Pharmacology & Therapeutics 198 (2019) 1–19

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Cathepsins: Potent regulators in carcinogenesis

Tejinder Pal Khaket [a], Taeg Kyu Kwon [b,*], Sun Chul Kang [a,*]

[a] Department of Biotechnology, Daegu University, Gyeongsan, Gyeongbuk 38453, Republic of Korea
[b] Department of Immunology, School of Medicine, Keimyung University, Dalseo-Gu, Daegu 704-701, Republic of Korea

ARTICLE INFO

Keywords:
Cathepsins
Cancer
Angiogenesis
Metastasis: Drug resistance: Inhibitors

ABSTRACT

Cathepsins (CTS) are mainly lysosomal acid hydrolases extensively involved in the prognosis of different diseases, and having a distinct role in tumor progression by regulating cell proliferation, autophagy, angiogenesis, invasion, and metastasis. As all these processes conjunctively lead to cancer progression, their site-specific regulation might be beneficial for cancer treatment. CTS regulate activation of the proteolytic cascade and protein turnover, while extracellular CTS is involved in promoting extracellular matrix degradation and angiogenesis, thereby stimulating invasion and metastasis. Despite cancer regulation, the involvement of CTS in cellular adaptation toward chemotherapy and radiotherapy augments their therapeutic potential. However, lysosomal permeabilization mediated cytosolic translocation of CTS induces programmed cell death. This complex behavior of CTS generates the need to discuss the different aspects of CTS associated with cancer regulation. In this review, we mainly focused on the significance of each cathepsin in cancer signaling and their targeting which would provide noteworthy information in the context of cancer biology and therapeutics.

Contents

1. Introduction

Proteolysis plays a crucial role in cancer progression *via* tumor proliferation, differentiation, invasion, metastasis, and angiogenesis, either directly by providing raw material generated from proteolysis or indirectly by activating other proteolytic cascades or degrading growth regulatory factors (reviewed in Gocheva & Joyce, 2007). It has been an intriguing topic for researchers in the quest for new anticancer therapies. Progression to malignancy is often associated with aberrant proteolysis regulating mechanisms. Previous proteolysis-based studies were mainly focused on matrix metalloproteinases (MMP) (a family of 23 endopeptidases) for cancer regulation. However, failure of clinical trials of broad-spectrum MMP inhibitors had led to the curiosity of cathepsins (CTS) based research. CTS are mainly lysosomal proteases that degrade proteins at acidic pH. In normal cells, CTS regulate the immune responses and signaling pathways. Aberrant CTS activity are widely implicated for commuted immunologic and physiological behavior that is attributable to cancers (reviewed by Gocheva & Joyce, 2007, Mason & Joyce, 2011; Olson & Joyce, 2015) and other disorders such as osteoporosis, arthritis, cystic fibrosis, neurodegenerative diseases, and cardiovascular diseases (Reviewed in Turk et al., 2012).

Several reports on CTS involvement in tumorigenic processes have provided sufficient evidence to understand their anti-cancer potential (Urbich et al., 2005; Gocheva et al., 2006; Sevenich et al., 2010; Gocheva et al., 2010; Shree et al., 2011; Withana et al., 2012; Bruchard et al., 2013; Ruffell, Affara, Cottone, Junankar, & Johansson, 2013; Akkari et al., 2014; Bengsch et al., 2014; Alatrash et al., 2017; Sudhan, Rabaglino, Wood, & Siemann, 2016; Palesch et al., 2016; Burton et al.,

* Corresponding authors.
E-mail addresses: kwontk@dsmc.or.kr (T.K. Kwon), sckang@daegu.ac.kr (S.C. Kang).

https://doi.org/10.1016/j.pharmthera.2019.02.003
0163-7258/

2017; Mitrovic, Pecar Fonovic, & Kos, 2017; Khaket, Singh, Khan, Bhardwaj, & Kang, 2018; Khan, Carmona et al., 2018; Pandey, Bakhshi, Thakur, Jain, & Chauhan, 2018; Dhawan, Hahn, Ramos-Vara, & Knapp, 2018). CTS also contribute toward processing various growth regulators such as cytokines and chemokines (Yin et al., 2012) that drive cancer cell growth and inflammation (Navab et al., 2008; Dennemarker et al., 2010; Bruchard et al., 2013). Likewise, extracellular CTS secretion are known to alter the tumor microenvironment through extracellular matrix (ECM) degradation that consequently leads to tissue invasion and metastasis (Joyce et al., 2004; Vasiljeva et al., 2006; Sevenich et al., 2014). Under physiological conditions, CTS activities are strictly controlled at the transcriptional and post-transcriptional levels through various regulators. However, the mechanism by which carcinoma cells evade this controlled CTS regulation and further consume CTS for their progression would be interesting to discuss. Moreover, enhancement of anticancer treatment sensitivities *via* CTS targeting has attracted researchers to explore their role in cancer therapeutics. This review focuses on the recent developments in the field of CTS based cancer regulation, and their therapeutic significance.

2. Cathepsins and cancer

Based on their catalytic amino acids, cathepsins are categorized as cysteine proteases (CTSB, C, F, H, L, K, O, S, W, and Z), serine proteases (CTSA and G) and aspartic proteases (CTSD and E). Of the various CTS known, CTSB, C, D, E, G, K, L, S and X/Z are the most widely studied in cancer progression, a process notably dependent on tissue/cell-specific expression of specific CTS. CTS are synthesized as preproenzymes and processed in the rough endoplasmic reticulum (RER) by removal of prepeptide, followed by glycation in the Golgi apparatus, finally transported to the lysosome and activated through controlled proteolysis of the propeptide (Kominami, Tsukahara, Hara, & Katunuma, 1988; Nishimura, Kawabata, & Kato, 1988). A compelling deliberation now arises whether all CTS are activated in the lysosome simultaneously; if not, then the mechanism by which their activation is controlled by the physiological conditions. In the following sections, we summarize recent CTS based researches to discover the exact mechanism associated with their functions in cancer.

