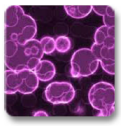
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Procathepsin D in cancer development

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Abstract

Over thirty years of research showed that procathepsin D is overexpressed and secreted by cells of several tumor types including lung, breast and prostate cancer. After secretion, it exhibits growth factor –like mitogenic activity. Subsequent *in vivo* and *in vitro* studies strongly support the hypothesis that the mitogenic effects are mediated via its activation peptide. Another potential cancer-related role of procathepsin D is the effect on resistance of cancer cell to chemotherapeutic drugs. The purpose of this review is to summarize the two major roles of procathepsin D in cancer development.

Keywords: Cathepsin D, procathepsin D, activation peptide, cancer, breast, lung, prostate, proliferation, siRNA, growth factro

Introduction

History of aspartic proteinases and recognition of their role in human physiology was marked by the work of Theodor Schwann [1], who recognized the proteolytic activity of the gastric juice and gave it the name pepsin. Later, Hedin described a proteinase present in bovine spleen with activity in higher acidic range [2]. This enzyme was later named cathepsin D. With subsequent improvements in isolation techniques and biochemical characterization, more and more members of this family of proteolytic enzymes were established. The most important aspartic proteinases are represented by pepsin A, gastricsin, renin, cathepsin D, cathepsin E and HIV and retroviral proteinases.

These proteinases are widely distributed in organisms and accomplish various functions. However, they share common features such as low pH of action and sensitivity to three specific inhibitors – pepstatin A, diazoacetyl norleucine methylester, and 1,2-epoxy-3-(p-nitrophenoxy) propane. Another common feature is the high similarity of their primary structures. Mature aspartic proteinase consists of a chain of app. 300 amino acid residues, with the resulting molecular weight around 35, 000 Da, that is often dependent on the degree of glycosylation. Regarding the activation, three possible routes are involved: total self-activation, self-activation complemented by assisted activation, and totally activated activation [3]. Readers seeking detailed information should see [4].

The subject of this review is aspartic proteinase cathepsin D (CD), and its involvement in cancer. Its name comes from the Greek *kata*- "down from" and *hepsein* "boil" and also "digest food", based on [5] who introduced this term for an intracellular peptidase with acidic pH optimum. Subsequent studies showed that the protein is formed by two peptidic chains with a pro-form of higher molecular weight as a precursor of the final hydrolytically processed form. The existence of an inactive precursor (procathepsin D; pCD) was later confirmed [6,7]. In the following years, numerous studies were focused toward several directions: intracellular trafficking and processing of pCD was studied [6,8,9], characterization of the gene of human CD [10,11] and determination of the three-dimensional structure [12,13].

Cathepsin D cleaves denatured polypeptides in an endopeptidase mode of action with hydrophobic amino acids at the scissile bond [14]. As specific inhibitor, pepstatin, a reversible peptidomimetic inhibitor of aspartic peptidases, inhibits cathepsin D with K_i in pM range [15]. A significant number of CD inhibitors was developed based on pepstatin structure and its statin residue which acts as a transition-state mimic [16]. With respect to structure and formation, CD is synthesized in rough endoplasmic reticulum in the form of pre-pro-enzyme precursor which is about 400 amino acids long. The primary structure of human CD precursor (52 kDa) is posttranslationally modified by two major processes – proteolytic cleavage and glycosylation. Proteolytical removal of the signal peptide occurs during the translocation across the membrane of the rough endoplasmatic reticulum. Procathepsin D is then targeted to lysosomes where, upon acidification, undergoes proteolytic activation. The activation processing of pCD requires proteolytic removal of the activation peptide from the zymogen molecule [8,9]. Subsequently, CD is subjected to additional proteolytic processing which converts the single-chain molecule into

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two-chain molecule formed by heavy and light chains (34 kDa and 14 kDa, respectively). The cleavage is likely to be performed by other lysosomal peptidases [17].

