Cathepsin K in the bone microenvironment: link between obesity and prostate cancer

I. Podgorski*†, B.E. Linebaugh* and B.F. Sloane*†

Abstract
The skeleton is the most common site of metastasis in patients with advanced prostate cancer. Despite many advances in targeting skeletal metastases, the mechanisms behind the attraction of prostate cancer cells to the bone are not known. Osteoclast cathepsin K, due to its ability to effectively degrade bone matrix collagen I, has been implicated in colonization and growth of prostate tumours in the bone. Identification of new cathepsin K substrates in the bone microenvironment and the recent findings demonstrating its involvement in obesity and inflammation suggest additional roles for this enzyme in skeletal metastases of prostate cancer.

Bone microenvironment and bone metastasis
Skeletal metastasis is the result of interaction of the tumour cells with the bone microenvironment and requires processes such as proteolytic degradation and osteoclastic bone resorption. The preferred sites for prostate tumour growth in the bone are the axial skeleton and long bone metaphyses, sites known to be under active remodelling. Recent studies suggest that accelerated bone remodelling may be a critical factor responsible for homing of tumour cells to the bone. This is made evident by the increased metastasis in response to experimental treatment with calcitropic hormone [1] or to androgen ablation [2]. Other known factors contributing to dysregulated bone remodelling are obesity and aging, both of which correlate positively with a shift in the composition of the bone marrow to fat cells (adipocytes) at the expense of bone-forming cells (osteoblasts). With the increased number of adipocytes, osteoclast activity within the marrow increases, resulting in osteoporosis [3]. Obesity has recently been identified as an important risk factor for prostate cancer, especially in the development of a more aggressive form of the disease with higher recurrence and higher mortality rates. This raises an intriguing question: do obesity-induced changes in bone composition promote homing of prostate tumours to the bone?

Proteolysis and bone metastasis
The key enzyme responsible for osteoclastic bone resorption is the cysteine protease, cathepsin K, a unique osteolytic enzyme capable of degrading the bone matrix protein collagen I [4]. Cathepsin K expression is high in osteoclasts as compared with other cells and its overexpression results in accelerated bone turnover. In contrast, deficiency in this protease leads to an osteopetrotic phenotype in mice and the bone-sclerosing disorder pycnodysostosis in humans [4]. Expression of cathepsin K has been demonstrated in many malignancies including prostate and breast cancers [5,6], both of which have a high propensity to metastasize to bone. So far, a role for cathepsin K in bone metastasis has been mainly attributed to its ability to effectively degrade native collagen I, a process necessary for the expansion of tumour within the bone. Recent studies by others and us suggest that cathepsin K also cleaves several other proteins of the bone matrix (Table 1), and thus affects the function of these proteins within the bone marrow. Furthermore, osteoclasts are no longer considered the exclusive source of cathepsin K in the bone. Other cells within the bone marrow milieu (e.g. macrophages and adipocytes) express cathepsin K, and are likely contributors to the metastatic process.

Cathepsin K–SPARC (secreted protein acidic and rich in cysteine) interactions
SPARC, one of the most abundant non-collagenous matrix proteins in the bone, is abnormally expressed in prostate cancer. SPARC is known to interact with collagen I and other matrix proteins and to attract and anchor metastatic tumour cells in the bone. In fact, only tumour cells that have the propensity to metastasize to bone are stimulated by SPARC [7]. SPARC has been suggested to act on precursor cells in the marrow to direct them into an adipogenic or osteoblastic pathway. Expression of SPARC strongly correlates with obesity and it coincides with overexpression of cathepsin K, which is capable of cleaving SPARC [8]. We have previously demonstrated that SPARC is cleaved in vivo in prostate bone tumours, an event preceded by an increase in enzymatic activity of cathepsin K [9]. Our recent studies utilizing co-cultures of primary human bone marrow stromal cells with prostate carcinoma cells further confirm coincident up-regulation of cathepsin K and SPARC (I. Podgorski and B.F. Sloane, unpublished work). We speculate that up-regulation of both

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Key words: adiponectin, bone metastasis, cathepsin K, prostate cancer, secreted protein acidic and rich in cysteine (SPARC), vascular endothelial growth factor (VEGF).

Abbreviations used: MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; SCF, stem cell factor; SDF-1, stromal-derived factor 1; SPARC, secreted protein acidic and rich in cysteine, VEGF, vascular endothelial growth factor.

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cathepsin K and its substrate might be a potential mechanism by which the cell increases processing of the substrates extra-cellularly. This would lead to an increase in cleavage products with functions distinct from those of the full-length protein.

**VEGF (vascular endothelial growth factor) cleavage and bone resorption**

VEGF is a known angiogenic factor, expression of which positively correlates with metastatic prostate cancer. In the bone microenvironment, VEGF is involved in tumour cell migration in response to SPARC and bone matrix, and in osteoclast differentiation, migration and survival [10,11]. The bioavailability of matrix-bound VEGF can be regulated through cleavage by MMPs. This also affects the pro-angiogenic properties of VEGF, which differ for cleaved and cleavage-resistant protein [12]. Our recent results indicate that cathepsin K is capable of cleaving VEGF and thereby potentially modulating its activity (I. Podgorski and B. F. Sloane, unpublished work). Similarly to SPARC, levels of VEGF are increased upon interaction of prostate carcinoma cells with human bone marrow cells and they coincide with overexpression of cathepsin K (I. Podgorski and B. F. Sloane, unpublished work). This suggests a potential involvement of cathepsin K in regulation of VEGF, an event that might stimulate recruitment of osteoclasts and promote invasion.