2.1. Cysteine cathepsins

2.1.1. CTSB

CTSB is a lysosomal cysteine protease having both *endo*- and carboxypeptidase activity. Pro-CTSB is activated by CTSD, CTSG, urokinase-type plasminogen activator (uPAR), tissue-type plasminogen activator, and elastases (Matas, Thygesen, Stacey, Risch, & Sim, 1997; Mueller-Steiner et al., 2006; Liang, Ouyang, Schneider, & Zhang, 2011; reviewed in Aggarwal & Sloane, 2014) (Fig. 1). Cathepsin B is a bilobed protein encompassing a catalytical triad of cysteine, histidine, and aspartate (Musil et al., 1991) with an additional occluding loop that can regulates its endopeptidase and carboxypeptidase activity by controlling substrate access to the active site (Illy et al., 1997; Quraishi et al., 1999). CTSB overexpression has been reported for numerous malignancies including brain, lung, prostate, breast, and colorectal cancers (Krepela, Vicar, & Cernoch, 1989; Krepela, Kasafirek, Novak, & Viklicky, 1990; Rempel et al., 1994; Sinha et al., 2007; Bian et al., 2016). Likewise, proteomic studies on cystic fluids from ovarian, breast, thyroid, and colorectal cancer patients have also revealed enhanced CTSB protein levels as compared to normal (McKerrow et al., 2000; Srisomsap et al., 2002; Wulfkuhle et al., 2002; Kolwijck et al., 2010). Consistent with these studies, overexpression of CTSB is also noted in the serum of 60% of gastric cancer patients and 37% of oral squamous cell carcinoma patients with advanced stages and lymph node metastasis (Ebert, Kruger, Fogeron, Lamer, et al., 2005; Yang et al., 2016), thereby implying significant utility of CTSB in cancer progression. Several studies have been undertaken to determine the mechanism underlying the CTSB upregulation and tumor progression. In myeloid tumor cells, the transforming growth factor (TGF)-β1-mediated upregulation of CTSB expression also supports its canonical role in carcinogenesis (Reisenauer et al., 2007). Similarly, overexpression of CTSB in mammary cancer cells facilitates the invasiveness and tumor progression (Sevenich et al., 2011; Bengsch et al., 2014). Likewise, in the RIP1-Tag2 PanNET mouse model and MMTV-PyMT mammary carcinoma mouse models, CTSB deletion attributed to declined tumor volume and cancer cell proliferation (Vasiljeva et al., 2008; Sevenich et al., 2010). Intriguingly, CTSB deletion has no effect on cancer progression in the K14 HPV16 mouse model of squamous cell carcinoma (SCC), which endorses its tissue-specific role in tumor regulation (Ruffell et al., 2013).

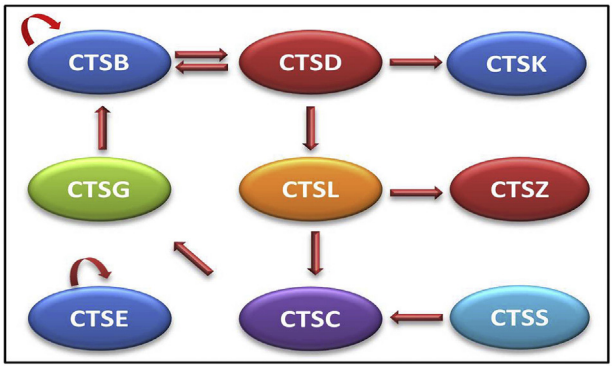

Fig. 1. Proteolytic activation of CTS cascade. CTS are synthesized as preproenzymes. After removal of prepeptide in the rough endoplasmic reticulum (RER), proCTS are transported to the lysosome and activated by removal of the propeptide through CTS cascade. Among the CTS, proCTSB is activated by CTSD and also by autoactivation, CTSB activates proCTSD, CTSD cleaves CTSK and CTSL, CTSL induces the release of the pro part of CTSZ and CTSC, CTSS can also activates proCTSC, consequently proCTSC, and CTSC activates CTSB by removal of propeptide from proCTSG. CTSE is unique in this network, and yet it is predicted to be activated by self-removal of the propeptide. This CTS cascade is complex and explored mostly through *in vitro* studies; the mechanism of action of this complex network in physiological conditions remains to be identified. Moreover, compensatory activities of CTS for each other (not shown in the figure) also complicate the physiological web of these proteases.

Consistent with these results, it is well documented that oncogenes (such as HRAS, HER2, and Sp1) and proto-oncogenes (such as Sp3 and Ets1) lie upstream of CTS, and their activation consequently enhances the expression of CTSB (Yan, Berquin, Troen, & Sloane, 2000). This provides a clue about their association with cancer progression. Recently, Tripathi et al. (2018) have ascribed that tyrosine kinases such as Abl and Arg (Abl-related gene) are able to activate transcription factors (namely Ets1, Sp1, and NF-κB/p65) and subsequently CTSB expression. Moreover, Luan et al. (2018) predicted that CTSB/L expression is negatively regulated by STUB1 (STIP1 homology and U-Box containing protein 1) or CHIP (C terminus of HSC70-Interacting Protein) in ErbB2 + and other breast cancer cell lines. Thus, regulation of CTS expression by targeting upstream proto-oncogenic factors, including tyrosine kinases [such as Abl and Arg (Abl/Arg)) and CHIP can provide new therapeutic opportunities to treat cancers.

Indeed, the constitutive loss of CTSB downregulates the phospho-extracellular signal-regulated kinases (ERK)/mitogen-activated protein kinases (MAPK) signaling in pancreatic cancer, thereby attenuating cell proliferation (Gopinathan et al., 2012) (Fig. 2). However, no significant alteration in MAPK signaling was observed in the absence of CTSB in colorectal cancer, which further indicates its tissue-specific functioning (Bian et al., 2016). In addition to MAPK signaling, CTSB is capable of cleaving p27Kip1, a cell cycle regulator that negatively affects cyclin-CDK complex and helps the cell to determine between proliferation and cell cycle exit. Therefore, p27Kip1 degradation promotes cell cycle progression associated with higher cyclin B while the loss of CTSB increases the p27Kip1 level resulting in abrogation of tumor proliferation (Bian et al., 2016). Bruchard et al. (2013) demonstrated that CTSB promotes the inflammasome-mediated interleukin (IL)-1β release

