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Research paper

The unresolved role of systemic factors in bone metastasis

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ABSTRACT

Systemic factors including cytokines, cell-free nucleic acids, microvesicles, and platelets are appreciated as important regulators of adenocarcinoma progression. Research findings using pre-clinical mouse models have revealed that many such systemically acting factors are either secreted by or responsive to peripheral tumors and impact bone and bone marrow (collectively referred to as the bone microenvironment) to initiate processes that ultimately govern disease progression, even in the absence of detectable bone metastases. In some cases, cancer-driven modulation of the bone microenvironment involves mobilization of bone marrow hematopoietic and mesenchymal cells into the circulation that are subsequently recruited into peripheral tissues and tumors. In other cases, systemic factors alter bone marrow cell (BMC) differentiation and/or gene expression to render the BMCs pro-tumorigenic even prior to their mobilization into the circulation. Given their effect on the bone microenvironment, it stands to reason that such systemic factors might also influence metastases in the bone; however, this hypothesis remains to be comprehensively tested. Here, we briefly review what is known, and not known, about systemic factors that regulate the bone microenvironment and thereby influence bone metastases. We also pose a number of currently unanswered questions in this active area of research. A better understanding of systemic processes that influence bone metastasis should aid discovery of therapeutic approaches that aim to eradicate or reduce disease burden in the bone, which is the cause of significant patient mortality and morbidity and is currently incurable.

1. Is there a role for systemic factors in formation of pre-metastatic niches in the bone?

Bone is a common site for metastatic spread of solid tumors, particularly for patients with metastatic breast and prostate cancers [1]. Here, we specifically focus on the factors impacting the bone microenvironment that thereby influence bone metastasis, which is the cause of significant patient mortality and morbidity and is currently incurable. At present, very little is known about systemic processes that influence bone metastasis. Increasingly, efforts are being directed toward this area of investigation with the notion that a better understanding of systemic processes that influence bone metastasis should aid discovery of therapeutic approaches that aim to eradicate or reduce disease burden in the bone.

Results from studies using pre-clinical metastasis models have revealed that primary tumor-derived circulating factors can affect various tissue microenvironments, even in the absence of observable metastases to those tissues, to make them a more hospitable environment for seeding and colonization of tumor cells that eventually disseminate from the primary tumor [2,3]. This process was termed “pre-metastatic niche” formation and most of what is known in this regard was gleaned from pre-clinical studies of lung metastasis. Much less is known about cancer-derived circulating factors that establish pre-metastatic niches in the bone. On one hand, the paucity of information may be due to the fact that there are very few bone metastasis models currently available to researchers. On the other hand, the bone microenvironment may inherently provide a favorable environment for disseminated tumor cells, thus eliminating the need for pre-metastatic modulation.

The fact that disseminated tumor cells are frequently detected in bone marrow aspirates of cancer patients who are tested in this manner [4] favors the idea that disseminating tumor cells find a ready-made niche in the bone microenvironment. Traditionally,

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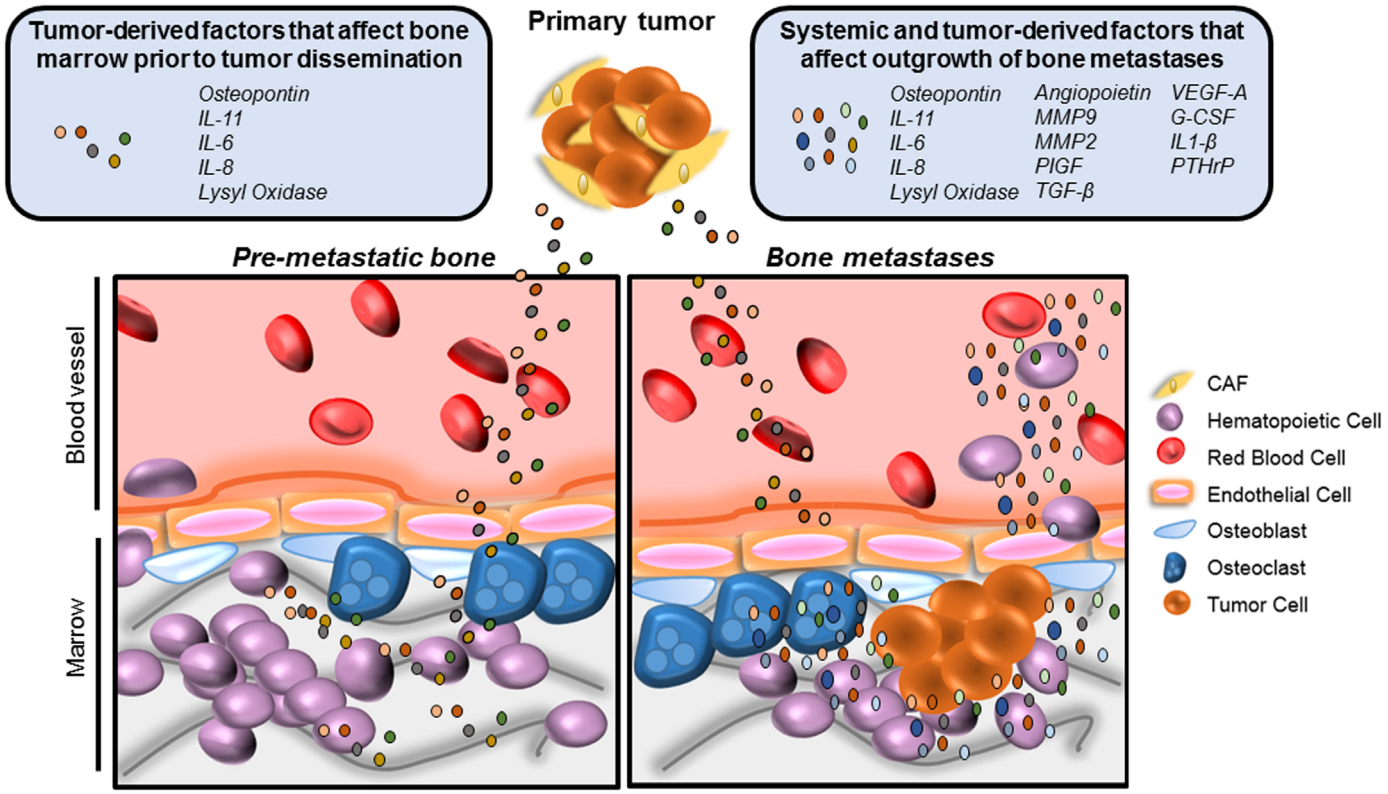

