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EXPRESSION OF CATHEPSINS B AND S IN THE PROGRESSION OF PROSTATE CARCINOMA

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Cathepsins B and S (CatB, CatS) are lysosomal cysteine proteases which, among other functions, appear to play a role in cancer progression in different tumor models due to their matrix-degrading properties. To investigate their possible involvement in the development of prostate carcinoma, we immunohistochemically analyzed CatB and CatS in 38 primary human prostatic adenocarcinomas, as well as concomitant high-grade prostatic intra-epithelial neoplasia, nodular hyperplasia and normal tissue. CatB expression was observed in 28 (74%) and CatS in 32 (84%) carcinomas, being concomitant in 24 cases (63%). High-grade intra-epithelial neoplasia expressed CatB in 20/23 cases (87%), and a similar result was obtained for CatS, with expression of both coinciding in 18 cases (78%). In non-neoplastic tissue, strong expression of both proteases was observed in macrophages, inflamed glands and transitional metaplasia, whereas atrophic glands and basal cells of normal glands displayed intense CatB positivity. We conclude that CatB and CatS are often expressed together in neoplastic prostatic cells from preinvasive to invasive and clinically detectable stages, suggesting a putative role in local invasion, though other functions cannot be ruled out.
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Key words: *cathepsins; prostate; carcinoma; proteases; PIN*

The ability of cancer cells to invade the extracellular matrix (ECM) and eventually metastasize involves the use of different types of protease, and an increasing number of such enzymes and their inhibitors are currently under study, to evaluate their potential role in tumor progression. Cathepsins B and S (CatB, CatS) are lysosomal cysteine proteases of the papain family. Their involvement has, among a number of functions, been proposed in tumor progression through their matrix-degrading properties, angiogenesis or activation of other latent proteases.[1–5] A great deal of information is available on the functions and expression of CatB in several normal and neoplastic human tissues. CatB is a protease involved in the normal turnover of proteins in mammalian cells and is expressed by several types of neoplasm such as melanomas and breast, colon, lung, esophagus, bladder and head-and-neck carcinomas.[1,6–8] Interestingly, CatB expression in colon carcinomas is associated with advanced stage of disease and shortened survival,[9] and similar results have been reported for head-and-neck tumors.[10] Far less studied, CatS is a protease that is highly expressed by macrophages and other antigen-presenting cells, and it is believed to regulate antigen presentation by processing the MHC class II–associated invariant chain in splenocytes and dendritic cells.[11–16] CatS also has potent elastolytic activity and is capable of degrading several ECM molecules at neutral pH.[2,11,17] Finally, this protease is involved in the maintenance of normal retinal function, possibly through the regulation of other lysosomal enzymes, such as CatD.[18,19]

Prostate carcinoma is a frequent neoplasm in which, like other human organs, local extension and metastases are determinant of the prognosis of the disease and are most likely regulated, among other factors, by increased proteolytic activity of tumor cells. Initial studies in series of prostate carcinoma have demonstrated CatB expression in benign and neoplastic cells, where it could be involved in tumor progression and apoptosis.[20–22] On the contrary, to our knowledge, no information regarding CatS expression in human prostate carcinoma is available.

Our aim was to analyze the expression of CatB and CatS in a series of primary human prostate carcinomas and to compare this expression with that of pre-malignant lesions and different components of benign and normal prostatic tissue, to establish their possible concomitant presence and role in prostate carcinoma progression.

MATERIAL AND METHODS

Tissue samples

Thirty-eight consecutive T2 and T3 cases of prostatic adenocarcinoma were routinely processed with formalin fixation, paraffin embedding, 2 μm sectioning and hematoxylin and eosin histopathological evaluation. Twenty-two cases corresponded to low grade (Gleason's combined scores 2–6) and 16 cases to high grade (7–10). All patients were Caucasian, with ages ranging from 46 to 75 years (mean 62 years, SD = 6.6). High-grade prostatic intra-epithelial neoplasia (HGPIN) was observed and studied in 23 of the above cases. Normal prostatic tissue was also studied in most cases, as were 13 hyperplastic nodules. Representative sections of each case were selected for immunohistochemical staining.

