding author. Tel.: +81 52 853 8992; fax: +81 52 853 8996.
E-mail address: futakuch@med.nagoya-cu.ac.jp (M. Futakuchi).

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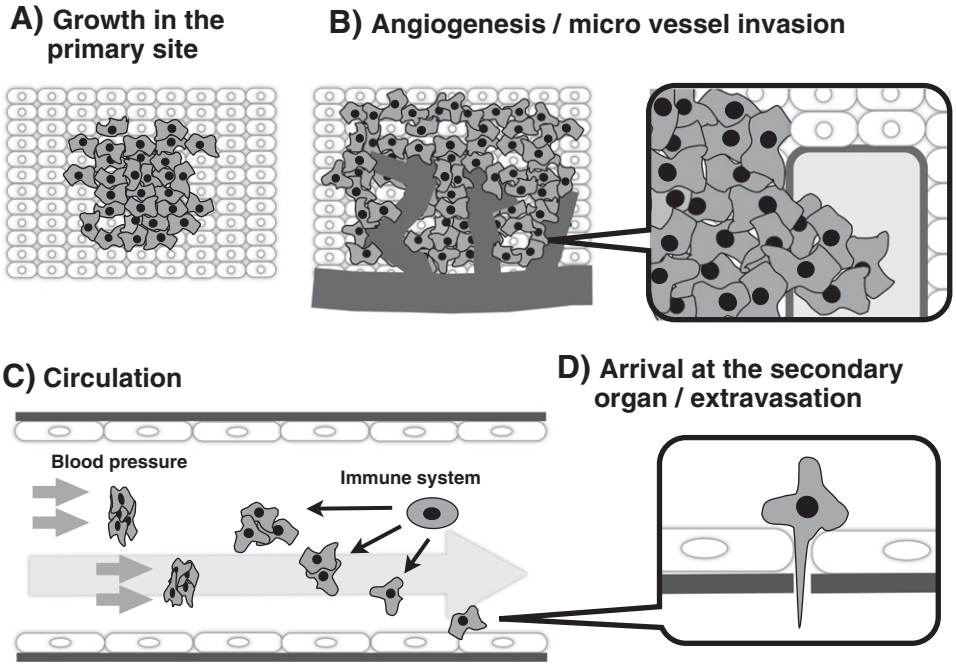

Fig. 1. Metastatic Cascade. A. Tumor growth at the primary site. Tumor growth at the primary site is progressive with nutrients for the expanding tumor mass initially supplied by simple diffusion. B. Angiogenesis/microvessel invasion. The synthesis and secretion of angiogenic factors establish a capillary network from the surrounding tumor tissue. C. Circulation. After detachment from the primary site, tumor cells need to survive the mechanical stress of blood pressure and attack from the immune system in the circulation. D: Arrival at the secondary organ/extravasation. After the tumor cells have survived the circulation, they are trapped in the capillary beds of distant organs. Thin-walled venules, such as lymphatic channels, offer very little resistance to penetration by tumor cells and provide the most common route for tumor-cell entry into the tissue.

complete all of these processes to form metastases. Metastatic tumor cells are often compared to a decathlon athlete who is skilled in all ten track and field events [2]. Because tumor cells are exposed to the host response in each process [3], the vast majority of potentially metastatic cells from the primary tumor, which are often detected in the serum of advanced cancer patients [4], are eliminated before they are able to successfully form a metastasis. Therefore, tumor metastasis is a selective process, and through this process results in phenotypic diversification of the metastatic tumor cells arise from the genetically and phenotypically unstable primary tumor [5]. Although only a few cells from a primary tumor are able to give rise to a metastasis [6,7], the tumor cells with metastasis phenotype gained through the selective cascade of metastasis can provide new insight into the biological heterogeneity of metastatic tumor cells.

2. Mechanism for bone metastasis

Bone is the most common organ of metastasis of two of the most common cancers, prostate and breast cancers. Bone metastasis is particularly clinical important because of the consequent morbidity and complex demands on health care resources. The clinical symptoms of bone metastases can be extensive, often accounting for the poor prognosis of patients with bone metastasis that is associated with advanced prostate or breast cancer.

There are different patterns in the metastatic bone lesions, ranging from mostly destructive or osteolytic to mostly bone forming or osteoblastic, based on the radiographic or histological observation of the bone metastatic lesion. The homeostatic balance between resorption and formation in the bone is clearly dysregulated in bone metastases. In breast cancer bone metastases, although the dominant bone lesion is destructive and osteolytic, local bone forming and osteoblastic lesions are also observed [8]. Similarly, in the case of prostate cancer, although bone lesions are diagnosed as bone forming and osteoblastic, it is clear that destructive, osteolytic lesions play important roles in bone metastasis formation of prostate cancer. Most patients with bone metastasis regardless of cancer type would have symptoms of both osteolytic and osteoblastic change [9].

The mechanism of bone metastasis is complex and involves cooperative reciprocal interactions among tumor cells, osteoblasts, osteoclasts, and the mineralized bone matrix [10]. The excess of soluble and cellular components, signaling network, and coordinated gene expression has been shown to contribute the interplay among bone degradation, bone formation, and tumor growth. The mechanism of these interplays is gradually being unraveled. The interaction between the metastatic tumor and bone stromal cells has been commonly referred as the "vicious cycle" [8]. Tumor cells that reach in the bone microenvironment secrete factors such as parathyroid hormone related peptide (PTHrP), that stimulate osteoblasts. Activated osteoblasts increase the expression of the TNF family member receptor activator of nuclear κB ligand (RANKL) (Fig. 2). RANKL, by binding to its receptor RANK, has been shown to be essential in mediating osteoclast activation [11], and activated osteoclasts degrade the bone matrix by producing strong acid and proteinases such as the cathepsins and matrix metalloproteinases (MMPs) [12]. Bone degradation by osteoclasts releases TGFβ and other growth factors stored in the bone matrix into the bone microenvironment. These growth factors in turn stimulate tumor growth and lead to increased levels of tumor derived PTHrP (Fig. 2). This vicious cycle accelerates tumor stromal interaction in the bone microenvironment, providing a particularly fertile soil to promote aggressive behavior of the malignant tumor cells that arrived at the bone microenvironment.

Once tumor cells start re-growing in the bone microenvironment, which is manifested as bone metastatic lesions by clinical examination, most of the lesions begin to exert resistant to the conventional chemotherapy [13]. To develop new therapeutics that are effective for bone metastatic lesions, appropriate targets need to be identified and tested that would interfere with metastatic tumor cells establishing a new microenvironment. Currently, such studies are circumscribed by limited availability of appropriate animal models that precisely dissect the tumor–stromal interaction, contributing to metastatic establishment and progression.