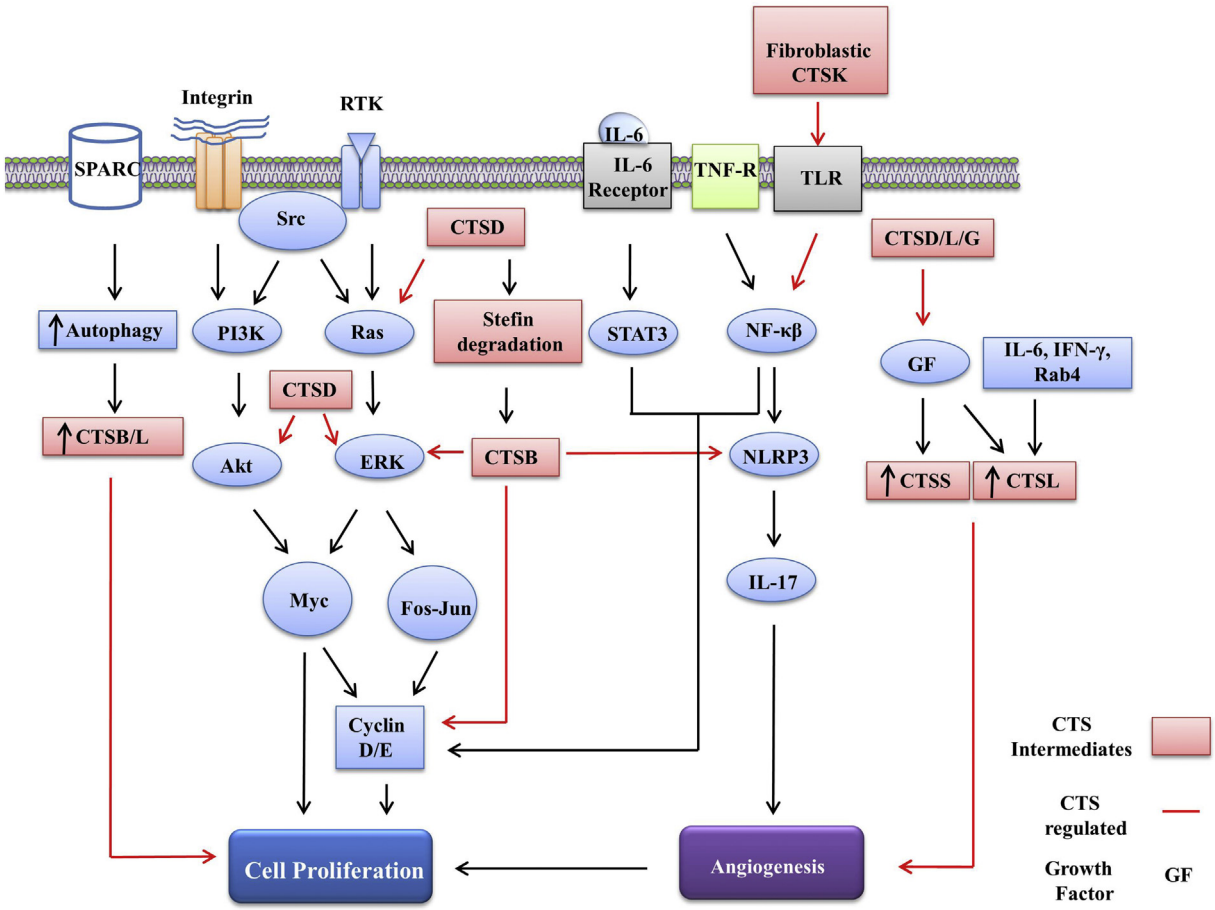

Fig. 2. Schematic representation of CTS implications in cancer growth and proliferation. This figure illustrates how CTS play a crucial role in the regulation of the signaling pathways involved in tumor progression. During cancer progression, SPARC induces CTSB/CTSD activity by promoting autophagy that can regulate tumor cell proliferation by proteolysis, ERK, and inflammasome-mediated angiogenesis. CTSD is also entailed in the promotion of autophagy degradation, AKT, and ERK-mediated trafficking. CTSD, in association with CTSL and CTSS, also actively facilitates the upregulation of growth factor-mediated angiogenesis and thereby cancer proliferation. Furthermore, CTSD is also implicated in enhancement of CTSB mediated tumor growth by degrading cysteine CTS inhibitor stefin. Tumor-secreted growth factors [VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), nerve growth factor (NGF)] induces CTSL and S expression. In addition to growth factors, some other cytokines including interferon gamma (IFNγ), IL-6, and Rab4α also enhance CTSL level. This increased CTSL and S expressions subsequently upregulate angiogenesis. Red arrows and red box indicate CTS mediated signaling and intermediates. SPARC: Secreted Protein, Acidic and Rich in Cysteine, AKT: Protein kinase B, ERK: Extracellular signal–regulated kinases, GF: growth factors.

that consequently boosts tumor growth by upregulating angiogenesis, in myeloid-derived suppressor cells exposed to gemcitabine and 5-fluorouracil. Inflammasome activation also promotes the infiltration of myeloid cells, such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells, that further stimulate breast cancer progression (Guo, Fu, Zhang, Liu, & Li, 2016).

CTSB are able to translocate to the extracellular space and mediate pleiotropic functions. To completely understand the mechanism of CTSB in the extracellular milieu, it is crucial to understand the translocation mechanism from lysosomal to extracellular space. Recently, Shao et al. (2018) revealed that epidermal growth factor (EGF)-induced neural precursor cells express developmentally down-regulated protein 4 (NEDD4) ligase activity that conceivably promotes the extracellular secretion of lysosomal CTSB. This secretion most likely occurs through the regulation of endosomal sorting complexes required for transport (ESCRT) complex-mediated membrane fusion between secretory lysosomes and plasma membrane, or through the formation and trafficking of autophagosomes (Mi et al., 2016; Shao et al., 2018). Extracellular CTSB degrades the extracellular matrix proteins including laminin, fibronectin, and collagen IV, at neutral and acidic pH (Ugarova, Ljubimov, Deng, & Plow, 1996). Similarly, CTSB also activates other proteolytic enzymes such as urokinase-type plasminogen activator and collagenase I, has also been reported in CTSB gene silencing-based studies in osteosarcoma cells during bone metastasis (Krueger et al., 1999; Withana et al., 2012; reviewed by Aggarwal & Sloane, 2014). In addition, Girotti, Rernandez, Lopez, Camafeita, et al. (2011) demonstrated that secreted protein acidic and rich in cysteine (SPARC), regulates the extracellular level of CTSB. SPARC was reported to promote CTSB-dependent melanoma invasiveness through cleavage of collagen I and α2β1 integrins. In invasive melanoma and glioblastoma, collagen-I exhibited increased CTSB activity in a β1 integrin-dependent manner (Klose et al., 2006; Gole, Duran Alonso, Dolenc, & Lah, 2009). In agreement with these findings, combined targeting of CTSB and uPAR resulted in inhibition of α3β1 integrin and tetraspanin-mediated downstream effects in glioma cells (Rao Malla et al., 2013). This extracellular CTSB consequently promotes cell migration through proteolysis of extracellular matrix and activation of Toll-like receptor 3 (TLR3) and uPA (Kobayashi et al., 1991; Buck, Karustis, Day, Honn, & Sloane, 1992; Garcia-Cattaneo et al., 2012) (Fig. 3). In addition, CTSB also mediates the IL-8/CXCR2-activated endothelial cell migration through cleavage of HB-EGF and activation of EGFR (Schraufstatter et al., 2003). Thus, extracellular CTSB plays a crucial role in ECM degradation and cell migration.

Angiogenesis is a complex process involving vascular sprouting, endothelial cell migration, and invasion through the extracellular matrix, tube formation, and proliferation. CTSB is also potently engaged in angiogenesis through degradation of the basement membrane for new blood vessel generation in the tumor environment, as predicted by the

