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Cathepsin B Inhibitors for Targeted Cancer Therapy

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Abstract

Cathepsin B is a ubiquitous and tightly controlled cysteine protease having been implicated in a wide variety of cellular processes such as protein conversion, activation, and signaling. Cathepsin B has also been found to have many roles in several stages of tumor progression up to and beyond metastasis. As a result, current research has focused on either identifying potential cathepsin B inhibitors that can directly be used for treatment or as a model for drug development. Development of cathepsin B inhibitors is still in progress with none currently reaching clinical trials. Some drugs such as VBY-825 and the quinolone antibiotic nitroxoline have shown promise in direct application, while others such as chalcones, curcumin, and IGFBP-4 can be used as models for developing future cathepsin B inhibitors for clinical use. Drugs already successful in clinical trials to treat other conditions unrelated to cathepsin B, such as osteoporosis with odanacatib, have similar analogues that have been shown to inhibit cathepsin B and not only could be used as a model for new cathepsin B inhibitor development, but also result in reaching the market sooner due to a known high safety profile. Further studies beyond developing cathepsin B inhibitors should focus on a combinatory treatment of cathepsin B inhibitor with chemotherapy, radiation, and/or inhibition of other proteins involved with tumor progression. This combinatory approach has been shown to be highly effective in tumor cell sensitization and death.

Keywords: Cysteine cathepsins; Cathepsin B; Cathepsin B inhibitor; Antibiotics; Urokinase; Plasminogen; MMP

Background Information

Cysteine cathepsins have been widely implicated as playing a causal role in cancer by facilitating tumor progression. There are almost a dozen cysteine cathepsins which are primarily lysosomal proteases that catalyze the hydrolysis of proteins, originally being studied for their role in protein turnover [1]. One such cysteine protease, cathepsin B, has been widely studied for decades due to its uniqueness among the cysteine cathepsin family. Cysteine cathepsins generally have either endopeptidase or exopeptidase activity. Cathepsin B is one of two cysteine cathepsins having both protease activities, specifically due to a structure distinctive to only cathepsin B termed the occluding loop [2]. The occluding loop of cathepsin B confers substrate accommodation changes to the active site, determining larger substrate endopeptidase activity or smaller substrate exopeptidase activity. Movement of the occluding loop and subsequently changes to cathepsin B protease activity is actuated by alterations in pH.

Cathepsin B is ubiquitous, having a wide variety of substrates it binds and indeed has been implicated in many cellular processes and found on cell surface membranes and in the extracellular matrix. Cathepsin B is involved with the activation of β-galactosidase, renin, and trypsin [3]. It is involved with TNF-α induced apoptosis and the processing of proteins for MHC II antigen presentation. In addition, cathepsin B has also been shown to be critical in the maturity of the postnatal central nervous system [4]. Due to its role in many processes, regulation of cathepsin B is tightly controlled including compartmentalization, optimal pH activation, zymogen activation, and regulatory endogenous inhibitors [5].

Cathepsin B and Cancer

Cathepsin B is probably the most well studied of the cathepsin family for its role in tumor progression, being highly expressed in a variety of malignant tumors [6]. In order for a tumor to become malignant, cells must invade beyond the tissue it originated and enter circulation [7]. The formation of a microenvironment that favors tumor growth is the first step in cancer invasion. Cathepsin B functions optimally in a low pH environment such as that found in lysosomes and the microenvironment formed during cancer progression, making the microenvironment an ideal digestive environment for cathepsin B [8]. Understanding the mechanisms of and altering this microenvironment is an important aspect of cancer research [7].

Tumor progression can be defined in several steps with respect to cysteine cathepsins (Figure 1). The first step requires that surrounding tissue be cleared to create a pathway for growth by modification and degradation of the extracellular matrix and basement membrane by cysteine cathepsins. Cathepsin B is one of the cathepsins that has been directly linked to extracellular matrix degradation [1]. The second is a proteolytic cascade where cysteine cathepsins activate matrix metalloproteinases and urokinase plasminogen activator (uPA), resulting in further tissue invasion [4]. Cathepsin B has a direct role in activating uPA, plasminogen, plasmin, and enhances activity of matrix metalloproteinases by degrading their inhibitors [9]. The last is cleavage of E-cadherin at adherin junctions, detaching cells to enter circulation and migrate [4]. Cathepsin B also has a role in mediating the cleavage of E-cadherin via activation of TGF- β1 mediating fibroblasts release of MMP-3 [10-14]. Cathepsin B has a clear role in the primary steps of tumor invasion and if the cancer cells enter circulation and then survive at a secondary location, metastasis has occurred [4]. In addition, cathepsin B has also been shown to have a significant role in activating signaling pathways involved with angiogenesis, the formation of new