Immunohistochemistry

Two-micron sections were deparaffinized in xylene and rehydrated with graded alcohols, water and PBS. Samples were sequentially incubated with blocking serum (30 min, room temperature), primary affinity-purified antibodies (overnight, 41°C) (CatB, rabbit, 0.004 mg/ml; CatS, rabbit, 0.0018 μg/ml) and biotinylated secondary antibody (room temperature). After avidin-biotin labeling, CatS staining was developed with alkaline-phosphatase–fast red for 15 min and Cat B with peroxidase/diaminobenzidine for 7 min. The specificity of the antibodies has been previously demonstrated.[9,16,23,24] Positive controls were colon carcinoma for CatB and spleen for CatS. Macrophages served as positive internal controls in all samples. Negative controls con-

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sisted of substitution of primary antibodies by normal rabbit IgG fraction at the same protein concentration. For CatS, further negative controls were pre-adsorption of the antibody with peptide for 1 hr at 37°C, which markedly decreased immunostaining in the 3 positive cases tested. A case was considered positive when >10% of cells had cytoplasmic expression.[9] Semi-quantitative gradation of the intensity was performed, with intensities ranging from weak (+) to strong (+++). Categorical data were analyzed by means of contingency tables. Probability was calculated using Fisher's exact test. Data were analyzed using the BMDP (Los Angeles, CA) New System statistical package. Significance was accepted with an alfa-risk of 0.05.

RESULTS

Normal and benign prostatic tissue

Luminal epithelia of normal prostate glands were usually negative for CatB, except for atrophic or inflamed glands (Fig. 1*a,b*). Positivity in normal and hyperplastic glands was limited to strong expression in the basal cell layer, though focal positivity in luminal cells was observed in 6 cases. The strongest positivity in prostatic tissues was always observed in transitional epithelium of periurethral prostatic ducts and transitional metaplasia (Fig. 1*c*). Intraglandular and interstitial histiocytes were always strongly positive for CatB and served as an internal positive control. CatS was mostly negative in normal prostate luminal epithelium, though slight granular positivity was observed in the basal pole of the epithelium in some glands. Interestingly, sporadic luminal cells showed strong diffuse cytoplasmic staining in many cases (Fig. 2*a*). Similar to CatB, CatS positivity was also found in intraglandular and peri-glandular histiocytes, transitional metaplasia and inflamed epithelium (Fig. 2*b,c*) but not in atrophic glands.

Expression of both cathepsins in hyperplastic nodules was similar to that in normal tissue. Peri-prostatic ganglion cells were strongly positive for both cathepsins. Weak expression of both proteases was observed in the normal stroma of the prostate in most cases.

HGPIN

Luminal cells of 20/23 HGPIN lesions (87%) showed CatB expression (Table I). A similar result was obtained for CatS, expression of both occurring concomitantly in 18 cases (78%) (Table II). CatS expression was more granular than that of CatB (Figs. 1*d,* 2*d*). The scarce basal cells of HGPIN glands were usually positive for CatB, whereas CatS expression was not evident.

Carcinomas

CatB expression was observed in 28 carcinomas (74%) (+, 13; ++, 14; +++, 1). CatS was expressed in 32 cases (84%) (+, 17; ++, 12; +++, 3). Expression of both diffuse and finely granular cytoplasmic CatB was observed in carcinomas, whereas CatS was mainly coarsely granular (Figs. 1*e,* 2*e*). CatS expression was more intense in the supranuclear area of the tumor cells in 5 cases. (Fig. 2*e,* inset). Expression of these proteases was heterogeneous in each case, usually sparing areas of the neoplasm, and positivity for both enzymes was observed in 24 cases (63%) (Table III). Expression of either cathepsin did not correlate with tumor grade or Gleason's pattern in a given area of the tumors.