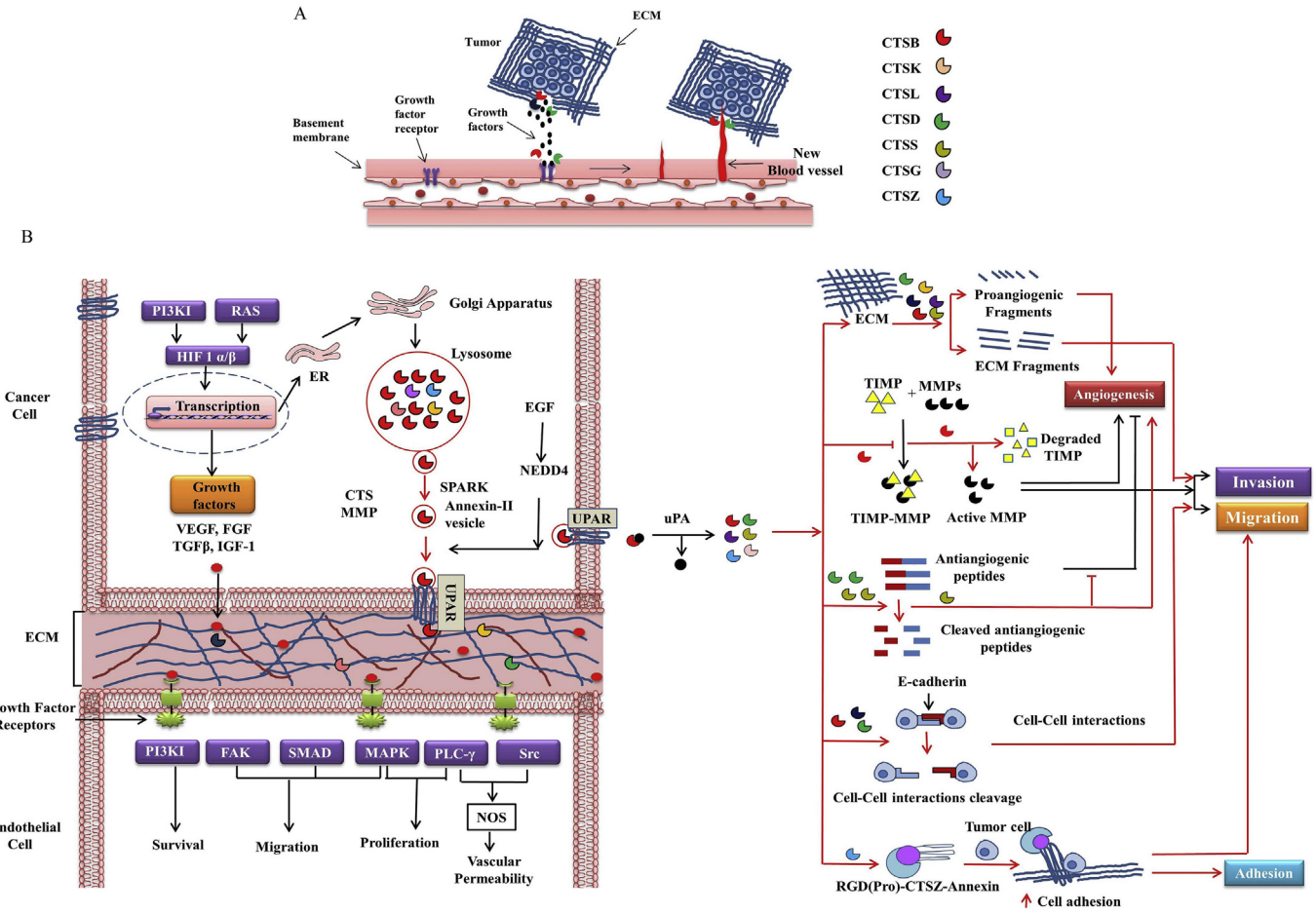

Fig. 3. Pleiotropic functions of CTS in provoking angiogenesis, invasion and metastasis. **A.** Overview of CTS mediated extracellular matrix degradation (ECM) degradation and angiogenesis promotion. Angiogenesis is critical for the growth of solid tumors and also aids in metastasis. The tumor induces angiogenesis either by itself or *via* the stimulation of host cells. The tumor promotes extracellular translocation of CTS and thereby ECM degradation, resulting in the release of growth factors which consequently induce angiogenesis after binding with their receptors. **B.** The detailed mechanism of CTS attributed for angiogenesis regulation, ECM degradation, and cell migration. In cancer cells, activated RAS and PI3K pathways promote HIF-1α induced transcription of growth factors (VEGF, FGF, TGFβ, IGF-1) and CTS. CTS are then activated in lysosomes and transported to the extracellular milieu where CTS promotes ECM degradation that supports the accessibility of growth factors to their receptors. This growth factor-receptors interaction further promotes vascular permeability and cell migration. Among the extracellular CTS, CTSB, K, L, and S promote activation of proangiogenic fragments; CTSB also activates matrix metalloproteases by degrading their inhibitors, and CTSS cleaves antiangiogenic peptides. As a result, these CTS cumulatively endorse angiogenesis. On the other hand, degradation of extracellular matrix by CTSB, K, L and S, cleavage of E-cadherin by CTSB, L and S, and activation of matrix metalloproteases by CTSB, leads to cell invasion and migration. Moreover, CTSZ induces cell adhesion by interacting with β-integrin through its proCTSX/Z. VEGF: Vascular endothelial growth factor, FGF: Fibroblast growth factors, TGFβ: Transforming growth factor, IGF-1: Insulin-like growth factor 1.

negative regulation of CTSB (Chang et al., 2009). Furthermore, CTSB also regulates the MMPs dependent proteolytic cascade through the degradation of their inhibitors (TIMP) (Fig. 3). Active MMPs degrade other protease inhibitors such as cystatin E, cystatin C, and cystatin M, finally resulting in the activation of complex proteolytic cascade within the tumor microenvironment (Kostoulas, Lang, Nagase, & Baici, 1999; Dean & Overall, 2007).

On the other side of the coin, cytosolic translocation of CTSB on lysosomal permeabilization hampers tumor growth and promotes cell death. The involvement of CTSB and CTSD in curcumin-mediated apoptosis has been reported in breast, lung, and other cancers (Chen et al., 2012; Terlikowska, Witkowska, Zujko, Dobrzycka, & Terlikowski, 2014; Moustapha et al., 2015). Curcumin-induced lysosomal membrane permeabilization (LMP), accompanied with cytosolic translocation of CTSB/D/L, cleaves the pro-apoptotic Bid and anti-apoptotic proteins such as Bcl-2 and Bcl-xL, thereby promoting apoptosis (Cirman, Oresic, Mazovec, Turk, et al., 2004; Droga-Mazovec, Bojic, Petelin, Ivanova, et al., 2008) (Fig. 4). CTSB enablement in the suppression of other forms of cell death mediated by sphingosine kinase 1 and receptor-interacting Ser/Thr protein kinase 1 and enforcing apoptosis has also been reported (reviewed in Olson & Joyce, 2015). Since CTS functions in a complex protein network, absence or deletion of one protease would be compensated by other proteases. For example, CTSL and CTSX/Z alternatively function for CTSB in the transgenic mouse model of pancreatic ductal adenocarcinoma, mammary carcinoma cells and myeloid-derived suppressor cells (MDSCs), respectively (Vasiljeva et al., 2006). Therefore, this obstacle of compensatory proteases needs to be considered in studies researching CTSB targeting. Although some crucial mediators have been identified, the exact mechanism of CTSB mediated tumor progression remains unknown. CTSB seems to promote cancer proliferation by regulating the MAPK pathway, cell cycle, and inflammasome formation that is further endorsed by angiogenesis, invasion, and metastasis. Considering these functions, targeting extracellular CTSB seems to be fruitful for cancer treatment, although its tissue-specificity reveals the complexity of its regulation.