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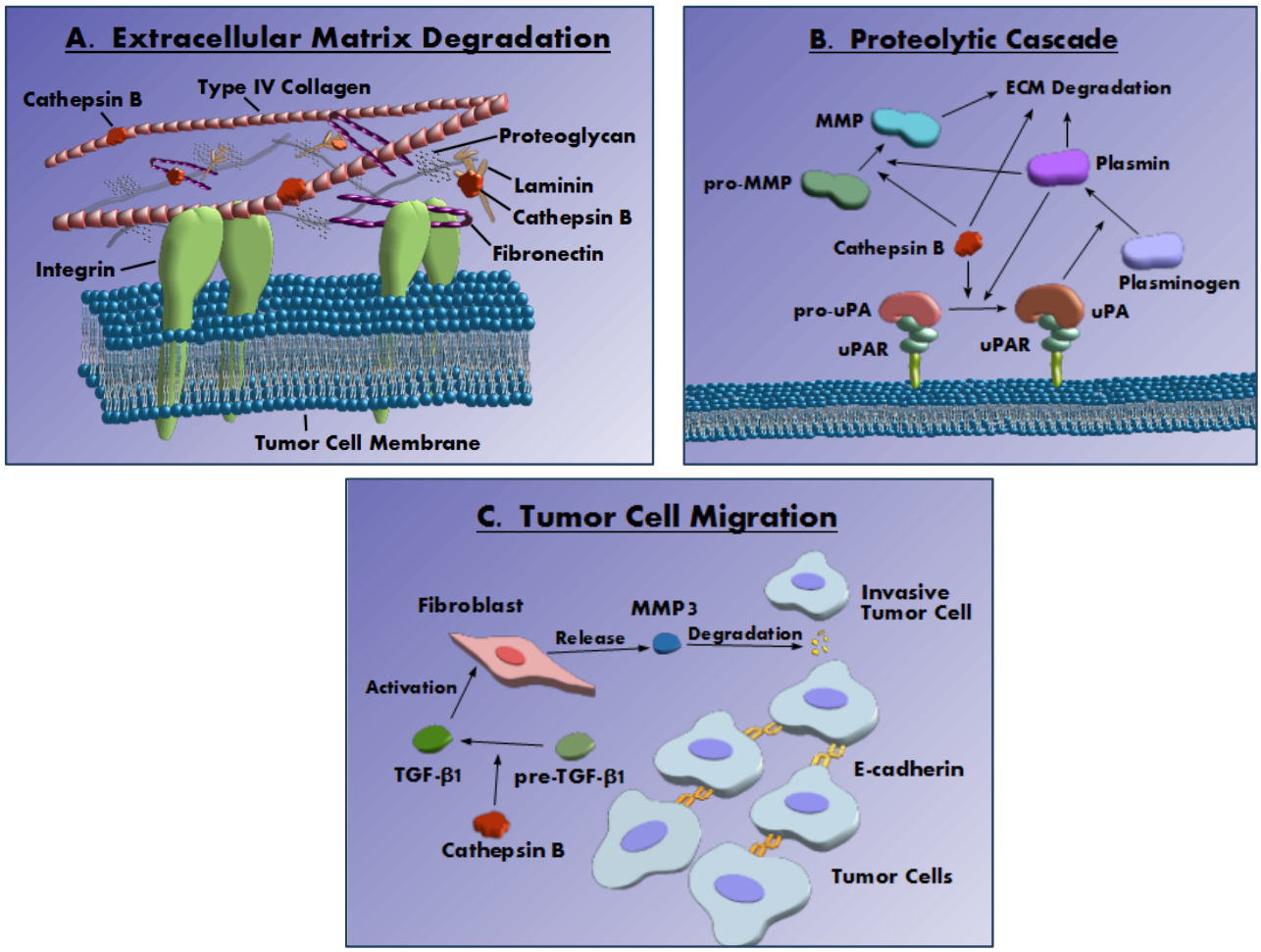

