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Mini Review

Cathepsin D: A cellular roadmap

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ABSTRACT

Cathepsin D is a normal and major component of lysosomes, it is found in almost all cells and tissues of mammals. Present review describes different events in cellular life of cathepsin D mainly its biosynthesis, co-translational and posttranslational modifications, targeting to lysosomes and proteolytic processing and maturation within lysosomes.

Cathepsin D (CatD, EC 3.4.23.5) is an intracellular aspartic protease of the pepsin superfamily. The involvement of CatD in several physiological functions such as protein degradation, apoptosis and autophagy [1] have been reported. Additionally, it is also found to be associated with certain pathological conditions such as cancer [2], Alzheimer's disease [3] and neuronal ceroid lipofuscinosis [4]. CatD is found in almost all mammalian cells and has a typical lysosomal localization [5,6]. Human CatD is synthesized as a single polypeptide that is proteolytically processed into mature CatD that exists as a two-chain form: an amino terminal light chain (14 kDa) and a carboxyl-terminal heavy chain (34 kDa). These chains remain associated with each other by hydrophobic interactions. Before the generation of this mature two-chain form, CatD undergoes several proteolytic stages. Therefore, the early isolations of cathepsin D showed various different forms that differed in size, number of associated polypeptides and iso-electric point but had similar activities [7]. Later on, site-directed covalent modifications demonstrated that CatD has a similar active site as pepsin, confirming its identity as an aspartic protease [8,9]. It was hypothesized that the two-chain form is derived from the single polypeptide form by proteolysis [10]. This was determined by N-terminal sequencing of different forms of porcine CatD [11]. Isolation of the cDNA clone [12] and the gene [13], detailed studies of biosynthesis [14], activation [15], substrate specificity [16] and determination of crystal structure [17,18] makes cathepsin D one of the best studied lysosomal proteases (reviewed in [19]). In this review we have discussed the journey of cathepsin D through cell; encompassing its biosynthesis, co-translational and posttranslational modifications, targeting to lysosomal compartments and proteolytic processing within lysosomes.

Transcription of cathepsin D gene

Eukaryotic gene expression is controlled by both, proximal and distal elements, generally located in the 5′ upstream region of the gene [20]. Several gene promoters contain a TATA box, that binds to the transcription factor IID (TFIID) and thus, define the transcription initiation site for that gene. Genes having such promoters are termed as facultative or regulated genes. On the contrary, the promoter region of the house keeping genes lack a recognizable TATA box and contain multiple GC boxes that are putative binding sites for transcription factors, like Sp1 [21]. The promoter region of cathepsin D has a mixed structure showing features of both housekeeping genes (high G + C content and several potential Sp1 binding sites) and regulated genes (TATAA sequence) (Fig. 1) [22].

Due to this mixed structure CatD promoter can direct both types of transcription initiations; TATA-independent and TATA-dependent [22]. Moreover, it has also been shown that transcription of CatD is initiated at five major transcription starting sites (TSS-I to TSS-V) spanning 52 bp (Fig. 1) [22]. The constitutive expression of CatD in human is TATA-independent initiating at one of the several transcription starting sites (TSS-II to -V), upstream of the TATA box, and is possibly directed by GC boxes and Sp1 factor as in many housekeeping genes. On the other hand, in estrogen stimulated breast cancer cells where CatD is reported to be overexpressed [23], transcription is TATA-dependent, starting about 28 bp downstream from the TATA box (TSS-I) [22] (Fig. 1).

Abbreviations: CatD, cathepsin D; M-6-P, mannose-6-phosphate; TSS, transcription starting sites

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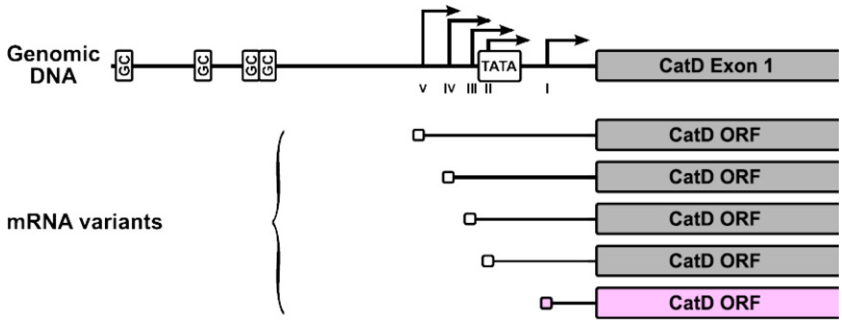