Cathepsin D is a glycoprotein with two N-linked oligosaccharides of high-mannose type [7,18]. The glycosylation is not required for the enzyme activity or folding but plays a significant role in its targeting, as the oligosaccharides are tagged by mannose-6-phosphate residues (for review see [19]). These tags allows for lysosomal targeting of CD via mannose-6-phosphate receptors [20]. However, an alternative transport associated with prosaposin has also been proposed [21].

Biological actions of cathepsin D

Cathepsin D has been described to be expressed in practically all tissues and organs and it was localized in lysosomes and in most prelysosomal compartments. In the early stage of CD research, the intracellular digestion of proteins has been postulated as its major function. However, data achieved over the last decades changed our understanding of the complex roles that cathepsin D plays both in physiology and pathology (for a review see [22,23]. Knock-out experiments demonstrated the importance of CD in the cell and tissue growth regulation which is supported by participation in tissue remodeling [24]. Physiological and pathophysiological actions of CD are usually controversial. In apoptosis, some studies based on KO model showed anti-apoptotic properties [25,26]. The anti-apoptotic properties of CD are also suggested to be responsible for CD protection of cancer cells treated with cytotoxic drugs [27]. However, pro-apoptotic functions of CD are now the subject of a growing number of studies which showed that the addition of CD to mitochondria resulted in substantial ROS generation and cyt c production [28] and that hydrogen peroxide cytotoxicity was mediated via CD mediated intralysosomal degradation of thioredoxin-1 [29].

Additional role of CD can be found in neurodegenerative diseases such as Alzeheimer disease and retinal atrophy, where the proteolytic activity of CD protected the development of type AA amyloid fibrils [30].

Increased levels of CD (both at the mRNA and protein levels) were first reported in several human neoplastic tissues almost 30 years ago [31,32]. These findings generated intense research in a possible role for CD in neoplastic processes. A strong predictive value was found for CD concentrations in breast cancer as well as many other tumor types [33-35]. However, despite numerous studies suggesting involvement of CD [36], the direct enzymatic involvement of mature enzyme in the invasiveness of cancer has never been demonstrated [37,38]. Later studies further questioned the basis for the prognostic value of CD concentrations. At any given time, three different components of CD are present: a) pCD; b) mature enzyme CD; and c) mature CD at different stages of proteolytic processing. Furthermore, the monoclonal antibodies that have been used for visualization of CD react with both CD and pCD.

Procathepsin D in cancer

The primary structure of a human pCD (enzymatically inactive; 52 kDa) is posttranslationally modified by two major processes – proteolytic cleavage and glycosylation. Removal of the signal peptide occurs during the translocation across the membrane of the rough endoplasmatic reticulum. Procathepsin D is then targeted to lysosomes and, upon acidification, undergoes activation processing requiring proteolytic removal of the activation peptide. This has been described to proceed both in an autocatalytic mode or with the assistance of other lysosomal enzymes [8]. The self-activation produces so-called pseudo-cathepsin D (51 kDa) that is enzymatically active but contains a portion of the activation peptide [39,40].

When it became clear that the fully mature enzyme CD has probably no direct role in cancer development [41], attention focused back on the original finding of overexpression of pCD in cancer cells. However, some new studies seem to suggest that cathepsin D might affect cancer growth by interaction with heat shock cognate 70 protein [42]. We would like to point out that this paper did not really showed if the responsible molecule is pCD or fully matured CD. Our own work initially focused on the question of whether pCD influenced growth of cancer cells with the working hypothesis that the pCD may function as a mitogen. Our experiments showed strong mitogenic activities of pCD which can specifically be inhibited by addition of anti-pCD antibodies. Numerous controls showed that mannose-6-phosphate receptors are not involved, as neither mannose-6-phosphate, soluble receptor or anti-mannose-6-phosphate receptor antibodies have any effects on inhibition of pCD-promoted cancer growth [43]. Studies of Glondu *et al.,* [44] further supported the fact that the amount of pCD synthesis strongly corresponds with the mitogenic properties of cancer cells.