Figure 1: Tumor progression and cathepsin B. (A) Cathepsin B directly degrades ECM constituents such type IV collagen, fibronectin, and laminin [1]. (B) Cathepsin B converts both pro-MMP and pro-uPA to MMP and uPA which results in a proteolytic cascade of further ECM degradation [4]. (C) Cathepsin B converts pre-TGF-β1 to TGF- β1 [11,12] which activates fibroblasts [13]. Fibroblasts release MMP3 which degrades E-cadherin facilitating tumor cell invasion [13,14].

blood vessels from existing ones, further mediating tumor progression and the ability of cancer cells to enter circulation [15].

Many studies have shown a clear link between cathepsin B expression and tumor invasion. Manipulation by increasing expression levels of cathepsin B in murine melanoma tumor cells increased the invasiveness of the tumor, while inhibition significantly reduced invasion, indicating that invasiveness is directly related to expression of cathepsin B [16]. Cathepsin B expression has been shown to be an accurate biomarker of more advanced endometrial cancer, pancreatic ductal adenocarcinoma in mice, glioblastoma cell lines, breast cancer, and can be used to predict aggressiveness of the tumors [17-20]. Studies are now beginning to show the pathways by which overexpression of cathepsin B occurs in tumor cells such as secretion of sphingosine-1-phosphate (S1P) in prostate cancer resulting in transcriptional upregulation of cathepsin B by activation and nuclear expression of Ets1 [21]. Another molecular mechanism has been determined in melanoma tumor cells showing that SPARC promotes cathepsin B expression and ultimately invasiveness of the tumor [22]. The promoter region of the cathepsin B gene is also altered in cancer cells with increased SP1 transcription factor binding sites [19]. Additionally, in breast cancer cells cathepsin B upregulation has been linked to ErbB2 induced myeloid zinc finger-1 transcription factor binding to the cathepsin B gene [23]. Cathepsin B overexpression in cancer cells also relies on control of the endogenous inhibitors, cystatins [24]. Endogenous cystatin inhibitors such as cystatin C, cystatin M, and stefin A have all been shown to have reduced expression in tumors in addition to a lower capacity to inhibit cysteine cathepsins. Degradation of the extracellular matrix could be favored by this new imbalanced ratio of cysteine cathepsins to endogenous cystatins.

Cathepsin B Inhibitors

Due to its causal role in tumor progression and invasion, efforts have been made to develop cathepsin B inhibitors. There has been progress in the past several years by using different strategies in developing inhibitors of cathepsin B that target the occluding loop, but none have made it to clinical trials [25]. Considering the important role cathepsin B has for protein turnover, potential toxicity must be taken into account when developing an inhibitor [26]. Inhibitors for cathepsin B that cannot enter the cell could have great therapeutic value, targeting secreted and cell surface cathepsin B that are part of the tumor microenvironment, but sparing intracellular cathepsins to limit toxicity. This could limit treatment as some studies have shown inhibition of only intracellular cathepsin B has a significant effect on tumor progression [16]. In addition, when targeting a protease

for inhibition, the drug should bind reversibly and selectively while having a high bioavailability [27]. Unfortunately, many of the peptidyl based inhibitors have reactivity toward other proteins and/or low bioavailability. Since synthetic cystatin based inhibitors have low bioavailability, being quickly degraded and excreted, focus has turned to designing other synthetic cathepsin B inhibitors. Some attention has been given to peptidomimetics to inhibit cysteine cathepsins [28]. One such class, called azapeptides, replace one α-CH with N. Many azapeptides have been developed that are specific for cathepsin B, some of which have extremely high affinity and selectivity.