Fig. 1. Schematic diagram of the cathepsin D promoter region. Five major transcription start sites (TSS-I to -V) for CatD gene are indicated by arrowheads. These five transcription initiation sites respectively map at −20, −44, −51, −60 and −72 from the first base of the initiation codon. In basal conditions expression of human CatD is TATA-independent and initiates at one of the several transcription starting sites (TSS-II to -V), upstream of the TATA box, and is possibly directed by GC boxes and Sp1 factor. In estrogen stimulated breast cancer cells where CatD is reported to be overexpressed, transcription is TATA-dependent, starting from TSS-I. The lower part of the figure illustrates schematic comparison between the lengths of different CatD mRNAs. The difference in length is only between the 5′ untranslated regions of mRNA (*the open reading frame of CatD gene is mentioned*). The first four mRNAs with longer 5′ untranslated regions are present in higher proportion in basal conditions where TATA-independent transcription is dominant. While in breast cancer cells the proportion of mRNAs with shorter 5′ untranslated regions (*pink*) is increased. (For interpretation of colour mentioned in this figure, the reader is referred to the web version of this article.)

Thus, estrogens not only increase transcription but also affect the pattern of initiation, with TATA-dependent transcription predominating. Therefore, in stimulated conditions, CatD mRNAs preferentially have short 5′ untranslated sequences, whereas in basal conditions where TATA-independent transcription is dominant, the proportion of longer CatD mRNAs is increased (Fig. 1).

Since the CatD gene is controlled by a mixed promoter, it has the advantage of being both constitutively expressed from TATA-independent start sites, and overexpressed in some physiological conditions such as development or tissue modeling by TATA-dependent transcription [22] and this TATA-dependent transcription is also exploited by cancer cells.

Translation, posttranslational modifications and lysosomal sorting of cathepsin D

Cathepsin D is synthesized on the rough endoplasmic reticulum as a pre-pro-enzyme. This pre-pro-cathepsin D in human comprises 412 amino acids (aa) and contains an N-terminal secretion signal peptide (S) that is composed of 20 aa. This signal peptide is removed during co-translational translocation of CatD across the ER membrane generating an inactive procathepsin D (392 aa, 52 kDa) (Fig. 2). Following this co-translational removal of signal peptide sugars are attached at two N-linked glycosylation sites at asparagine residues 134 and 263 (pre-pro-CatD numbering, UniProtKB/*Swiss-Prot*) that are widely separated on the surface of the folded protein. After glycosylation cathepsin D is transported to the Golgi stacks. Studies with mono-glycosylated and non-glycosylated CatD mutants have shown that glycosylation is not necessary for folding or enzyme activity but it is required for targeting of the enzyme to lysosomes [24].

Normal cellular life of CatD is characterized by a special feature i.e. its strict localization within acidic lysosomal compartments. Transport of pro-CatD from Golgi complex to the downstream acidic compartments is mainly mediated by the mannose-6-phosphate (M-6-P) [25] pathway. Thus, in the Golgi complex the two N-linked oligosaccharides of CatD are covalently modified and their mannose residues are phosphorylated at position six (Fig. 2) [26]. These M-6-P groups are recognized by cation-independent mannose-6-phosphate receptor (MPR300) [27] in *trans*-Golgi network that segregates lysosomal hydrolases and helps to package them into budding transport vesicles, that deliver their contents to late endosomes and thereby to lysosomes (Fig. 2).

