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Letter to the Editor

Metastatic breast cancer-derived exosomes and osteoclast-mediated bone metastasis

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Dear Editor,

In this letter, I would like to briefly highlight the important roles of exosome-mediated osteoclasts (OCs) in promoting bone metastasis with metastatic breast cancer (BC).

BC, one of the most lethal cancers in both men and women, is responsible for 11.7% of total cancer incidence and 6.9% of cancer-related mortality worldwide. Statistically, there were more than 2.3 million new BC cases with approximately 685,000 death cases reported globally in 2020 [1]. To date, the BC treatment methods preferably applied are mostly dependent upon the histological and molecular characterization [2]. However, recurrence or distant metastasis still relapses even with the most effective therapies [3] mainly owing to the extensive heterogeneity of BC subtypes and metastatic dissemination with different clinical features. Bone is one of the most common sites for bone metastases among the patients with BC [4], lung cancer [5] and prostate cancer [6]. BC bone metastasis diagnosed in approximately 70% of female patients with BC is one of the major causes for the high mortality rate among the patients with BC. Bone metastases cause a variety of skeletal-related events (SREs) such as, for instance, pathologic fractures, spinal cord compression, skeletal fragility, and muscle weakness. Therefore, better understanding of the pathological features and specific mechanisms underlying BC bone metastasis is prerequisite to establish the effective therapeutic strategies to improve outcomes in the patient with BC bone metastasis.

Brief Overview of the Role of Osteoclastic Activity in BC Bone Metastasis

The progress of bone metastases mainly depends upon the interaction among the cells of the bone microenvironment such as endothelial cells, hematopoietic stem cells (HSCs), mesenchymal stromal cells (MSCs), immune cells and bone cells [bone-forming osteoblasts (OBs) and bone-resorbing OCs], strengthening the growth, migration, dormancy and reactivation of metastatic BC cells [7]. To date, many excellent reviews have elaborately described the multiple regulatory mechanisms underlying BC bone metastasis [4,8-10]. Of these, osteoclasts (OCs), differentiated from HSCs, account for bone destruction, bone remodeling and homeostasis [11-15], are thought to be a regulatory hub of BC bone metastasis [4,7,9,10,16]. During the "*vicious cycle of bone metastases*", OCs are activated directly or indirectly by metastatic BC cells, resulting in pathological bone destruction. During this process, several growth factors such as transforming growth factor β (TGF-β) are released from the bone matrix, further accelerating OC activation and tumor growth [5,6]. Albeit the contribution of OBs to bone metastasis development is neglected, and poorly investigated, recent researches have revealed the important role of OBs in driving the progression of BC bone metastasis, suggesting that OBs might be the potential cellular targets for prospective clinical treatments [17,18]. To hopefully achieve efficient therapeutic strategies, a thorough comprehension of the relationship among tumor cells and cells of the bone microenvironment is mandatory. In this letter, the regulatory function of OCs on BC bone metastasis would be focused purposely.

Initially, the resorption process, followed by the recruitment of pre-OCs, which differentiate into activated OCs, is mainly regulated by OBs. OBs produce macrophage colony stimulating factor (M-CSF) and receptor activator of NFκB (RANKL), which respectively bind to their specific receptors, c-fms and RANK, on the cell surface of pre-OCs, which leads to OC differentiation, activation, and

maturation [19]. OBs also produce osteoprotegerin (OPG), a decoy receptor of RANKL that curtails OC activation [19], suggesting that the ratio of RANKL to OPG is important for OC activation. The entry of BC cancer cells into the bone microenvironment synergistically enhances the complexity of cell-cell interactions. The tumor cells produce a variety of growth factors, most notably parathyroid hormone-related protein (PTHrP). The role of PTHrP in bone metabolism remains incompletely understood; nevertheless, it is demonstrated to upregulate RANKL and downregulate OPG, thereby augmenting OC activity and bone degradation [5,6]. In the process, growth factors accumulated in the matrix including, for instance, TGF-β, vascular endothelial growth factor (VEGF), insulin-like growth factors (IGFs), bone morphogenic proteins and fibroblast-derived factors, as well as calcium, are released into the bone microenvironment. These factors can further stimulate the tumor cells to proliferate as well as produce more growth factors and PTHrP, which further promote the vicious cycle of bone metastases [5,6]. Besides, cytokines such as, for instance, Interleukin (IL)-6, IL-8 and IL-11 secreted by metastatic BC cells also promote OC differentiation and bone resorption [20-22].

Metastatic BC Cell-Derived Exosomes and Osteoclastic Activity in Bone

Exosomes, which are a type of extracellular vesicles (EVs) with a diameter ranging from 40 to 100 nm, are released from various cell types and carry proteins, nucleic acids (DNA, mRNA), receptors, enzymes, extracellular matrix proteins, ncRNAs (miRNAs, lncRNAs and circRNAs), lipids, and other biologically active components [23,24]. Exosomes have emerged as crucial players in extracellular communication. Many excellent reports including ours indicate that cancer cells actively release exosomes into the surrounding microenvironment, and these vesicles have pleiotropic capacity in regulating tumor growth and progression, neovascularization, immune escape, promoting invasion and metastasis [25-29]. Importantly, recent studies have substantiated that tumor-derived exosomes contribute to generating ideal microenvironment for engraftment and colonization of metastatic tumor cells. BC-derived exosomes could destroy vascular endothelial barriers in distant organs to increase the incidence of brain and lung metastasis [30,31]; moreover, it significantly affected upon osteolytic bone metastasis through forming pre-metastatic microenvironment [16]. Furthermore, recent study suggested that BC-derived miRNAs played a house-keeping role in regulating the outgrowth and metastasis of breast tumor and microenvironment of metastatic sites, and especially OC differentiation via enhancing NFATc-1 up-regulation. However, metastatic BC cell-derived miR-21 contribute to establishing OC-driven pre-metastatic niche for BC bone metastasis remains unclear.

In view of the above-mentioned, I propose two key suggestions for future research as follow:

(1) To continue to evaluate the regulatory effects of metastatic BC cell-derived exosomes on osteoclastic activity by testing other exosomal components transmitted into OCs.

(2) To test whether BC cell-derived exosomes influence OBs, osteocytes, and immune cells, etc., to further understand the mechanisms underlying exosome-mediated regulation of OC-induced BC bone metastasis.

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