2.1.2. CTSC

CTSC is a ubiquitously expressed dipeptidyl aminopeptidase. CTSC is highly expressed in the secretory granules of cytotoxic cells, mast cells, and neutrophils where it is actively involved in the activation of serine proteases including granzymes A and B, mast cell proteases 2 and 4, and neutrophil elastase, through cleavage of their pro-form that leads to the death of infected cells. CTSC also actively regulates

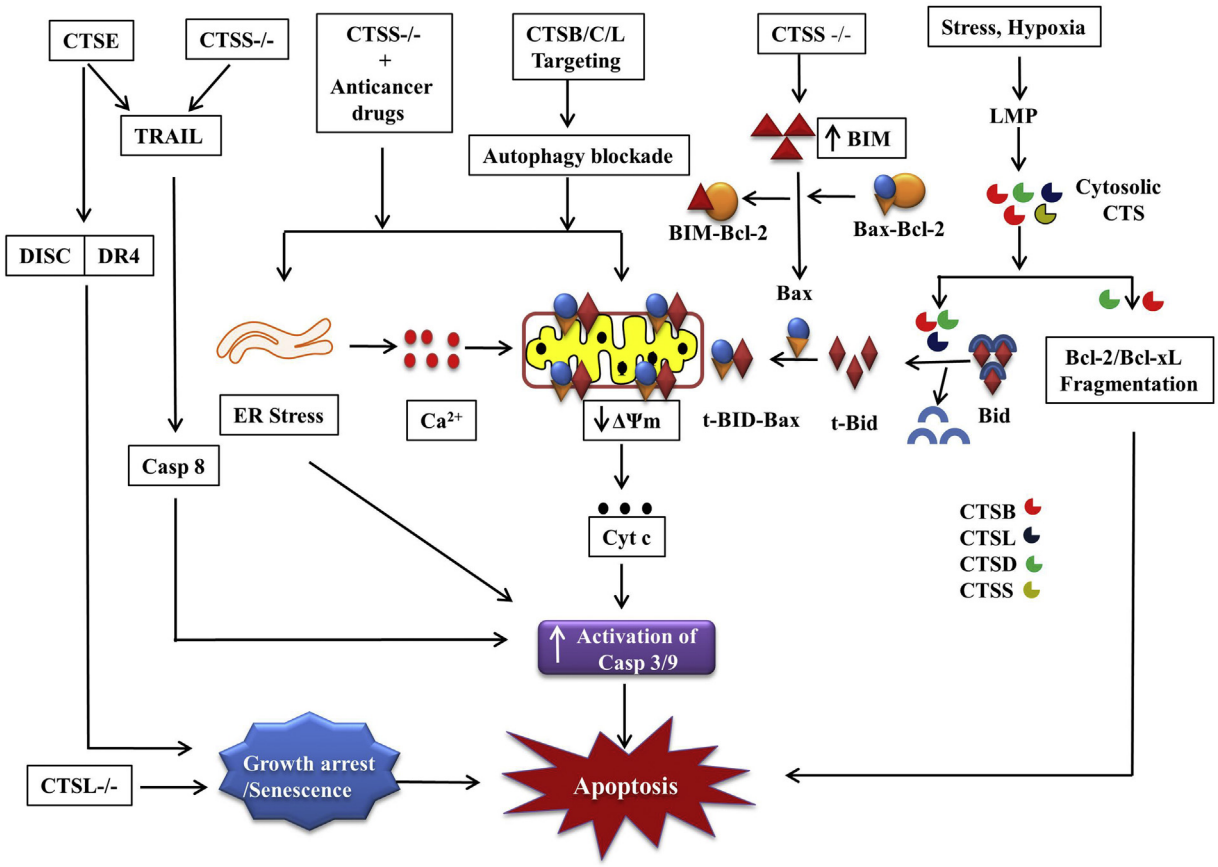

Fig. 4. CTS are the driving switch of apoptosis in cancer cells. Under stress conditions, lysosomal membrane permeabilization leads to cytosolic translocation of CTS that consequently promotes apoptosis by mitochondrial membrane permeabilization through the cleavage of the BID. Conversely, targeting of CTSB, C, L, and S also results mitochondrial membrane permeabilization and endoplasmic stress-mediated apoptosis. CTSL silencing causes senescence that consequently leads to apoptosis. CTSS silencing and CTSE are also implicated for TNF-related apoptosis-inducing ligand (TRAIL) mediated caspase-8 dependent apoptosis. Individually, CTSE promotes apoptosis on binding with the death-inducing signaling complex and Death receptor 4 (DR4).

other protease activities by generating inhibitory peptides against other proteases (McGuire, Lipsky, & Thiele, 1993; Turk, Dolenc, & Turk, 1998; Pham & Ley, 1999; Khaket, Dhanda, Jodha, & Singh, 2016; Khaket & Singh, 2017; Korkmaz et al., 2018). On stimulation, neutrophils, mast cells, and lymphocytes release CTSC into the extracellular milieu. CTSC is a homotetrameric protease with four different active sites exposed to the solvent (Turk et al., 2001). The exclusion domain built on the papain-like structure is responsible for the aminopeptidase activity of CTSC as it blocks the active site of the protease beyond the S2 pocket. CTSC is also expressed as proCTSC, which is further activated by CTSS (Hamon et al., 2016) (Fig. 1). Upregulation of CTSC expression is observed in various cancers, including colorectal cancer, breast cancer, pancreatic islet and squamous carcinogenesis (Lilla & Werb, 2010; Andreu et al., 2010; Ruffell et al., 2013; Khaket et al., 2018). Its enhanced expression and cleaving ability suggest a crucial role in cancer progression (Ruffell et al., 2013), although the exact mechanism is yet to be deciphered. In cancers, the statistically significant correlations of α-mannosidase, CTSB and CTSC with the differentiation levels of adenocarcinoma of gastroesophageal junction corroborate its implications in cancer cell differentiation (Altorjay et al., 2005). Significant reduction of squamous carcinogenesis on CTSC gene silencing indicates that CTSC is the main factor driving the cancer progression (Ruffell et al., 2013). Mikhaylov et al. (2011) have further discerned altered immune infiltration, reduced keratinocyte proliferation, and vascularization in CTSC-deficient mice during squamous cell carcinogenesis.

Moreover, in premalignant skin, CTSC deficiency attenuates the infiltrating leucocytes, invasive squamous carcinoma, and development of angiogenic vasculature as well as squamous cell carcinoma growth (Ruffell et al., 2013). Intriguingly, bone marrow-derived cells are able to sustain long-term tumor growth only in the presence of CTSC and CTSC-proficient neoplasia associated factors (DeNardo et al., 2011). Indeed, bone marrow transplantation experiments and add-back of CTSC-expressing cancer-associated fibroblasts facilitates cancer progression, thereby demonstrating the enablement in the promotion of tumor growth and angiogenesis (Ruffell et al., 2013). CTSC is also entailed for branching morphogenesis of mammary glands during breast cancer progression (Lilla & Werb, 2010), and is known to regulate the downstream proteolytic cascade in the neoplastic skin of K14-HPV16/CTSC/mice (Wolters, Pham, Muilenburg, Ley, & Caughey, 2001; Adkison, Raptis, Kelley, & Pham, 2002). However, no functional significance has been reported for pancreatic islet carcinogenesis (Ruffell et al., 2013). Recently, CTSC fragments in combination with argin, arylsulfatase A, and glial fibrillary acidic proteins have been identified as potent urinary biomarkers for reduced skeletal muscle density in hepato pancreato-biliary cancers (Husi et al., 2018), thereby supporting the involvement of CTSC in cancer cachexia. However, no functional significance of CTSC deficiency on cancer progression was observed in PanNET or mammary cancer (Gocheva et al., 2006). In the light of facts as discussed earlier, we can speculate the tissue-specific role of CTSC in cancer promotion.