Subsequent experiments were oriented toward deeper understanding of the responsible moiety of the pCD molecule. As the CD was not active, the only difference between pCD and CD was the activation peptide. Using synthetic activation peptide, we demonstrated that the pCD-related effects were in fact caused by this molecule. Subsequently, we prepared individual fragments of the activation peptide and specific monoclonal antibodies and demonstrated that the growth factor activity of activation peptide is localized in nine amino acid stretch (AA 36-44) of the activation peptide molecule [45]. We demonstrated that the activation peptide itself stimulates growth of breast, prostate and lung cancer cells *in vitro* and *in vivo* as much as native pCD molecule [46-49].

The role of pCD in cancer has also been shown *in vivo*. The original experiments have been done by Rochefort's group. Using rat tumor cells transfected with human pCD vector, Garcia *et al*., showed the increased metastasis corresponding to the level of pCD DNA expression [50]. Our group used different experimental design employing athymic nude mice injected with human estrogen receptor-negative breast cancer cell

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line MDA-MB-231. Upon establishing the cancer growth, we injected these mice with synthetic microspheres containing anti-activation antibodies and found inhibited growth of human cancer cells up to 8 weeks after injection [51].

In our subsequent studies, we focused our attention on the possibilities to regulate pCD synthesis or release from cancer cells. We prepared numerous clones of four different breast cell lines and, using several types of genetic manipulations, we obtained clones with either higher, lower or no secretion of pCD. In all cases we managed to show that the level of pCD fully reflects cancerogenic properties of the cells [51-54]. Additional experiments confirmed that the downregulation of pCD expression by antisense gene inhibited lung metastasis of breast cancer cells but had no effect on invasion *in vitro* [44]. In addition, Tedone *et al.,* showed that downregulation of pCD expression resulted in decreased invasion of MCF-7 cells *in vitro* [36].

To further analyze the biological effects of the whole pCD molecule, we prepared cDNA vectors producing entire pCD, active-site mutated pCD, pCD without activation peptide, and pCD mutated in the activation peptide region. In addition, we prepared these clones in three different breast cancer cells. Using a series of pCD mutants stably transfected in breast cancer cells, we managed to clarify the molecular basis of pCD actions that is clearly associated with the activation peptide structure. For this purpose, we used two different approaches. First, using the above mentioned transfected lines, we evaluated proliferative potential of each transfected cell line in MTT assay and showed clear correlation between pCD secretion and proliferative effects. Next, we used these clones in cancer growth experiments. For this purpose, we designed catalytically inactive ribozymes by changing the G-A in the catalytic domain, and suppressed the pCD expression. To ensure that the downregulation of pCD was due to the ribozyme activation, RT-PCR analysis was performed using pCD, RZ and actin primers. The anti-pCD ribozymes were capable of downregulating pCD mRNA expression significantly by 60%, while no change was observed in control RZ- or empty vector-transfected cells. When the synthesis of pCD was inhibited by specifically designed ribozymes, the proliferation of breast cancer cells was suppressed in all four cases. Similar results were later achieved using siRNA inhibition [55,56].

To answer the question whether the expressed pCD and its individual mutants are proteolytically active, the conditioned media of cells expressing wild-type and various mutants of pCD were analyzed for proteolytic activity. In order to finally prove AP's importance for mitogenic activity of pCD, we introduced several single point mutations into region of AP. The mutations were focused on the region crucial for binding. These mutants had similar proteolytic activity as native pCD, which is evidence of their correct folding, but lacked the mitogenic activity. By this experiment, we have proved on a molecular level the mitogenicity responsible part of pCD. In case of HBL-100 clones, wild-type pCD, monoglycosylated and non-glycosylated mutants of pCD displayed proteolytic activity, whereas mutated pCD failed to exhibit any proteolytic activity. Further, pCD completely without activation peptide was found to be catalytically inactive [56].

