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Bone sialoprotein and osteopontin in bone metastasis of osteotropic cancers

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Contents

Abstract

The mechanisms underlying malignant cell metastasis to secondary sites such as bone are complex and no doubt multifactorial. Members of the small integrin-binding ligand N-linked glycoproteins (SIBLINGs) family, particularly bone sialoprotein (BSP) and osteopontin (OPN), exhibit multiple activities known to promote malignant cell proliferation, detachment, invasion, and metastasis of several osteotropic cancers. The expression level of BSP and OPN is elevated in a variety of human cancers, particularly those that metastasize preferentially to the skeleton. Recent studies suggest that the "osteomimicry" of malignant cells is not only conferred by transmembrane receptors bound by BSP and OPN, but includes the "switch" in gene expression repertoire typically expressed in cells of skeletal lineage. Understanding the role of BSP and OPN in tumor progression, altered pathophysiology of bone microenvironment, and tumor metastasis to bone will likely result in development of better diagnostic approaches and therapeutic regimens for osteotropic malignant diseases

Keywords: Bone sialoprotein; Osteopontin; Bone metastasis; Malignancy

1. Introduction

Primary bone cancers such as osteosarcoma, chondrosarcoma, or Ewing sarcoma family of tumors are quite rare comprising <1% of all cancers with only 2300 new cases of primary bone cancer in the U.S. each year [1].

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Table 1
Incidence of bone metastasis associated with various malignancies.

Primary tumor	Bone metastasis (%)	Lesion type(s)
Multiple myeloma	95–100	Osteolytic
Prostate cancer	65–75	Osteoblastic
Breast cancer	65–70	Mixed: osteolytic > osteoblastic
Thyroid cancer	60	Osteolytic
Lung cancer	30–40	Mixed: osteolytic > osteoblastic
Renal cancer	20–25	Mixed: osteolytic > osteoblastic

However, bone is one of the most common sites for metastasis of other cancers, particularly but not exclusively, those with epithelial cell origins. The worldwide incidence of bone metastasis reveals several malignancies have propensities to metastasize to bone including multiple myeloma and breast, thyroid, prostate and lung cancers [2] (Table 1). Under normal circumstances, bone is constantly undergoing continuous remodeling wherein osteoblasts contribute to bone deposition and osteoclasts mediate bone resorption thereby maintaining appropriate bone structure and Ca^{2+} homeostasis. Osteotropic malignancies that metastasize to bone upset this balance causing lesions that are either osteoblastic, osteolytic, or both [3,4]. Regardless of the type of lesion, the patient outcome is usually the same and may include pathologic fractures, bone pain, hypercalcemia, anemia, spinal instability, spinal cord and nerve compression, and decreased mobility [2].

The mechanisms underlying malignant cell metastasis from primary sites to secondary tissues such as bone are complex and poorly understood. Malignant cells must be able to detach from their primary tissues, evade the host immune system, cross the walls of the vasculature, penetrate through extracellular matrix in tissue, and finally take up residence and survive in tissues quite different from their origins. Studies over recent years suggest that small integrin binding ligand N-linked glycoproteins (SIBLINGs) may mediate many of the activities necessary for bone metastasis of osteotropic malignancies. In fact, the expression of SIBLINGs by malignant cells of osteotropic cancers may be intimately associated with their ability to metastasize to bone.

The SIBLINGs are primarily involved in bone morphogenesis and include bone sialoprotein (BSP), osteopontin (OPN), matrix extracellular phosphoglycoprotein (MEPE), dentin matrix protein 1 (DMP1), and dentin sialophosphoprotein (DSPP). The genes that code for them (*IBSP* for BSP, *SPP1* for OPN, *MEPE*, *DMP1*, and *DSPP*, respectively) are clustered on the long arm of chromosome 4 as a tandem array [5]. Originally thought to be expressed exclusively within mineralized tissue such as bone and dentin, SIBLINGs are now known to be produced by epithelial cell tumors that are osteotropic and in some cases produce microcalcifications [6]. These soluble secreted glycoproteins undergo extensive post-translational modifications including glycosylation, sulfation, phosphorylation, and sialylation, which in part, may confer their bioactivities. The five members of this family exert their activities in both paracrine and autocrine fashion and through multiple functional domains share the ability to bind similar proteins and exert similar activities. For example, all of the SIBLINGs bind integrins *via* both classical RGD motifs as well as cryptic binding sites [5]. The siblings OPN and DMP1 also bind CD44, a cell surface polymorphic hyaluronate receptor that participates in numerous cellular functions including lymphocyte activation, recirculation, homing, hematopoiesis, and tumor metastasis. SIBLINGs may regulate cell adhesion, motility, and survival of tumor cells by binding to integrins and/or CD44 expressed on tumor cells. Also, SIBLINGs bind and activate specific matrix metalloproteinases (MMPs) which may promote angiogenesis, tumor progression, and metastasis [7]. In addition, SIBLINGs bind compliment factor H (CFH) which blocks antibody-complement mediated cell lysis [8]. When these moieties are bound by SIBLINGs to the cell surface *via* integrins or CD44, these activities are conferred to the cell, facilitating trans-migration through tissue or extracellular matrix as well as escaping complement-mediated cell lysis. SIBLINGs also regulate cell proliferation and differentiation by activation of NF-κB [8]. Thus, SIBLINGs appear to provide most, if not all, of the activities required for tumor cell progression including the ability to metastasize to secondary sites such as bone. The involvement of BSP and OPN in tumor growth and metastasis has been more extensively studied than for the other SIBLINGs. This review article summarizes recent studies on the association of BSP and OPN with tumor progression and bone metastasis.

2. Bone sialoprotein

Human bone sialoprotein (BSP), a 33 kDa glycoprotein, is a major non-collagenous extracellular protein of mineralized tissues such as bone, dentin, cementum, and calcified cartilage [9]. BSP has an apparent molecular weight of 60–80 kDa due to extensive post-translational modifications including N- and O-linked glycosylation, serine and threonine phosphorylation, tyrosine sulfation, and sialylation. BSP is produced by osteoblasts, osteoclasts, osteocytes, and hypertrophic chondrocytes during bone morphogenesis [5,10]. The high glutamic acid content of BSP (22%) suggests it is the focal point for mineralization of hydroxyapatite during bone formation [11–14]. The activity of BSP in bone homeostasis may be dependent on additional regulatory factors in the bone microenvironment. For example, Xu and colleagues report that BSP-collagen implants placed into surgically created rat calvarial defects stimulate osteoblast differentiation and bone repair [15]. Conversely, BSP contributes to receptor activator of nuclear factor-κB ligand (RANKL)-mediated bone resorption by inducing osteoclastogenesis and promotion of osteoclast survival [16]. Also, BSP increases survival of bone marrow derived monocyte/macrophages by enhancing NF-κB activation and diminishing apoptosis in these cells