Antibiotics have been shown to be effective in inhibiting cathepsin B. Nitroxoline, a quinolone antibiotic, is one such that non-covalently and reversibly inhibits cathepsin B, again by interacting with the occluding loop, while also having a K_i value similar to other inhibitors [29]. Nitroxoline has low toxicity and was shown to impair tumor progression by decreased extracellular matrix degradation. Derivatives of nitroxoline have also been developed that are even more potent and highly selective at inhibiting cathepsin B, while still maintaining therapeutic results of significantly reducing extracellular matrix degradation and tumor progression [30]. Nicotinamide which is an antimicrobial, compound of the vitamin B_3 group, and precursor to the synthesis of NAD+, has recently been shown to be an inhibitor of a cathepsin B like compound in *Trypanosoma brucei*, the organism that causes African trypanosomiasi [31]. Inhibition of the cathepsin B like compound has been shown to be the causal agent in cell death of these organisms. Since nicotinamide does not produce cell death in mammalian cells, but does show protease inhibitory activity, its effect was tested on pancreatic cancer cells resulting in increased chemosensitivity and decreased tumor invasiveness [32].

Chalcones, natural aromatic ketones, have shown to be antibacterial, antifungal, antitumor, and anti-inflammatory compounds in addition to having a safe profile. Recent attention has been turned to them as a pool of potential new drugs based on derivatives. Interestingly, panduratin A and nicolaioidesin, natural chalcones, are inhibitors of cathepsin B as shown in human cell lines and are cytotoxic to prostate cancer cells [33]. Efforts have been made to synthesize dihydroxychalcone analogues which has resulted in novel inhibitors of cathepsin B which could be a promising direction for synthesis of new drugs [34,35].

Curcumin, found in the root turmeric, has long been known to produce anti-inflammatory and anti-tumor effects and the root has been used in ancient Chinese and Indian medicine [36]. Many studies have shown curcumin to inhibit cancer cell types such as colon, ovarian, lymphomas and breast. Surprisingly, curcumin inhibits cathepsin B, potentially being one mechanism responsible for the effects and therapeutic benefits as shown in these previous studies. Some researchers have tried alternative methods of reducing cathepsin B such as targeting the lysosome itself in tumors to initiate cell death and reduce the expression of cathepsin B [37]. Others are focused on finding additional endogenous compounds that can inhibit cathepsins. For instance, insulin like growth factor-binding protein 4 (IGFBP-4) has been shown to have anti-angiogenic and anti-tumor effects [38]. One fragment present (CIPB-4), blocks cathepsin B activity and could be responsible for the reduced tumor growth seen. This could provide yet another therapeutic potential in the development of new drugs that replicate the CIPB-4 domains that interact with cathepsin B.

Virobay, founded as a protease inhibitor drug discovery company, has made much progress in developing cathepsin B inhibitors. One such, VBY-825, is a potent and reversible inhibitor of many cathepsins, including cathepsin B, and its efficacy was shown in significantly decreasing pancreatic islet cancer tumor cells [39]. Virobay has filed several patents exploring many potential formulas for inhibition of cathepsin B, with the most recent filed March 25th, 2014 for the treatment of bone cancer [40].

While there have not been clinical drug trials specifically for cathepsin B inhibitors, efforts have been made to test drugs that target other cathepsins or cathepsin like proteases [9]. These drugs have already entered preclinical or clinical drug trials and could help speed up treatment options for deadly cancers such as metastatic neuroblastoma where radiation treatment is not always as viable for children. One drug named K11777, developed to treat Chagas disease, has already shown promise at inhibiting cathepsin B and causing cell death in neuroblastoma cells [41]. This same study also showed dipeptidyl nitrile cathepsin K inhibitors can inhibit cathepsin B, producing the same effects on neuroblastoma cells. Odanacatib, a dipeptidyl nitrile cathepsin K inhibitor, was developed to treat osteoporosis and has already completed a phase III clinical trial [42]. Considering the success and low toxicity profiles of these drugs during clinical trials, there is potential for using them as a model to quickly move forward with developing and testing cathepsin B inhibitors for therapeutic cancer treatment.

Although cathepsin B has an integral role in cancer progression, care must also be taken when considering using cathepsin B inhibitors for cancer therapy. Much in the same way chemotherapy drugs have adverse effects on normal cells in the body, cathepsin B inhibitors could potentially come with side effects. For instance, TNF-α mediated apoptosis is dependent on cathepsin B in hepatocytes, neuronal cells, and certain immune cells. Apoptosis is one of many integral processes involved with maintaining homeostasis in the body and dysregulation can result in pathological conditions [43]. Cathepsin B is also involved in the degradation of MMP-2 which is a protease involved in extracellular matrix remodeling [44]. Inhibition of cathepsin B has been shown to deregulate MMP-2 resulting in increased levels which could potentially lead to unchecked tissue damage and inflammation in organ systems.

