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Review

Cathepsin B and tumor proteolysis: contribution of the tumor microenvironment

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Abstract

Tumor–stromal interactions induce expression of matrix metalloproteinases and serine proteases and, as shown recently, the cysteine protease cathepsin B. We speculate that such interactions upregulate the transcription factor Ets1, resulting in increased cathepsin B expression. This would be consistent with the observed concomitant upregulation of matrix metalloproteinases and serine proteases as well as with the ability of extracellular matrices and their binding partners to alter cathepsin B expression and secretion. Using a confocal assay to analyze the contribution of tumor–stromal interactions to proteolysis, we have been able to confirm enhanced degradation of extracellular matrices by all three classes of proteases.

Keywords: Cysteine proteases; Stromal elements; Inflammatory cells; Bone; Endothelial cells

Contents

Abbreviations: MMP, matrix metalloproteinase; uPA, urokinase plasminogen activator; PAI-1, plasminogen activator inhibitor-1; PIN, prostatic intraepithelial neoplasia; AIIt, annexin II heterotetramer; MDCK, Madin–Darby canine kidney; uPAR, urokinase receptor

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1. Introduction

The interactions of a tumor with its microenvironment are known to affect the expression of matrix metalloproteinases (MMPs) and serine proteases (for reviews, see [1–4]). Increased expression of MMPs and serine proteases in tumors may reflect changes in levels of expression within the tumor cells themselves but are as likely to reflect the contribution of proteases expressed by other cell types in the tumor microenvironment. These other cells may include stromal fibroblasts; myofibroblasts; inflammatory cells such as macrophages, neutrophils and mast cells; capillary-associated cells such as endothelial cells and pericytes; and bone-associated cells such as osteoblasts and osteoclasts. Expression of MMPs by stromal cells can be induced by tumor–stromal interactions [5]. In a transgenic mouse model for squamous cell carcinogenesis, MMP-9 is expressed predominantly by inflammatory cells (neutrophils, macrophages, mast cells), rather than by the tumor cells, and has been shown to enhance proliferation and invasion [6]. On the other hand, mast cells in the same model contribute serine proteases, i.e., chymase and tryptase, which have been shown to facilitate angiogenesis of the premalignant lesions [7]. The cell type expressing a particular protease can differ from cancer to cancer as well as with stage of progression. For instance, MMP-9 is expressed in the vascular cells of a xenograft neuroblastoma model and is responsible for recruiting pericytes and promoting angiogenesis [8]. Expression of a particular protease within a single cell type can be modulated by treatment with protease inhibitors, by stage or by age. Subsequent to treatment with the broad-spectrum MMP inhibitor Batimistat, expression of the serine protease uPA (urokinase plasminogen activator) in stromal fibroblasts is increased in a xenograft breast carcinoma model [9]. Increases in expression of MMP-2 and -9, but not MMP-14, occur in endometrial carcinoma cells during progression from histologic Grade 1 to Grades 2 and 3 [10]. In breast carcinomas, expression of uPA, its inhibitor PAI-1 (plasminogen activator inhibitor-1) and MMP-2 is increased with the age of the tumor-derived stromal breast fibroblasts and may contribute to progression of these cancers [11]. Less is known about how the interactions of a tumor with its microenvironment affect the expression of cysteine proteases. In this chapter, we concentrate on carcinomas and discuss how the interactions of carcinomas with their microenvironment can modulate expression of one specific cysteine protease, cathepsin B, and in turn how these interactions may impact overall proteolysis. As early as 1957 [12], there was an indication that cysteine proteases are affected by the microenvironment when Sylven and Malmgren reported that catheptic activity, assessed at acidic pH in the presence of cysteine activator, was high in the periphery of transplanted solid tumors, i.e., in cells adjacent to surrounding host tissue. The reagents available at that time for identifying the responsible protease would not have discriminated among the various human cysteine proteases. The data discussed in this chapter are consistent with the high cysteine protease activity in the periphery of Sylven and Malmgren's transplanted tumors representing activity of cathepsin B. Whether other cysteine proteases are affected when carcinomas interact with their microenvironment has not been analyzed.

2. Expression of cathepsin B in tumors

A consistent finding in human and murine tumors is an increase in expression of cathepsin B (for review, see [13]). Increases in expression are often observed in the epithelial cells of premalignant lesions, e.g., Min mouse adenomas [14] (cf. normal mouse intestine in Fig. 1A with adenomas in Fig. 1B and C), human high grade prostatic intraepithelial neoplasias (PIN) [15] (cf. normal prostate in Fig. 1D with PIN in Fig. 1E) and human Barrett's esophagus [16]. In human colon tumors, increases in expression are found in tumor cells, inflammatory macrophages associated with the tumors and stromal fibroblasts [17]. In some cases, macrophages at the invasive front of colon tumors express high levels of cathepsin B, but tumor cells do not [18]. In prostate tumors, macrophages also can be seen to express high levels of cathepsin B, yet the tumor cells express less cathepsin B than is found in high grade PIN [15] (cf. prostate carcinoma in Fig. 1F with PIN in Fig. 1E). On the other hand, levels of cathepsin B are elevated in prostate carcinoma cells at the invasive front as compared to prostate carcinoma cells within the bulk of the tumor mass [19]. In human breast cancer, macrophages and stromal fibroblasts adjacent to the carcinoma cells stain for cathepsin B, as do the carcinoma cells themselves [20]. Studies in transgenic mouse tumor models have established a functional role for cysteine proteases, including cathepsin