The second M-6-P independent pathway for targeting of pro-CatD to lysosomes is carried out by interaction of pro-CatD with pro-saponin [28]. This pathway is not fully understood and is also not the major pathway for intracellular trafficking of cathepsin D. However, it is suggested that the two molecules i.e pro-CatD and pro-saponin form complexes and travel together to acidic compartments [28]. According to a very recent report transport of CatD is speculated to be partially dependent on sortilin that is a multifunctional receptor that cycles between the *trans*-Golgi network and endosomal compartments [29].

Proteolytic processing and maturation of cathepsin D in lysosomal compartments

Once segregated into the endolysosomal compartments, the pro-CatD undergoes several proteolytic processing events to generate mature cathepsin D [19]. First of all at the low pH of late endosomes the pro-CatD dissociate from M-6-P receptors and subsequently the phosphate group is removed. The initial proteolytic step is the removal of pro-peptide (44 amino acids) from pro-CatD to generate an active intermediate (48 kDa, 348 a.a) single-chain molecule (Fig. 3). The pro-peptide (also termed as activation peptide) of CatD is reported to be essential for the correct folding, activation and delivery of the protein to lysosomes [30,31].

The 48 kDa single-chain intermediate is not generated by autocatalytic activity of CatD, because proteolytically inactive mutant of CatD was normally processed to the mature form of the enzyme when transfected in CatD-deficient cell lines. Instead, the involvement of cysteine proteases other than CatL and CatB was observed [32].

The 48 kDa intermediate is further processed into mature two-chain form of cathepsin D, this processing step is carried out by cathepsin B or L [32]. The two-chain form consists of an amino terminal light chain (14 kDa) and a carboxyl-terminal heavy chain (34 kDa) (Fig. 3). These chains remain associated with each other only by hydrophobic interactions. Additionally, seven amino acid residues between the heavy and light chain are removed [33]. Several more amino acids are removed from the carboxyl terminus of the 34 kDa heavy chain [34].

In vitro studies have demonstrated that upon acidification pro-CatD auto-catalytically generates a proteolytically active pseudo-CatD [35,36], an enzyme form that retains 18 residues (27–44) of the propeptide. But recent studies have reported that the formation of pseudo-CatD is not a required intermediate for CatD processing in cells and it is a mere *in vitro* artifact [32].

The two-chain form of human CatD is generated by the proteolytic processing of CatD at a specified region [19] that forms a puta-