In order to assess the effect of various mutations of pCD on proliferation of breast cancer cells, expressed pCD and its mutants were affinity purified. Using a proliferation assay, we found that purified pCD along with monoglycosylated mutants stimulated proliferation in the three cell lines tested, but pCD lacking the activation peptide or pCD with mutated activation peptide had no activity.

Based on all the presented data, we can conclude that pCD acts as a mitogenic factor for cancer cells, and that this activity is mediated via its activation peptide. The level of glycosylations plays no significant role [56-58]. The mechanism of these autocrine mitogenic effects of pCD is still not fully known. We proposed that the mitogenic function is related to extracellular presence of pCD interacting with a thus far unknown receptor. This interaction leads to activation of NFκB. The question of pCD/CD receptor remains unclear. Most papers showed that the common mannose-6-phosphate receptor is not involved in effects of these molecules on cancer [41], but efforts to find and characterize the receptor were not successful. Only recently, the results of Beaujouin *et al.,* [59] showed that pCD/CD interacts by a domain around the connection of heavy and light chains of CD with LPR1 receptor and this interaction leads to promoted growth of fibroblasts. The binding moiety on cancer cells remains a mystery.

In adition to the direct effects of pCD on cancer cells, recent reports suggested another possible role of pCD in regulation of cancer growth. Beaujouin *et al*., used 3Y1-Ad12 cancer cells and etoposid and concluded that overexpression of pCD enhanced the etoposid induced apoptosis and decreased the chemoresistance of the cells while concurrently showing that this induction of apoptosis is not connected to the proteolytic activity of CD [60]. On the other hand, Sagulenko used neuroblastoma cells and doxorubicin as chemotherapeutic agents and demonstrated that the high secretion of pCD leads to chemoresistance to doxorubicin which is brought on by high anti-apoptotic signaling caused by pCD [27]. We followed up these studies using three different breast cancer cell lines, ZR-75-1, MCF-7 and and MDA-MB-231 cells which were transfected by either native pCD or pCD mutated at different positions (as mentioned above). We tested the chemosensitivity of these cell lines to common chemotherapeutic drugs 5-fluorouracil, doxorubicin and cyclophosphamid and asked whether the overexpression of pCD leads to a) changes in resistence; b) whether the resistance is consequence of intra- or extracellular effects of pCD; and c) if there is any correlation with apoptosis. We have used three different chemotherapeutic substances with

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different primary cytostatic mechanisms of action but with the same apoptotic ending.

Our study clearly showed that pCD expression level correlates with the resistance to tested chemotherapeutic drugs. The control cells (empty vector) have not shown any changes in the resistance and at the same time excluded the possibility that the changes in resistance are caused by some effects of the transformation. Another supporting fact indicating a positive influence of pCD overexpression on the resistance is based on results of silencing the pCD production in the parent cell line—the silencing dramatically increased the sensitivity to all three drugs. Based on this observation, we proposed that the resistance involves the extracellular functions of pCD. This can be documented by the activity of antibodies (which are acting extracellulary) and by the increased resistence when external pCD is added to the media of native cells or cells transfected with siRNA inhibiting the translation of pCD. The experiment testing the effects of Brefeldin (which inhibits secretion of proteins) also supports these conclusions [61]. Based on these results, we concluded that the production of pCD has influence on the chemoresistance. The mechanisms of these actions are not clear and experiments trying to characterize these mechanisms are currently under way.

Conclusion

From three decades of intensive research, one can conclude that pCD has significant effects on cancer progression, both directly via interaction with cancer cells-related receptor and indirectly via increased chemoresistance of tumor cells. Additional role of pCD in stromal cells (both overexpression and possible interaction) is possible, but currently not fully documented. The roles of the pCD could, in fact, be an important fact for prediction of resistence and help in selection of optimal chemotherapy.

Competing interests

The authors declare that they have no competing interests.

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