Of the 9 CatB-negative carcinomas, HGPIN could be concomitantly evaluated in 6 and 3 were CatB-positive. Only 1/6 CatS-negative cases had coincidental HGPIN, which was positive.

CatB-positive macrophages were frequently seen within neoplastic glands (Fig. 1*e*). However, scattered stromal positive histiocytes were observed in tumor foci of 3 cases. Similar results were obtained for CatS (not shown).

DISCUSSION

One of the most important events during tumor development and progression is local invasion through degradation of ECM components, and increasingly proteases and their inhibitors involved in this process are being identified. Among the former, cysteine proteases appear to be produced by different types of malignant human neoplasm. We have previously demonstrated that CatB is frequently expressed by colon carcinomas and that this expression correlates with stage of disease and survival.[9] Breast, lung, larynx and other types of malignancy can produce these and other cathepsins; this production might have important prognostic implications.[25–30] In this study, we observed that two types of cathepsin, B and S, are frequently present in malignant prostatic cells (in both pre-invasive and invasive stages) and that their expression often occurs concomitantly. An immunohistochemical approach to analyzing the expression of these types of protease is considered mandatory given the ubiquitous presence of macrophages in many normal and neoplastic tissues, in which tissue extracts for immunoblot, Northern blot or RT-PCR would most likely be highly contaminated by non-tumoral products.

The strongest expression of both molecules was found, as expected, in macrophages within normal gland lumina and the stroma of inflammatory foci, most likely related to their involvement in antigen processing and presentation, as previously mentioned.

The presence of CatB and CatS in the epithelium of inflamed glands suggests active involvement of these cells in the processing of other enzymes and proteins activated during the inflammatory process. Indeed, the capacity of CatB for generating antigenic peptide fragments from larger molecules as well as the involvement of CatS in invariant chain proteolysis and peptide loading are well known.[2,13] Moreover, expression of CatS in inflamed areas might be related to cytokine induction. Strong concomitant expression of these proteases has also been observed in glands with transitional metaplasia, which contains cells. CatB expression has been reported in normal urothelium and bladder carcinoma,[8] suggesting that this protease could be constitutionally expressed by cells with this phenotype. Although, to our knowledge, no information regarding CatS expression in urothelium is available, a similar explanation could be true for this other cathepsin.

In contrast to CatS, intense CatB immunopositivity was observed in atrophic epithelium. However, no conclusions could be drawn from our study. Nevertheless, we postulate that it might be related to CatB involvement in apoptosis[20,31,32] or in remodeling of the basement membrane of glands undergoing changes in size or luminal tension. Similarly, CatB was strongly expressed by basal cells of normal prostatic glands, which might be related to basement membrane turnover or other cell–ECM interactions. The intense expression of CatS in sporadic cells of isolated normal glands (Fig. 1*b*), whose topographical distribution suggests a neuroendocrine nature,[33] deserves special attention. Besides the intensity, the diffuse distribution of positivity in these normal cells highly contrasts with the coarse granular expression in most carcinomas, suggesting a different cytoplasmic processing and/or function in normal and neoplastic epithelia.

Pre-invasive phenotypic changes of epithelia frequently precede malignant transformation in many human organs, thus providing a multistep model of cancer development. One such organ is the human prostate, where a well-characterized pre-malignant state is frequently associated with carcinoma.[34] Previous studies have shown expression of CatB in human pre-malignant proliferations (dysplasia) in organs such as the bladder and colon.[8,35] The frequent presence of CatB and CatS in prostate carcinomas and their pre-malignant lesions suggests an important role in the initial steps and progression of this type of neoplasm. Although the precise function of these enzymes in tumor progression cannot be definitively established from our results, we postulate that, similar to CatD and collagenases,[36,37] expression of CatB and CatS in HGPIN may be related to the direct remodeling of the surrounding ECM prior to stromal invasion or to involvement in the cytoplasmic processing of other proteases or proteins with roles in this process. The existence of several cases of CatB-negative carci-