**Adipocytes and bone**

A clear link has been established between fat cell formation in the marrow and accelerated bone resorption. Both of these processes involve cathepsin K, and both have been linked to aggressive prostate cancer. Our recent studies suggest that cathepsin K-mediated degradation of collagen I is an important element in adipocyte differentiation. Our results also suggest an involvement of cathepsin K in regulation of the fat hormone, adiponectin (I. Podgorski and B. F. Sloane, unpublished work). Adiponectin possesses anti-inflammatory, anti-angiogenic and antitumorigenic properties and its levels are significantly decreased in obesity and advanced prostate cancer. Importantly, adiponectin plays a role in regulation of bone formation through interaction with its receptors on osteoblasts and osteoclasts [13,14]. This biological activity of adiponectin appears to be regulated by its cleavage.

**Summary**

Given the recent recognition that accelerated bone remodelling stimulates the attraction of prostate carcinoma cells to the skeleton, and the newly identified functions for cathepsin K described herein, we hypothesize that this protease is the link among obesity, inflammation and prostate cancer. In addition to its presence in osteoclasts, cathepsin K is an important regulator of fat cell formation. We speculate that adipocyte cathepsin K contributes to macrophage recruitment and the creation of a pro-inflammatory state in the marrow (Figure 1). This is made evident by a recent report that inflammation-induced cathepsin K levels in the bone marrow correlate with mobilization of progenitor cells, a process suggested to play a role in homing of tumour cells to specific organs [15]. Cathepsin K thus would play a causal role in metastasis of

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**Table 1 | Major targets of cathepsin K activity in the bone microenvironment**

<table>
<thead>
<tr>
<th>Target</th>
<th>Functions</th>
<th>Potential significance of cathepsin K-mediated cleavage</th>
<th>References</th>
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<tbody>
<tr>
<td>Collagen I</td>
<td>Bone strength and integrity</td>
<td>Bone matrix solubilization, release of growth factors, tumour expansion in the bone</td>
<td>[4,16]</td>
</tr>
<tr>
<td>SPARC (osteonectin)</td>
<td>Collagen binding, regulation of angiogenesis, MMP (matrix metalloproteinase) expression, cell proliferation, cell-matrix interactions, maintenance of bone mass, adipocyte differentiation</td>
<td>Stimulation of angiogenesis and tumour growth, increased levels of VEGF, dysregulation of bone remodelling, attracting and anchoring metastatic tumour cells in the bone</td>
<td>[4,9,17]</td>
</tr>
<tr>
<td>VEGF</td>
<td>Osteoclast differentiation, migration and survival, regulation of angiogenesis</td>
<td>Release of matrix-bound VEGF and stimulation of osteoclast recruitment and invasiveness, progenitor cell mobilization, establishment of metastatic lesions</td>
<td>[11]</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Inhibition of inflammation, angiogenesis and tumour growth, regulation of bone formation</td>
<td>Negative regulation of bioactivity, loss of antitumorigenic properties</td>
<td>[14]</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>Negative regulation of stem cell migration, homing, anchorage, proliferation</td>
<td>Progenitor cell mobilization, establishment of metastatic lesion</td>
<td>[15]</td>
</tr>
<tr>
<td>SDF-1</td>
<td>Chemotactic recruitment, development and survival of osteoclasts, recruitment and adherence of tumour cells to bone</td>
<td>Weakened stem cell anchorage, mobilization of progenitor cells into circulation</td>
<td>[15]</td>
</tr>
<tr>
<td>SCF</td>
<td>Proliferation, differentiation, and recruitment of progenitor cells</td>
<td>Weakened stem cell anchorage, mobilization of progenitor cells into circulation</td>
<td>[15]</td>
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Figure 1 | Proposed model for the role of cathepsin K in obesity-induced bone resorption and homing of prostate tumours to the bone

With obesity and aging, there is a shift in bone marrow composition to adipocytes. Marrow adipocytes secrete inflammatory cytokines [e.g. IL-6 (interleukin-6) and MCP-1 (monocyte chemotactic protein-1)], adipokines (e.g. leptin and adiponectin), SPARC and cathepsin K (Cat K). This leads to a pro-inflammatory state within the marrow, manifested by increased secretion of MCP-1, cathepsin K, TNFα (tumour necrosis factor α) and RANKL [receptor activator of NF-κB (nuclear factor κB) ligand] and decreased levels of the anti-inflammatory adiponectin. Cathepsin K plays a role in adipocyte–macrophage interactions due to its ability to regulate multiple factors within the bone marrow microenvironment (i.e. SPARC, VEGF and adiponectin). This leads to an increase in recruitment of osteoclasts followed by accelerated bone resorption. In addition, inflammation leads to cathepsin K-mediated cleavage of the stem cell niche components SDF-1, SCF and osteopontin, proteins implicated in attraction of tumour cells to the bone. Downstream effects of the adipocyte–macrophage interactions contribute to prostate-cancer-induced osteolysis of the bone.

prostate tumours to the bone by regulating multiple critical factors within the bone microenvironment.

References


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