In the current scenario, autophagy research has gained momentum for the regulation of tumor growth. Autophagy is a cellular homeostatic pathway that degrades the dysfunctional cytoplasmic organelles and damaged proteins, thereby providing raw material and adaptability under conditions of metabolic stress; autophagy is therefore attributed

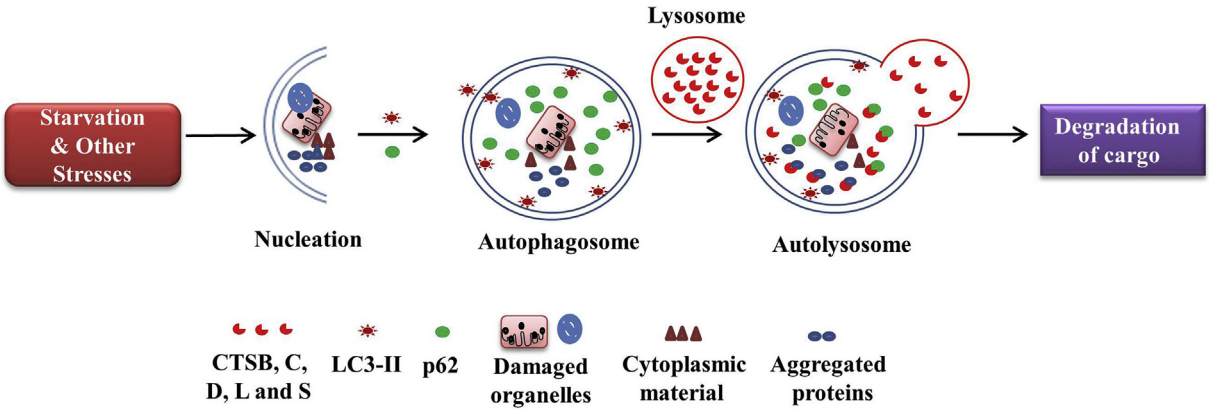

Fig. 5. Canonical role of CTS in autophagy progression. Under stress conditions, autophagy is initiated with sequestration of aggregated proteins and damaged organelles, resulting in the formation of a phagophore which further expands into a double-membrane autophagosome. This autophagosome fuses with a lysosome, (which supplies CTS) and forms an autolysosome where the CTS degrade the phagosomal proteins, thus resulting in macromolecules being recycled in the cytosol.

for homeostasis and cell viability. Recently, we identified the potential involvement of CTSC in autophagy regulation (Khaket et al., 2018) by the significant impediment of autolysosomal degradation. In combination with other cathepsins like CTSL and CTSD, CTSC is crucially involved in autophagic turnover, by promoting tumor growth and proliferation under stressed conditions like hypoxia, limited oxidative stress, and starvation (Fig. 5). CTSC targeting significantly reduces colorectal cancer cell growth and proliferation, thus indicating the direct involvement of CTSC in autophagy-mediated cancer progression (Khaket et al., 2018). In fact, a study by Bullon et al. (2018) on Papillion-Lefevre syndrome supports the direct involvement of CTSC in autophagy promotion. Thus, CTSC promotes cancer cell growth and progression by promoting autophagy, angiogenesis, and proteolytic cascades, or by regulating tumor microenvironment. However, the exact mechanism of CTSC in these processes is yet to decipher. Furthermore, the involvement of CTSC in autoimmune disorders was largely marginalized in favor of CTSC targeting based immune-dependent cancer regulation.

2.1.3. CTSK

Cathepsin K (CTSK), a lysosomal endoprotease implicated for the resorption of the bone matrix (Drake et al., 1996). Pro-CTSK is released from the endoplasmic reticulum and activated by CTSD (Bromme, Okamoto, Wang, & Biroc, 1996; Bossard et al., 1996) (Fig. 1). It has been identified as the principal protease in osteolytic lesions of giant cells in bone tumors (Lindeman et al., 2004). Expression of CTSK is upregulated in chondrosarcoma (Soderstrom, Ekfors, Bohling, Aho, & Vuorio, 2001), perivascular epithelioid cell tumors (PEComas) (Rao et al., 2013), and alveolar sarcoma (Zheng et al., 2013). In addition, its expression is entailed in the invasive growth of primary tumors in prostate cancer (Brubaker, Vessella, True, Thomas, & Corey, 2003), thyroid cancer (Mikosch et al., 2008), sub-cutaneous squamous cell carcinoma (Leusink et al., 2018), breast cancer, lung cancer, cervical cancer (Chen & Platt, 2011), renal cancer (Martignoni et al., 2012; Zheng et al., 2013), gastric carcinomas (Ren et al., 2012), melanoma (Rao et al., 2014), and glioblastoma multiforme (GBM) (Verbovsek et al., 2014). CTSK overexpression is also associated with a decline in the 5-year tumor-specific survival in both stromal and tumor cells of oral squamous cell carcinoma patients (Leusink et al., 2018).

Cancer cells shed cytokines such as IL-1α, IL-6, IL-8, and TGF-β1, which in turn facilitate CTSK expression in stromal fibroblasts, leading to tumor progression in squamous carcinoma cells (Xie et al., 2011). In non-melanoma skin cancers, IL-1α and chemokine CCL2 enhance the CTSK expression in both cancer and tumor-associated fibroblasts (Yan et al., 2011; Ishida, Kojima, & Okabe, 2013). In head and neck carcinoma, CTSK modulates cancer cell signaling by regulating the TLR pathways (Yuan, Xue, & Fan, 2014) *i.e.*, CTSK targeting attenuates the Toll-like receptor 9 dependent activations of T helper 17 cells and other downward cancer promoters (Asagiri et al., 2008); this further confirms the implication of CTSK in cancer growth.

Apart from inducing cancer growth, extracellular CTSK is involved in the cleavage of several proteins including collagen I, osteonectin, vascular endothelial growth factor (VEGF), adiponectin, osteopontin, stromal cell-derived factor 1 (SDF-1), and stem cell factor (SCF), which in turn are involved in augmenting angiogenesis, mobilization, and metastasis to the bone during prostate carcinoma (Brubaker et al., 2003; Novinec et al., 2007; Herroon et al., 2013) (Fig. 3). Involvement of CTSK is also observed in the invasion and migration of glioma stem-like cells by cleaving SDF-1 in glioblastoma to support their migration (Hira et al., 2015). CTSK deficiency hampers cleaved Notch1, Hes1, Hey1, Hey2, VEGF, Flt-1 and phospho-Akt protein levels in ischemic muscles. Hence, CTSK seems to hold substantial promise for neovascular promotion. Consistent with these studies, transplantation of bone marrow-derived mononuclear cells from $CatK^{+/+}$ mice were able to recapitulate the CTSK knockdown mediated defective endothelial cell invasion, proliferation, and tube formation (Jiang et al., 2014), which further reinforces the significance of CTSK in neovascularization. It is also known to facilitate metastatic tumor growth in an organic bone matrix in association with the parathyroid hormone-related protein (BPTHrP) mediated mineral solubilization (Tomita et al., 2008). Previously, Ren et al. (2012) reported that CTSK is also entailed in coronin 3 (a tumor progression-associated protein) promoted metastasis in association with MMP-9. It is also indulging for lymph node metastasis of gastric cancer cells (Leusink et al., 2018); therefore CTSK implications in metastasis are not be underestimated. The involvement of CTSK has mainly been explored considering its activity-based bone metastasis, while CTSK mediated promotion of TLR and Notch signaling in cancer progression presents another potential for targeting based cancer therapeutics.

