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Review

Contribution of acidic extracellular microenvironment of cancer-colonized bone to bone pain☆

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ABSTRACT

Solid and hematologic cancer colonized bone produces a number of pathologies. One of the most common complications is bone pain. Cancer-associated bone pain (CABP) is a major cause of increased morbidity and diminishes the quality of life and affects survival. Current treatments do not satisfactorily control CABP and can elicit adverse effects. Thus, new therapeutic interventions are needed to manage CABP. However, the mechanisms responsible for CABP are poorly understood. The observation that specific osteoclast inhibitors can reduce CABP in patients indicates a critical role of osteoclasts in the pathophysiology of CABP. Osteoclasts create an acidic extracellular microenvironment by secretion of protons via vacuolar proton pumps during bone resorption. In addition, bone-colonized cancer cells also release protons and lactate via plasma membrane pH regulators to avoid intracellular acidification resulting from increased aerobic glycolysis known as the Warburg effect. Since acidosis is algogenic for sensory neurons and bone is densely innervated by sensory neurons that express acid-sensing nociceptors, the acidic bone microenvironments can evoke CABP. Understanding of the mechanism by which the acidic extracellular microenvironment is created in cancer-colonized bone and the expression and function of the acid-sensing nociceptors are regulated should facilitate the development of novel approaches for management of CABP. Here, the contribution of the acidic microenvironment created in cancer-colonized bone to elicitation of CABP and potential therapeutic implications of blocking the development and recognition of acidic microenvironment will be described. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

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1. Introduction

Common solid cancers such as breast cancer, prostate cancer and lung cancer preferentially spread to bone [1]. Rare primary bone malignancies such as osteosarcoma, Ewing's sarcoma, and chondrosarcoma also aggressively expand in bone [2]. Multiple myeloma, which is a malignant plasma cell disorder accounting for approximately 10% of all hematologic cancers, exclusively colonizes bone [3]. These bone-colonizing cancers induce the development of either osteolytic, osteosclerotic or mixed bone disease by disrupting the homeostasis of bone environment. In addition, they are associated with skeletal-related events including bone pain, pathologic fractures, hypercalcemia, spinal cord compressions, palliative radiotherapy to bone and surgery to bone to treat or prevent a fracture during the clinical course of the disease [4]. Of these, bone pain is one of the most common and detrimental complications associated with cancer colonization in bone [5]. Cancer-associated bone pain (CABP) profoundly diminishes quality of life, impairs host immune surveillance and delays recovery from the illness, leading to increased secondary death. Accordingly, control of bone pain is a major goal for medical oncologists to achieve in the management of cancer patients. However, current treatments for CABP are not satisfactory and adequate and have serious side effects. Thus, new effective therapeutic interventions for CABP with reduced adverse effects need to be developed. Despite these circumstances, little is known about the mechanism of CABP.

Although the mechanism of CABP is poorly understood, accumulating clinical studies have shown that the specific inhibitors of osteoclasts, bisphosphonate and denosumab, significantly reduce CABP [6,7]. Osteoclasts are the principal bone resorbing cells in physiological and pathological conditions associated with increased bone resorption [8]. They play a central role in the pathophysiology of cancer colonization in bone [1]. These results collectively suggest that factors released at the tumor–bone interface during osteoclastic bone resorption may be an important mechanism of CABP. However, it should be noted that suppression of osteoclastic bone resorption fails to prevent the progression of CABP as the disease advances [7], confirming that not only osteoclasts but also cancer cells contribute to the pathophysiology of CABP.

In cancer-colonized bone microenvironment, osteoclasts, cancer cells, and cancer-associated stromal cells and inflammatory immune cells produce varieties of algogenic mediators that can excite and sensitize peripheral nociceptive sensory neurons and evoke pain through binding to their cognitive receptors present on the sensory neurons [9–11]. Protons are one of these algogenic mediators [9–11]. Of note, osteoclasts release protons via the plasma membrane (a3 isoform) vacuolar-H^+-ATPase coupled with chloride channels to secrete hydrochloric acid to degrade bone minerals during bone resorption [8,12]. In addition, it has been well-recognized that aggressive cancer cells secrete substantial levels of protons/lactate into the extracellular environments to avoid intracellular acidification due to elevated aerobic glycolysis known as the Warburg effect [13]. Thus, protons released from osteoclasts and cancer cells co-operatively create an acidic extracellular microenvironment in cancer-colonized bone.

