Review

Matricellular proteins as regulators of cancer metastasis to bone

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Abstract

Metastasis is the major cause of death in cancer patients, and a frequent site of metastasis for many cancers is the bone marrow. Therefore, understanding the mechanisms underlying the metastatic process is necessary for future prevention and treatment. The tumor microenvironment is now known to play a role in the metastatic cascade, both at the primary tumor and in metastatic sites, and includes both cellular and non-cellular components. The extracellular matrix (ECM) provides structural support and signaling cues to cells. One particular group of molecules associated with the ECM, known as matricellular proteins, modulate multiple aspects of tumor biology, including growth, migration, invasion, angiogenesis and metastasis. These proteins are also important for normal function in the bone by regulating bone formation and bone resorption. Recent studies have described a link between some of these proteins and metastasis of various tumors to the bone. The aim of this review is to summarize what is currently known about matricellular protein influence on bone metastasis. Particular attention to the contribution of both tumor cells and non-malignant cells in the bone has been given.

Introduction

Metastasis is a complicated, multi-step process that remains a major challenge in the treatment of cancer. Indeed, roughly 90% of cancer patient mortality is due to metastasis [1]. Though the impact of metastasis on patient outcome is clear, this process as a whole remains poorly understood. An early theory describing the mechanism of metastasis, known as the “seed and soil” hypothesis, was proposed by Stephen Paget in 1889 [2]. Paget theorized that cancer cells (seed) need a compatible microenvironment (soil) to survive and form a distant metastasis. This concept, that the microenvironment supports tumor growth and metastasis at local and distant sites, has become the focus of intense study over the past two decades and has changed the way we think about tumor biology.

One of the most common sites of metastasis is the bone marrow. Post-mortem analysis revealed that roughly 70% of patients with breast or prostate cancer had bone metastases [3]. This figure is relatively high in thyroid, lung and renal cancer as well, with an incidence of approximately 35–40% in each case [3]. In addition, multiple myeloma, a hematologic malignancy of B cells, predominantly localizes to the bone marrow and progresses from primary bone sites to new bone sites [4]. High frequencies of bone metastasis in these cancers can be viewed somewhat as a result of high blood flow to the bone marrow [5]. However, many studies demonstrate that the bone microenvironment plays a critical role in attracting metastatic tumor cells and supporting subsequent growth in bone [6]. The bone marrow microenvironment is a complex system composed of a number of cell types, such as osteoblasts and osteoclasts. In addition is a non-cellular component that includes soluble signaling mediators, such as hormones and cytokines. Finally, the extracellular matrix (ECM) is a meshwork of

secreted proteins that provides both structural support and biochemical cues for cells in the bone marrow. It is comprised primarily of type I collagen, but also contains other structural proteins such as fibronectin [7]. However, a group of molecules exist in the ECM that do not serve a structural function. Rather, these proteins fine-tune cell-ECM interactions and cellular functions [8]. Accumulating evidence has shown that these so called "matricellular" proteins are often dysregulated in cancer, both by cancer cells and by host cells (covered in more detail in [9,10]). In this review, we will introduce matricellular proteins in the bone ECM and summarize what is known about their involvement in cancer metastasis to bone.

Small leucine-rich proteoglycans (SLRPs)

SLRPs are a family of 18 relatively low molecular weight proteins (~36–42 kDa). SLRPs are characterized in part by a central domain containing a variable number of tandem leucine-rich repeats (LRRs) with the conserved motif LxxLxLxxNxL; where L represents leucine but can be substituted with isoleucine, valine or other hydrophobic amino acids, and X can be any amino acid [11]. The majority of these proteins contain glycosaminoglycan chains (GAGs) that are differentially processed during aging or development. They are involved in ECM assembly, hydration, and cytokine binding in interstitial connective tissue, such as bone and tendon, as well as other tissues [12]. In addition, SLRPs can affect signaling through membrane receptors, such as receptor tyrosine kinases (RTK) and toll-like receptors (TLR). They are involved in a wide variety of biological processes, particularly inflammation, bone morphogenesis and neural development [11–13].

Decorin is the most well studied SLRP in bone metastasis. This protein is found in normal connective tissues, including the bone, where it binds to and cross-links collagen fibrils [14]. Decorin is also found in tumor ECM and is mainly attributed to surrounding, non-malignant stromal cells (tumor cells express little decorin) [15–17]. However, decorin expression is decreased in stromal cells of many tumors compared to normal tissues and inversely correlates with prognosis of breast and lung carcinomas [16,18,19]. Declined decorin in the bone marrow matrix is also associated with the clinical progression of multiple myeloma [20]. Interestingly, decorin acts as a tumor suppressor in a number of cancers, including breast, prostate, ovarian and colon [16,21–23]. This function is partially due to the ability of decorin to bind to and inhibit function of RTKs such as epidermal growth factor receptor (EGFR), insulin-like growth factor receptor I (IGF-IR) and hepatocyte growth factor receptor (c-Met) [24–26]. For example, recombinant decorin reduces hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor A (VEGF-A) in MDA-MB-231 breast cancer cells through inhibition of c-Met, as well as induces anti-angiogenic molecules thrombospondin-1 and metalloproteinase inhibitor 3 (TIMP3) in these cells [27]. Sub-cutaneous injection of a Matrigel plug containing MDA-MB-231 cells, hepatocyte growth factor (HGF) and decorin results in decreased angiogenesis compared to a plug containing cells and HGF alone [27]. In addition, recombinant human decorin decreases adhesion of breast and colorectal cancer cell lines, whereas conditioned media from breast cancer cells reduces expression of decorin in fibroblasts in vitro [28].

With regards to the bone marrow, decorin expression is decreased in mesenchymal stem cells (MSCs) and osteoblasts from myeloma patients compared to healthy individuals [29]. Decorin expression is further decreased in these cells from myeloma patients with osteolytic disease compared to non-osteolytic patients. Osteoblasts express decorin at higher levels than MSCs [30]. Decorin expression by osteoblasts also suppresses myeloma cell survival, even when cultured with osteoclasts, and inhibits tube formation by HUVEC cells as well as differentiation of osteoclasts in vitro [30]. Myeloma cells co-cultured with osteoblasts decrease decorin expression in osteoblasts, but antibody-mediated neutralization of myeloma cell-derived macrophage inflammatory protein-1α (MIP-1α) inhibits this effect [31]. In addition, knock-in of decorin in osteotropic MDA-MB-231 breast cancer cells results in decreased bone metastasis along with diminished osteoclast numbers [32]. Moreover, systemic delivery of Ad.dcn, an oncolytic adenovirus carrying human recombinant decorin, inhibits skeletal metastasis of PC-3 prostate cancer cells and decreases osteoclast numbers and tartrate-resistant acid phosphatase 5b (TRAP5b) levels in vivo [33]. Thus decorin is not only involved at the primary tumor site, but is also active in the bone where it protects against bone metastasis and destruction.

Currently, very little is known about other SLRPs in the process of bone metastasis. Bone marrow stromal cell-derived biglycan may have similar anti-bone metastatic functions as decorin. Biglycan in an ECM scaffold produced by mammary mesenchyme cells can "normalize" breast cancer cells in vitro [34]. In addition, decreased biglycan is found in paired bone metastases compared to primary tumors in breast cancer patients [35]. Biglycan expression is increased in mouse osteoblastic cells by a secreted isoform of ErbB3 from prostate cancer cells, although the effects of this change are currently unknown [36]. Asporin is upregulated in bone marrow stromal cells in a bone xenograft model of prostate cancer [37]. Although asporin is poorly