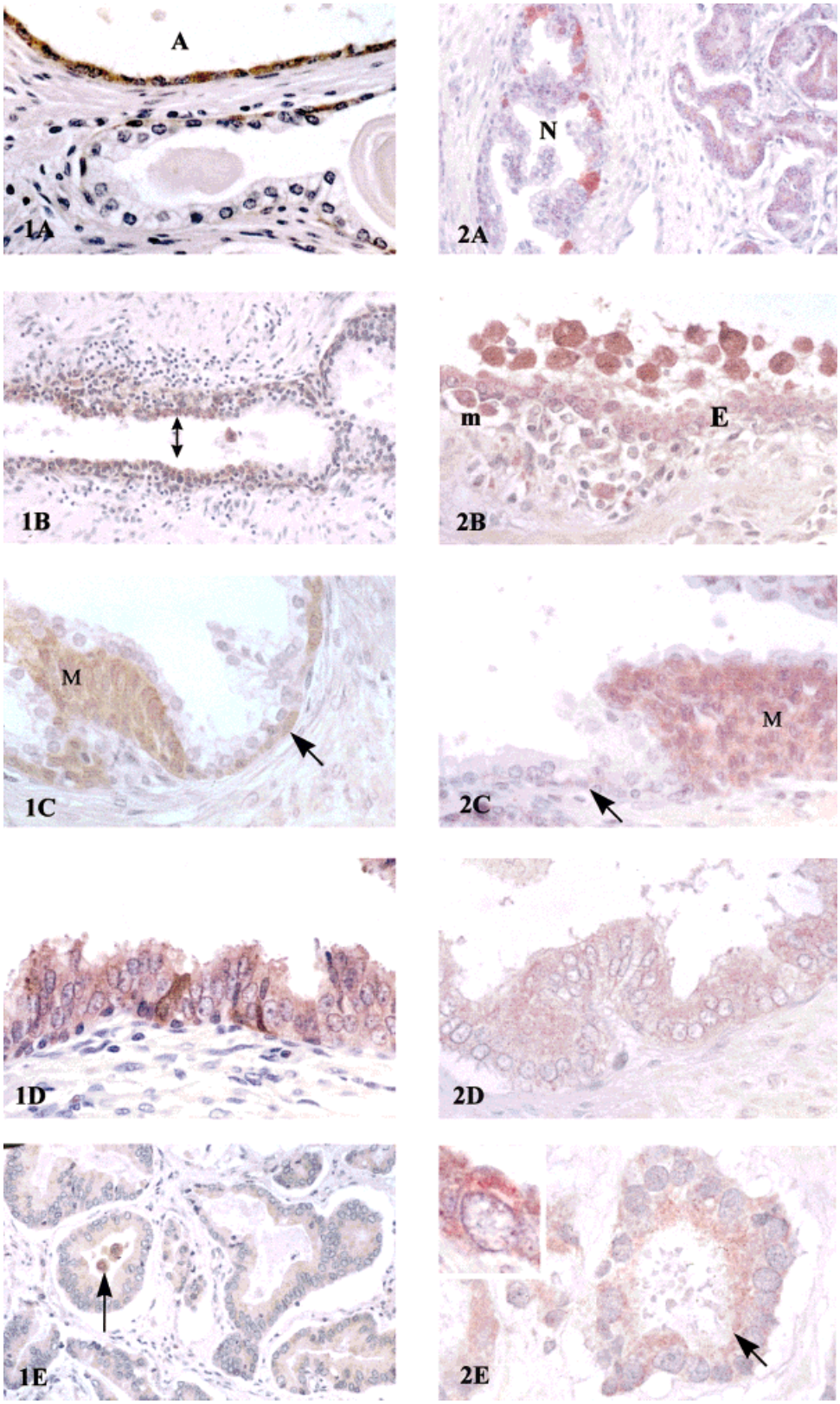

Figure 1 – *(a)* Normal prostate gland (bottom) with CatB-negative luminal cells as well as scattered positive basal cells. A strongly positive atrophic gland is seen at the top. ×400. *(b)* Normal gland with intense epithelial expression of CatB in inflamed areas (arrows). ×200. *(c)* Strong CatB expression in transitional metaplasia (M) and normal basal cells (arrow). ×400. *(d)* HGPIN strongly expressing CatB. ×400. *(e)* Prostate carcinoma diffusely expressing CatB. Intraluminal macrophages show intense CatB expression (arrow). ×200.