Here we will overview the role of the acidic microenvironment created by protons/lactate released from bone-resorbing osteoclasts and bone-colonizing cancer cells in the pathophysiology of CABP with our recent experimental observations.

2. Acidic extracellular microenvironment in cancer-colonized bone

2.1. Osteoclastogenesis

Osteoclasts are multinucleated giant cells formed by the fusion of mononuclear progenitors of the monocyte/macrophage lineage [8]. They are the principal bone resorbing cells and play a central role in the formation of the skeleton and regulation of its mass. For osteoclast formation from the osteoclast precursors, macrophage colony-stimulating factor (M-CSF) and receptor for activation of nuclear factor kappa B (NF-κB) (RANK) ligand (RANKL) [14] produced in neighboring osteoblasts or stromal cells are essential [8] (Fig. 1). RANKL is a member of the tumor necrosis factor family and primarily a membrane-bound cytokine. Therefore, osteoclast precursors that express receptors for RANKL, RANK, need to contact with osteoblasts or stromal cells to differentiate into mature osteoclasts. Osteoprotegerin (OPG) is a natural soluble decoy receptor that competes with RANK for RANKL and thus inhibits RANKL-induced osteoclast formation and bone resorption [8]. The balance between the expression of RANKL and OPG (RANKL/OPG ratio) controls osteoclastogenesis and the degree of resulting bone resorption. Mice lacking M-CSF, RANKL or RANK showed osteopetrosis due to decreased osteoclastogenesis and dysfunction of mature osteoclasts [14]. On the other hand, mice deficient of OPG exhibited severe osteopenia due to increased osteoclastogenesis and bone resorption [14]. The mutations in the signal peptide region of the RANK protein cause familial expansile osteolysis, a rare autosomal dominant disorder characterized by focal areas of enhanced bone resorption, and familial Paget's disease [15]. OPG deficiency due to homozygous loss-of-function mutations within the *TNFRSF11B* gene is a cause of juvenile Paget's disease [16]. Thus, osteoclasts are evidently the principal causative player in diverse bone disorders.

2.2. Role of osteoclasts in cancer colonization in bone

In cancer-colonized bone and bone metastasis, osteoclasts are increased and activated to destroy bone by factors produced by cancers [1,17,18]. Bone destruction, in turn, further stimulates the colonization of cancer cells in bone via the release of bone-stored growth factors including transforming growth factor-β (TGF-β) and insulin-like growth factors (IGFs). This interactive process between bone-colonizing cancer cells and bone-resorbing osteoclasts is called “the vicious cycle” (Fig. 2). Thus, osteoclasts are a central regulatory player in the pathophysiology of cancer colonization in bone and bone metastasis. However, their role in CABP remains poorly understood.

2.3. Bone resorption and proton release by mature osteoclasts

Significant reduction of bone pain by the specific inhibitors of osteoclastic bone resorption, bisphosphonates and denosumab, in patients with multiple myeloma and solid cancers [6,7,19,20] indicates a critical role of osteoclasts in the pathophysiology of CABP. Consistent with these clinical observations, Honore et al. [21] reported that OPG, which inhibits osteoclast formation and bone resorption through interfering RANKL binding to RANK [8], suppressed CABP using an experimental animal model. We also showed that the most potent bisphosphonate zoledronic acid significantly reduced CABP [22]. It is therefore important to understand how osteoclasts resorb bone to gain better insights into the mechanism underlying CABP.

Bone resorption by mature osteoclasts is a dynamic multi-step process [8]. First, osteoclasts migrate and attach tightly to the bone surface targeted for degradation and removal via the $\alpha_v\beta_3$ integrin, thereby forming a tight “sealing zone”. Plasma membrane then polarizes to form the resorption organelle, called “ruffled border”. The ruffled border is a unique folded highly permeable membrane facing the resorbing bone surface. To dissolve bone minerals, protons (H^+) and chloride ions (Cl^-) is released via the plasma membrane (a3 isoform) vacuolar H^+-ATPase proton pump [23] and chloride ion-proton anti-porter ClC-7 [24] clustered in the ruffled border into the resorption lacunae, acidifying the resorptive lacunae to a pH of ~4.5 [8]. Concomitantly, the cysteine peptidase cathepsin K [25] degrades bone matrix. The degraded bone matrix is trans-endocytosed from the resorption lacunae to the “functional secretory domain” and released into the extracellular environment [26]. Finally, osteoclasts gone through bone resorption detach from the bone surface and undergo apoptosis [8].