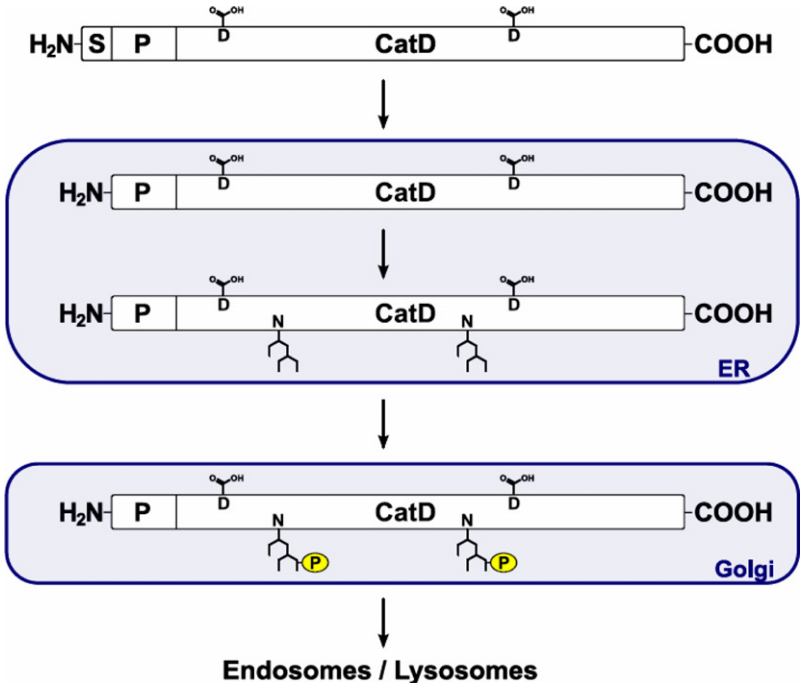

Fig. 2. Intracellular trafficking of cathepsin D. Cathepsin D is synthesized as a pre-pro-enzyme (412 aa, human) on rough endoplasmic reticulum that contains an N-terminal secretion signal peptide (S) of 20 aa and a propeptide (P) of 44 aa (*catalytic Asp* (*D*) *residues D97 and D295 are also depicted*, pre-pro-CatD numbering, UniProtKB/*Swiss-Prot*). The signal peptide is removed during co-translational translocation of pre-pro-CatD across the endoplasmic reticulum (ER) membrane generating an inactive procathepsin D (pro-CatD). In ER sugars are attached at two N-linked glycosylation sites at asparagine residues N134 and N263 (pre-pro-CatD numbering, UniProtKB/*Swiss-Prot*). In Golgi complex the two N-linked oligosaccharides of pro-CatD are covalently modified and their mannose residues are phosphorylated at position six. These M-6-P tags are recognized by cation-independent mannose-6-phosphate receptor (MPR300) in *trans*-Golgi network that segregates lysosomal hydrolases and help to package them into budding transport vesicles that deliver their contents to lysosomes *via* endosomes.

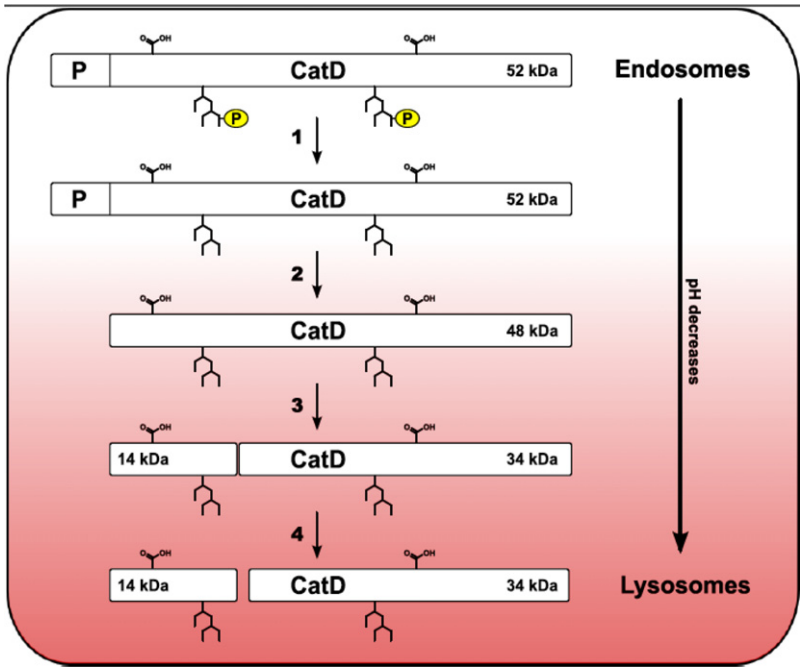

Fig. 3. Major proteolytic steps in maturation of cathepsin D within endolysosomal compartments. In acidic compartments, the pro-CatD undergoes several proteolytic processing events to generate mature cathepsin D. M-6-P pathway delivers CatD like other lysosomal hydrolases, initially to late endosomes from where they are sorted to lysosomes. Here, the major transformation steps are depicted by numbered arrows. (1) First of all at the low pH of late endosomes the hydrolases dissociate from their receptors and subsequently the phosphate group is removed. (2) The initial proteolytic event is the removal of pro-peptide (44 amino acids) in several steps from pro-CatD to generate an active intermediate (48 kDa, 348 a.a) single-chain molecule. The removal of propeptide is independent of CatD autocatalytic activity and is mediated by cysteine proteases other than CatL and CatB. (3) The 48 kDa single-chain molecule is further processed by cathepsin B or L into mature two-chain form comprising an amino terminal light chain (14 kDa) and a carboxyl-terminal heavy chain (34 kDa). (4) During this conversion seven aa (from putative β-structure) (see text for details) between heavy and light chain and several other residues are removed from carboxyl terminus of the heavy chain.