Figure 2 – *(a)* Normal prostate gland (N) showing predominantly CatS-negative epithelium with scattered strongly positive cells. A focus of CatS-positive carcinoma is seen on the right. ×200. *(b)* Inflamed normal gland containing macrophages that express CatS. CatS expression is also observed in epithelial cells (E) and migrating macrophages (m). ×400. *(c)* Strong expression of CatS is seen in transitional metaplasia (M), whereas normal epithelium is negative (arrow). ×400. *(d)* HGPIN expressing granularly CatS in luminal cells. ×400. *(e)* Granular CatS expression in prostate carcinoma. Positivity is more intense over the nucleus (arrow). ×600. Inset shows accumulation of immunopositivity toward the apical pole. Oil immersion ×1,000.

TABLE I – EXPRESSION OF CATHEPSINS B AND S IN PROSTATE HGPIN AND CARCINOMAS

	CatB		CatS	
	–	+	–	+
PIN	3	20	3	20
Carcinoma	10	28	6	32

TABLE II – CONCOMITANT EXPRESSION OF CatB AND CatS IN HGPIN

PIN	CatS	
	–	+
CatB		
–	1	2
+	2	18

TABLE III – CONCOMITANT EXPRESSION OF CatB AND CatS IN PROSTATE CARCINOMA

Carcinoma	CatS	
	–	+
CatB		
–	2	8
+	4	24

noma whose associated HGPIN expresses this protease further stresses the possibility of specific functions for CatB in the first stages of malignant transformation in the prostate, which could, in some cases, be lost during tumor progression. Functions similar to those proposed for HGPIN may apply to expression of these proteases in invasive carcinomas, though contrary to colon and bladder neoplasms,[8,9] this expression was not significant in the invasive edges of tumors. Another difference with the above tumor models is that, although some macrophages expressing both cathepsins were also observed within some neoplastic glands, no significant presence of these cells was detected in the stroma surrounding malignant glands, which might be related to the usually scarce stromal histiocytic infiltrate of prostate carcinomas.

Our immunohistochemical study allowed precise evaluation of the cytoplasmic expression of both cathepsins, which showed different patterns of positivity. Indeed, CatB was mostly finely diffuse, whereas CatS appeared to reflect a distribution in coarse cytoplasmic granules, sometimes with a predominant location toward the lumina, which might indicate a secretory function. Differences in their roles might explain the above findings; and the observation of diffuse, non-granular staining of CatB in colorectal and bladder carcinomas has been previously interpreted as a truncated form of the protein that is free in the cytosol or membrane-associated with enhanced ECM degradative capacity.[1,8]

One of the main findings of our study is the frequency of concomitant expression of CatB and CatS (63% of cases). Breast,[7,25] head-and-neck,[10,27,29] melanoma[38] and other types of human malignancy have been demonstrated to express several types of cathepsin and their inhibitor stefins, with different prognostic implications. Initial studies have reported CatB expression in prostate carcinomas and proposed a role in angiogenesis and stromal invasion.[21,22,39] Concomitant expression of CatB and CatS in early tumor progression was also observed in the pre-invasive stages of the transformed prostate epithelium in our series of cases, suggesting a collaborative role in the development of prostate neoplasms. To further explore the involvement of these proteases in late stages of prostate carcinoma progression, detailed immunohistochemical analyses in metastases are mandatory, though the difficulty in obtaining this (usually not biopsied) type of material hinders this approach.

In summary, CatB and CatS are frequently co-expressed in prostate carcinomas, and this expression appears early in tumor development. The absence of comparable immunopositivity in normal tissue suggests a role for these cysteine proteases in prostate-carcinoma progression. The possible prognostic implication of such expression will require further studies in larger series with adequate follow-up.

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