Fig. 1. Some of the systemic factors involved in dissemination and outgrowth of bone metastases. In the pre-metastatic bone, primary tumor-derived circulating factors can affect various tissue microdomains (hematopoietic cells, mesenchymal stromal cells, osteoblasts, osteoclasts, and vascular cells) to make them a hospitable environment for seeding of tumor cells that eventually disseminate from the primary tumor. After tumor cells have disseminated to bone, primary tumor-derived factors and other circulating cytokines of unknown origin can influence colonization of those tumor cells. Likewise, the tumor cells within the bone microenvironment secrete factors that disrupt normal bone homeostasis to fuel metastatic progression. Abbreviations: CAF, cancer-associated fibroblast, see Table 1 for growth factors.

bone metastatic niches have been defined as microdomains within the bone that support tumor cell seeding and outgrowth via paracrine interactions, and can be comprised of hematopoietic cells, a variety of mesenchymal stromal cells, osteoblasts, osteoclasts, and/or vascular cells [1] (Fig. 1). Within these microdomains, a number of chemokines and integrins that are endogenously expressed by various bone stromal cells to regulate mobilization and homing of hematopoietic cells are also thought to aid tumor cell recruitment to bone [1]. For example, bone stroma derived CXCL12 (SDF-1α) has been demonstrated to recruit CXCR4-expressing neuroblastoma cells [5]. Likewise, differentiating osteoclasts secrete CCL22, which was shown to promote bone metastasis of CCR4-expressing breast cancer cells [6]. Additionally, osteoblasts express a number of factors, including CCL12, which has been correlated with increased tropism of CCR7-expressing metastatic breast cancer cells [7].

More recently, primary tumor driven generation of a bone pre-metastatic niche was observed in a mouse model of estrogen receptor-negative breast cancer metastasis. Specifically, lysyl oxidase (LOX) secreted into the circulation from hypoxic primary breast tumors disrupted bone homeostasis, thereby inducing osteolysis [8]. The osteolytic microdomains within the bone served as niches for subsequent metastatic tumor cells, and bisphosphonate administration in the pre-metastatic setting prevented development of metastatic disease. This work is the first reported observation of breast cancer induced osteolytic action-at-a-distance (breast cancers frequently induce osteolysis following their dissemination to bone, as we discuss later). These findings, if further supported, have important clinical implications and should prompt further investigation into systemic modulation of bone-specific pre-metastatic niches.

2. Do primary tumors that impact the bone microenvironment also influence bone metastases?

Interestingly, bone is a conduit during pre-metastatic niche formation in visceral tissues in nearly all reported studies to date [2]. In other words, pre-metastatic niche formation in extra-osseous organs involves mobilization, modification, and recruitment of bone marrow derived cells (BMDCs) that help create the niche. Even before the discovery of pre-metastatic niches, investigation into the role of BMDCs in primary tumor progression and metastasis was an active area of research, as it still is today.

Numerous studies have shown that tumor-derived systemically acting factors impact the bone microenvironment to expand and mobilize bone marrow cells (BMCs) into the circulation that are subsequently recruited to tumor sites where they instigate various processes that support tumor progression [9,10] (Table 1). For example, tumor-derived granulocyte colony-stimulating factor (G-CSF) and interleukin-1β (IL1β) mobilize tumor-supportive CD11b+/Gr1+ myeloid cells from the bone marrow into circulation, while vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) release hemangiogenic BMCs (VEGFR1+ cells) from the bone marrow into circulation [9]. Breast cancer-associated fibroblasts (CAFs) have been demonstrated to secrete CXCL12, which induces the release of pro-angiogenic hematopoietic progenitor cells into the circulation [11].

Tumor-derived microvesicles–membrane-bound particles released from a primary tumor that carry lipids, proteins, mRNAs and miRNAs–could also modulate cells in the bone microenvironment [12]. For example, melanoma exosomes were shown to 'educate' bone marrow progenitor cells toward a pro-metastatic phenotype [13]. More recently, OPN carried through the