Role of cathepsin A and cathepsin C in the regulation of glycosidase activity

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Abstract: Increased tissue activity of cathepsin A and cathepsin C can be observed in many pathological conditions. It is associated with an enhanced degradation of glycosaminoglycans, proteoglycans, and glycoproteins, and results in their decreased tissue content. Cathepsin C releases the glycosidases from complexes formed with cathepsin A, and reinstates their activity. In this review a current state of knowledge is presented concerning the regulation of selected glycosidases activity by cathepsin A (EC 3.4.16.1) and C (EC 3.4.14.1). (Folia Histochemica et Cytobiologica 2012, Vol. 50, No. 1, 20–24)

Key words: cathepsin A, lysosomal carboxypeptidase A, cathepsin C, dipeptidyl peptidase I, glycosidase activity

More than sixty lysosomal hydrolases digest macromolecular compounds: proteins, polysaccharides, lipids, and nucleic acids at acidic pH. The lack or deficiency of a certain lysosomal enzyme resulting from genetic defect or inactivation can lead to the development of a storage disease [1]. A disease can be classified as a lysosomal storage disorder if it fulfils the following three criteria: 1) the lack or decreased activity of at least one lysosomal enzyme, 2) the stored substance is normally degraded in lysosomes, and 3) it is stored inside the lysosomes [2].

Cathepsin A (EC 3.4.16.1) prevents the processes involved in lysosomal storage. Cathepsin A forms complexes with glycosidases, protecting them in this way against proteolytic inactivation [3, 4]. Decreased lysosomal content of cathepsin A leads to the inactivation of several glycosidases and accumulation of glycosaminoglycans. Cathepsin C (EC 3.4.14.1) is also involved in glycosaminoglycan metabolism. Cathepsin C releases the glycosidases from complexes formed with cathepsin A, and reinstates their activity [5].

Cathepsin A

Cathepsin A is multifunctional lysosomal protein that acts as a carboxypeptidase and forms complexes with glycosidases at pH between 4.5 and 5.5; it exhibits amidase and esterase activity at pH 7.0 [5, 6]. One molecule of cathepsin A is composed of 438 amino acid residues assembled into two subunits — cortical and apical one with molecular masses of 32 kDa (Ala1-Arg284) and 20 kDa (Met285-Tyr438), respectively (Figure 1). The subunits are held together with disulfide bonds C60-C361 and form a monomer of cathepsin A [7]. Its catalytic site is built of Ser150, Asp356, and His415 amino acid residues. Cathepsin A monomer has a molecular mass of 52 kDa and measures 60 × 50 × 70 Å [8].

Under acidic pH, 60–70% of cathepsin A exists as homodimers with 104 kDa molecular mass [6]. The remaining 30–40% is present in the form of a two-component, enzymatically active complex with beta-
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- galactosidase [7]. Its beta-galactosidase-binding contact surface is formed of Gln76-Tyr84 and Val306-E401 — amino acids of catalytic triad

Table 1. Amino acid composition of cathepsin A [44]

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<td>Val (V)</td>
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<td>Sum of amino acids</td>
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*Three-and one-letter code

Figure 1. Amino acid sequence of cathepsin A: A1-R284 — 32 kDa subunit; M285-Y428 — 20kDa subunit; C — C disulfide bond binding the subunits; S150-D356-H415 — catalytic triad; N17, N291 glycosylated rests; Q76-Y84, V306-E401 — beta-galactosidase binding sequences [8]

Figure 2. Model of cathepsin A molecule monomer [adopted from 9]. • – • – • — amino acids of catalytic triad
units as a result of the addition of the reducing compound. After reducing pH to 4.5, macrocomplex with 680 kDa molecular mass is formed again. The formation of this complex protects beta-galactosidase against degradation and proteolytic inactivation [10, 11]. Complex of cathepsin A with beta-galactosidase is isolated by means of affinity chromatography on p-aminophenyl-beta-D-thiogalactopyranoside-agarose [14]. Obtained complex of cathepsin A and beta-galactosidase is dissociated at pH 7.5 and fractioned into its components by means of gel chromatography technique with Shim-pack Dial-3000 column. About 1% of cathepsin A molecules is present as a polyezymatic macrocomplex with beta-galactosidase, N-acetyl-alpha-neuraminidase, and N-acetylgalactosamine-6-sulfate sulfatase [12, 13]. This macrocomplex has a molecular mass of approximately 1280 kDa [7, 14, 15]. Table 2 summarizes the characteristics of glycosidases that are bound by cathepsin A.

Inherited deficiency or point mutations in the amino acid sequence of cathepsin A (Q21R, S23Y, W37R, S61L, V104M, L208P, Y221N, Y351C, M365T, G389S, F398V) inhibit the formation of dimeric forms and complexes with glycosidases [16–18]. Degradation and inactivation of beta-galactosidase and neuraminidase are reflected by a secondary deficiency of those enzymes, leading to the accumulation of galactosaminoglycans and sialoglycosaccharides, and as a consequence to the storage disease – mucopolysaccharidosis IV B and galactosialidosis [19, 20]. Degradation of beta-galactosidase is catalyzed by cysteine cathepsins [21]. Leupeptin, an inhibitor of cathepsins, halts this process. Decreased activity of cathepsin A can be observed in the course of muscular dystrophy [22] and in multiple sclerosis [23].

Cathepsin C

Cathepsin C also participates in the regulation of glycosidase activity. It is a lysosomal cysteinylenpeptidase—an enzyme that cleaves off dipeptides from the N-terminus of peptides and proteins [24, 25]. Moreover, it hydrolyses dipeptide esters, amides, anilides, and beta-naphthylamides [26]. Additionally, cathepsin C shows the activity of transpeptidase [27]. It catalyzes hydrolysis at pH 5.0–6.0 and transpeptidation at pH 6.8–7.0 [4]. Cathepsin C is activated by chloride anions and sulfhydryl compounds [28].

One molecule of human cathepsin C is built of 206 amino acid residues, arranged in four polypeptide chains with a total molecular mass of approximately 200 kDa [29]. Its spatial model is presented in Figure 4.
The role of cathepsin C in the regulation of lysosomal enzymatic activity involves the release of beta-galactosidase and neuraminidase from complex with cathepsin A (Figure 5). This process requires the presence of chloride anions (Cl−) and sulfhydryl compounds [4, 30]. Released beta-galactosidase, neuraminidase, and cathepsin A exhibit normal activity. Genetic mutation and reduced activity of cathepsin C cause Papillon-Lefevre syndrome characterized by palmoplantar keratoderma, periodontitis, and muscular dystrophy [3, 42].

Increased tissue activity of cathepsin A and cathepsin C can be observed in many pathological conditions [24, 26, 31–34]. It is associated with an enhanced degradation of glycosaminoglycans, proteoglycans, and glycoproteins, and results in their decreased tissue content [35–40].

References

Figure 5. Proposed model of cathepsin C (CTSC) regulated dissociation of multienzyme complex: LCP A — cathepsin A; β-Gal — β-galactosidase; Neu — neuraminidase; GALNS — 6-N-galactosamine N-acetyl-6-sulfate sulfatase; Cl− — chloride ions; −SH — sulfhydryl group


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