Combinatory Approach to Cancer Treatment

One of the most progressive techniques in developing therapeutic cancer treatments involving cathepsin B is a combinatory approach of various treatments including a cathepsin B inhibitor paired with one or more of the following: chemotherapy drug, radiotherapy, or inhibiting other molecules in proteolytic pathways involving cathepsin B. Studies have shown that combining both a cathepsin B inhibitor with other modes of treatment have the greatest therapeutic result [9]. One study showed that knockdown of both urokinase plasminogen activator receptor (uPAR) and cathepsin B inhibited tumor migration and angiogenesis by decreasing expression of VEGF in glioma cells. Further, inhibiting both uPAR and cathepsin B also sensitized glioma cancer cells to radiation, ultimately inducing apoptosis. Obstacles to cancer treatment include chemotherapy drug resistance acquired during treatment and also partial resistance of the tumor by protection against apoptosis in early development [45]. Two anticancer drugs, gemcitabin (Gem) and 5-fluorouracil (5-FU), are often resisted by tumor cells during treatment [46]. One study has shown a further increase in cathepsin B secretion when administering these drugs, potentially counteracting the anti-tumor effects of these drugs indirectly. This adds further support to combining cathepsin B inhibitors with traditional cancer treatments and proposes that cathepsin B may be involved in a chemoprotective effect on the tumor. Another study

Cathepsin B Inhibitors	Attributes	Status	References
Cystatins	Endogenous inhibitor, derivatives have low bioavailability	Derivatives, but no clinical trials	[27]
Azapeptides	Peptidyl derivatives based on cystatins, low molecular mass, high bioavailability	Derivatives, but no clinical trials	[28]
Nitroxoline	Quinolone antibiotic, reversible inhibitor	Market, no clinical trials for cancer treatment	[29]
Nicotinamide	Antimicrobial, Cathepsin B like inhibitor	Market, no clinical trials for cancer treatment	[32]
Panduration A and Nicolaioidesin	Natural aromatic ketones (chalcones)	No derivatives or clinical trials	[33]
Curcumin	Natural (turmeric root)	No derivatives or clinical trials	[36]
CIPB-4	Inhibiting domain found on insulin like growth factor-binding protein 4 (IGFBP-4)	No derivatives or clinical trials	[38]
VBY-825	Potent and reversible	Preclinical studies	[39]
K11777	Irreversible inhibitor of cysteine proteases	Late preclinical studies	[41]
Dipeptidyl nitriles (Odanacatib)	Developed to reversibly inhibit cathepsin K	Phase III clinical trial of Odanacatib completed, good safety profile	[42]

Table 1: Cathepsin B Inhibitor Summary.

highlighting the effectiveness of combined therapy studied the effects of paclitaxel (Taxol), a chemotherapy drug, and JPM, a research grade cathepsin B inhibitor, on mammary tumor cells in culture [47]. Taxol treatment alone resulted in higher levels of cathepsin B detected in the microenvironment compared to non-treated cells. Following the combined treatment with Taxol and JPM, there was significant inhibition of tumor growth compared to treatment with only Taxol indicating cathepsin B is either directly or indirectly attenuating the effectiveness of Taxol as a chemotherapeutic agent on tumor cells. Combining cathepsin B inhibitors with other successful methods of cancer treatment as discussed could augment the therapeutic effect and provide efficacy at safer doses with less toxic side effects (Table 1).

Conclusion

While much progress has been made in understanding and treating cancer, the urgency for innovative new research is still great. Cancer is estimated to kill 1,600 people per day in the United States, being the second most common cause of death [48]. Original and more efficient methods of treatment are needed to not only improve patient outcome, but also reduce the long term treatment costs. Drug development is at the core of this and it begins with identifying a causal target and developing a way to minimize the causal effect of that target. Cathepsin B is a unique target due to how many tumor migration processes it is involved with. Inhibition of cathepsin B has repeatedly resulted in adverse effects to tumor cells and even greater results when combined with another mode of treatment. While little progress has been made in developing cathepsin B inhibitors for clinical use, there are many known models for inhibiting cathepsin B *in vitro*. Future directions should focus on the development and preclinical testing of novel cathepsin B inhibitors.

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