2.1.4. CTSL

Another lysosomal endoprotease, CTSL is upregulated in a wide range of human malignancies including ovarian, breast, prostate, lung, gastric, pancreatic, colon cancers and pediatric acute myeloid leukemia (reviewed in Suthan and Siemann, 2015; Sudhan, Pampo, Rice, & Siemann, 2016; Pandey et al., 2018). CTSL is crucial for cancer progression by regulating cell cycle, ECM degradation, angiogenesis, tumor invasion and metastasis, bone resorption, and drug sensitivity. Higher level of CTSL in body fluids such as plasma and urine is reported to be indicators of poor cancer prognosis for pancreatic and bladder urothelial cell carcinoma, respectively (Svatek et al., 2008; Singh et al., 2014). Its inverse correlation with steroid hormone receptors supports it as a predictor of tumor relapse and poor overall survival in breast cancers (Lah et al., 2000). Furthermore, chemotherapeutic treatment dependent

reduction of CTSL activity confirms its prognostic value for overall survival (Pandey et al., 2018).

CTSL activity and expression are tightly controlled by various physiological inhibitors and other regulatory molecules. However, a conspicuous imbalance between the levels of endogenous inhibitor and CTSL in varied invasion phases of different tumors indicates that endogenous inhibitors are not the only regulatory factors for CTSL activity in carcinogenesis. Tumor-secreted VEGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), nerve growth factor (NGF), interferon gamma (IFNγ), IL-6, and Rab4α can also augment CTSL promoter activity and thereby its expression (Barbarin & Frade, 2011; reviewed in Sudhan & Siemann, 2015) (Fig. 2). During tumor progression, the initial decline in CTS inhibitors are considered to be responsible for enhancement of CTSL expression and activity (Lah et al., 2000; Samaiya, Bakhshi, Shukla, Kumar, & Chauhan, 2011) while results of polyribosome profiling revealed that stress (hypoxia or starvation)-resistant mRNA translation is the causative factor for higher CTSL expression during breast tumor progression (Tholen et al., 2015). The crucial involvement of CTSL during tumor progression was also supported by *in vivo* studies in sporadic pancreatic carcinogenesis (RIP1-Tag2 PanNET mouse model). In this model, knockout of CTSL has a significantly impaired tumor burden as well as tumor transformation from benign to invasive carcinoma (Gocheva et al., 2006; Gocheva et al., 2010; Akkari et al., 2014) due to increased EGF recycling and deregulated autocrine mitogenic signaling (Tobin et al., 2002; Reinheckel et al., 2005; Dennemarker et al., 2010) that facilitates the regression of tumor development. Conversely, in breast cancer patients, the nuclear CTSL also degrades 53BP1 which alternatively acts as a replacement of BRAC1; as a result, cancer cells are able to evade the cell death pathways in the presence of CTSL (Grotsky et al., 2013).

It is now well-recognized that CTSL function is dependent on subcellular localization. Extracellular CTSL is crucially involved in ECM degradation and associated functions. Similar to CTSB, CTSL is able to degrade ECM components such as laminin, type I collagen, type IV collagen, fibronectin, and elastin (Ishidoh & Kominami, 1995; Novinec et al., 2007; Korenc, Lenarcic, & Novinec, 2015), along with the simultaneous activation of urokinase plasminogen activator, pro-heparanase, CTS, and certain MMPs (Laurent-Matha, Derocq, Prebois, Katunuma, & Liaudet-Coopman, 2006). Extracellular CTSL also diminishes the cell-cell adhesion by degrading E-cadherin and other adhesion proteins (Gocheva et al., 2006). However, nuclear CTSL activates the CCAAT-displacement protein/cut homeobox (CDP/Cux) transcription factor, thereby promoting tumor cell proliferation by accelerating entry into the S phase of the cell cycle (Fei, Qin, & Liang, 2007). CTSL knockdown also results in a dramatic reduction of phosphorylation of DNA checkpoint proteins such as ataxia-telangiectasia mutated (ATM), DNA-protein kinases, and CD133 expression that support the steep decline in the tumor cell cycle.

In addition to cell cycle promotion, activated Cux binds to Snail and the E-cadherin promoters in mesenchymal cells which in turn promote epithelial-mesenchymal transition (EMT) and cell migration/invasion that can be antagonized by CTSL inhibition by *Z*-FY-CHO (Burton et al., 2017). Also, overexpression of CTSL by ionizing radiation exposure and by other transcription factors like Forkhead box O3A (FOXO3a) also triggers cancer invasion and migration through the CUX1-mediated EMT signaling pathway (Yu et al., 2016; Wang et al., 2018). Moreover, β-FGF and X-ray induced CTSL expression promotes cancer cell migration through JNK mediated signaling and RhoA and CDC42 activity reduction, respectively (Jain, Bakhshi, Shukla, & Chauhan, 2010; Samaiya et al., 2011; Xiong et al., 2017). Furthermore, acidosis and hypoxic stress also promote CTSL associated ECM degradation, invasiveness, and metastasis which underlies the contemporary understanding of CTSL in metastasis (Sudhan & Siemann, 2013).

CTSL is also crucial effectors for neovascularization by promoting invasion of endothelial progenitor cells into the stroma, and their subsequent incorporation into blood vessels (Urbich et al., 2005). CTSL mediated heparanase activation controls the release of heparan sulfate-bound growth factors that, in turn, modulate angiogenesis and lymphangiogenesis (Hunter et al., 2013). Highly expressed CTSL enhances the recruitment of inflammatory cells and aortic wall matrix degradation in aneurysm development (Sun et al., 2011). Moreover, VEGF is also in coordination with CTSL expression, as a result, increased VEGF enhances CTSL expression and subsequently angiogenesis, in glioblastoma cells (Keerthivasan, Keerthivasan, Keerthivasan, Mittal, & Chauhan, 2007) (Figs. 2 & 3). CTSL is also widely implicated in proteolytic degradation of bone and cartilage matrix components (reviewed in Leto, Sepporta, Crescimanno, Flandina, & Tumminello, 2010). Its inhibition significantly mitigates osteolytic events and hypercalcemia in mice with bone metastasis. Thus, CTSL intervention strategies would not only impede the metastatic dissemination of tumor cells, but also alleviate both treatment-induced and cancer-associated osteolysis.

Contrarily, LMP mediated cytosolic CTSL also augments apoptosis through cleavage of various anti-apoptotic members, most notably Bid of the Bcl2 family members (Stoka et al., 2001) (Fig. 4). Thus, the involvement of CTSL in cancer progression highlights the significance and importance of targeting CTS for cancer treatment.

2.1.5. CTSS

CTSS possesses endoproteolytic activity and is potently involved in the progression of various cancers including lung, prostate, gastric, colorectal, hepatocellular carcinomas, melanomas and gliomas (reviewed by Zhang, Wang, & Xu, 2015). Previous studies indicate that CTSS plays a crucial role in antigen presentation and also acts as a vital protagonist of cancers. Modulation in CTSS expression is reportedly implicated in cancer progression, angiogenesis, cell invasion and migration (Wang et al., 2006; Ward et al., 2010). Conceivably, CTSS mediated autophagy promotion is reported to contribute toward tumor development by regulating the M2 phenotype of tumor-associated macrophages (TAMs) (Yang et al., 2014). Conversely, CTSS targeting induces reactive oxygen species-mediated autophagy in various cancer cells, including nasopharyngeal carcinoma cells, colon adenocarcinoma cells, epidermoid carcinoma cells, alveolar basal epithelial cells, and human squamous carcinoma cells (Li, Yang, Ming, & Liu, 2011; Yang et al., 2014), thereby suggesting the indirect involvement of CTSS in autophagy promotion. CTSS is also involved in dissolution and remodeling of connective tissue and basement membranes, which further enhance the tumor progression.