tive β-structure (β-hairpin loop) on the surface of human pro-CatD. Thus, it is exposed to proteolysis in the lysosomes where the cleavage occurs [37] and the two-chain form is generated. This region comprises the amino acid stretch P^{159}CQSASSASAL^{169}. Seven (i.e. S^{162}ASSASA^{168}) of these eleven residues are removed during single to two-chain maturation process [37]. The mutants lacking this region were reported to be very unstable [38]. It was suggested that this region is also important for lysosomal targeting of CatD. However, recently a new mutant is reported in which this region of human CatD was substituted with corresponding sequence of CatD from *Clupea harengus*. As CatD in *Clupea harengus* is found exclusively as a single-chain form [39]. This mutant existed as single-chain polypeptide that was stable, enzymatically active and properly targeted to lysosomes [39]. Hence, this β-hairpin loop is not involved in lysosomal targeting or stability of the protease and is only required for the formation two-chain form of CatD.

Trafficking and processing of CatD in cancer cells

Many breast and colorectal cancer cells secrete increased amounts of pro-CatD into the extracellular space where it has been shown to contribute to the invasive and metastatic potential of the cancer cells [40,41]. A number of hypotheses have been developed and tested to explain the potential causes for CatD secretion in cancer cells. For example increased expression of CatD [42], its altered binding to the cation-dependent M-6-P receptor (MPR46) instead of cation-independent M-6-P receptor (MPR300) [42], a failure of cancer cells to synthesize the M-6-P tag [43], and the absence or inactivating/missense mutations in the MPR300 [44]. Moreover, it was reported that the secretion of mature CatD directly from pericellular lysosomes contributes to CatD secretion by metastatic cancer cells [45]. Nevertheless, none of these studies have provided a satisfying elucidation for the secretion of pro-CatD by multiple cancer cell types [46]. Recently, Kokkonen et al. [46] have reported that defective acidification of endosomal compartments results in the aberrant secretion of pro-CatD in certain cancer cells. They reported that the defective acidification of endosomes in different breast and colorectal cancer cells mainly interferes with the normal disassembly of the receptor-enzyme complexes and efficient receptor reutilization in the Golgi complex.

Early studies suggested that metastatic potential of cathepsin D depends on its catalytic activity. The extracellular pH of the tumors is moderately acidic [47] therefore, it was hypothesized that pro-CatD secreted by cancer cells is converted in acidic extracellular milieu to enzymatically active pseudo-cathepsin D, that retains 18 residues (27–44) of the propeptide [35,36].

However, several recent studies have documented that pronounced mitogenic effect of CatD on breast cancer cells is independent of its catalytic activity [48]. Independent studies have established that pro-CatD secreted by cancer cells functions as a growth factor acting both in an autocrine and paracrine manner [49]. It is observed that propeptide of CatD is involved in binding of pro-CatD on yet unidentified cell surface receptors of breast cancer cells [1]. More recently it is reported that 27–44 amino acid region of propeptide is necessary for the stimulatory actions of pro-CatD on breast cancer cells [50].

Concluding remarks

Intracellular trafficking of CatD and proteolytic processing of pro-CatD to generate active form is very crucial topic. The importance of intracellular trafficking of CatD lies in the fact that targeting of enzyme to lysosomes is essential for its normal proteolytic function. Moreover, translocation of CatD from lysosomes to cytosol is associated with apoptosis [1,51] and increased secretion of CatD to extracellular space by cancer cells contributes to the invasive and metastatic potential of these cells [40,41]. On the other hand, proteolytic processing is also very important as CatD is reported to have an impact on several physiological and pathological processes as both an active enzyme and an inactive zymogen.

Cathepsin D is sorted to the lysosomal compartments mainly by M-6-P pathway like other lysosomal hydrolases. M-6-P independent pathway is also reported to be involved in targeting of CatD to lysosomes but this pathway is not clearly understood. In lysosomal compartments it is processed in to the mature enzyme that plays a pivotal role in protein catabolism. In some pathological conditions such as cancer CatD escapes the normal targeting mechanism and is secreted from the cells into extracellular matrix where it functions as a growth factor acting both in an autocrine and paracrine manner.

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