CTSS is known to regulate angiogenesis by generating both pro-angiogenic peptide and anti-angiogenic peptide from collagen XVIII and fragments from ECM protein laminin, thus demonstrating the complex nature of CTSS on angiogenesis regulation in the tumor microenvironment (Fig. 3). In the RIP1-Tag2 mouse model, CTSS modulates anti-angiogenic peptides such as canstatin, arresten, and tumstatin, and generates pro-angiogenic γ2 fragments from laminin-5, whereas CTSS knockdown results in significant reduction of tumor-associated angiogenesis and switching of neovascularization, revealing a functional role in angiogenesis promotion (Wang et al., 2006). Similar to CTSL, CTSS is also found downstream of VEGFA signaling, resulting in an increase of CTSS on VEGFA upregulation (Zhang et al., 2015). However, in human umbilical vein endothelial cells (HUVEC), gene silencing and inhibitory studies reveals CTSS expression dependent VEGF secretion; hence, we speculate that CTSS and VEGF work in a positive feedback loop mechanism and finally alleviate angiogenesis (Chen et al., 2010; Fan et al., 2012) as also reported for human colorectal carcinoma cell xenografts (Burden et al., 2009; Zhang et al., 2015).

Specific cleavage of cell-cell adhesion molecules has emerged as an essential mechanism of tumor promotion by CTSS secretion into the extracellular space. Indeed, a recent study has reported CTSS-mediated adhesion molecule shedding at a later step in the metastatic cascade. In the context of breast-to-brain metastasis, CTSS cleaves several junctional adhesion molecules (JAMs), especially JAM-B, thereby facilitating the passage of cancerous cells across the blood-brain barrier during breast-brain metastasis (Sevenich et al., 2014) (Fig. 3). Despite its direct

involvement in cancer progression, CTSS targeting selectively sensitizes human renal cancer cells to TRAIL-induced ROS-mediated p53 dependent apoptosis, a process corroborated with downregulation of Bcl-2 and c-FLIP (Seo et al., 2017). Recently, Seo, Woo, Min, and Kwon (2018) demonstrated that CTSS inhibition by *Z*-FL-COCHO (ZFL) upregulates the pro-apoptotic protein Bim expression, which contributes to anti-cancer drug-induced apoptotic cell death in renal carcinoma Caki cells independent of MAPKs and AMP-activated protein kinase (AMPK) pathways. CTSS mediated lysosomal degradation of Mcl-1 protein also alleviates TRAIL-induced apoptosis in the presence of YM155 and eupafolin (Han, Min, Woo, Seo, & Kwon, 2016; Woo, Min, Seo, & Kwon, 2016) (Fig. 4). These studies support the crucial role of CTSS in cancer progression by regulating autophagy, angiogenesis, and cell to cell interaction. Moreover, enhanced apoptosis on CTSS targeting further signifies its anticancer therapeutic utility.

2.1.6. CTSX/Z

CTSX (also known as CTSZ) is a cysteine carboxypeptidase localized in immune cells such as monocytes, macrophages, microglia, and dendritic cells (Kos, Vizin, Fonovic, & Pislar, 2015). Like other CTS, CTSX/Z is expressed in a pro-active form which is activated by CTSL (Fig. 1). CTSX/Z is upregulated in gastric, pancreatic, neuroendocrine tumors, prostate, and hepatocellular carcinomas (Akkari et al., 2014; reviewed in Kos et al., 2015), while decreased levels of CTSX/Z have been observed in lung tumors (Krueger et al., 2005) and malignant melanoma. Clinical studies have enlightened the direct relationship between CTSX/Z expression and malignancy advancement, especially in hepatocellular carcinomas, colorectal, gastric, and prostate cancer (Krueger et al., 2005; Nagler et al., 2010; Wang, Chen, Li, & Guan, 2011; reviewed in Kos et al., 2015), thereby suggesting the crucial cancer-promoting functions in different tumor microenvironments. Several molecular targets of CTSX/Z (Nagler et al., 2010; Turk et al., 2012) have been identified, including integrin receptors, enolase (Obermajer et al., 2008), chemokine CXCL-12 (Staudt et al., 2010), bradykinin, kallidin (Nagler et al., 2010), huntingtin and profilin 1 (Ratovitski, Chighladze, Waldron, Hirschhorn, & Ross, 2011; Pecar Fonovic et al., 2013). Genetic variations of the CTSX/Z sequence have also been reported for various tumors (De Marco et al., 2017; Jia, Lan, Wang, & Gao, 2018), but their functional significance in cancer is still not clear. In a tumor, CTSX regulates IGF-I phosphorylation and subsequently cell cycle and cancer progression (Kraus et al., 2011, 2012). CTSX/Z deficient murine embryonic fibroblasts and neonatal human dermal fibroblasts undergo accelerated cellular senescence, resulting in reduced proliferation rate and increased expression of senescence-associated genes such as p16, p21, p53, and caveolin. Teller et al. (2015) recognized RPLP0 as a CTSX/Z-interacting protein by applying the yeast (*Saccharomyces cerevisiae*) two-hybrid (Y2H) assay. Combined targeting of CTSX/Z-RPLP0 proteins attributes cell cycle arrest through CDK2, with a concomitant increase in apoptosis (Teller et al., 2015). Thus, CTSX/Z is canonically involved in cell cycle progression, and targeting CTSX/Z leads to senescence.

Similar to other CTS, a significant increase in epithelial CTSX/Z expression is observed in early tumor stages which further translocates to the sub-membranous region in cells of the invasion front. Indeed, CTSX/Z deficiency is known to delay tumor growth and metastasis in breast cancers as compared to wild-type mice (Vasiljeva et al., 2006; Bernhardt, Kuester, Roessner, Reinheckel, & Krueger, 2010; Sevenich et al., 2010). CTSX/Z is contemplating a relevant factor for cell-cell adhesion, and tumor cell anchorage to fibroblasts and basal membrane components through Mac-1 activation. Mediation of cell-to-cell interaction *via* CTSX/Z makes the cell adhesive, while its inhibition results in increased invasiveness of colon carcinoma cells (Obermajer et al., 2008; Jechorek et al., 2014). In addition, tumor-associated macrophages (TAMs) and CTSX/Z are proposed to be critically involved in tumor progression and metastasis through ECM modulation (reviewed by Joyce & Pollard, 2009 and Biswas, Allavena, & Mantovani, 2013). Furthermore, CTSX/Z can also mediates the adhesion and migration of tumor cells by interacting with β integrin receptor LFA-1 and profilin 1 (tumor suppressor) (Pecar Fonovic et al., 2013). This interaction between CTSX/Z and integrin receptors are strongly associated with tumor cell signal transduction, resulting in changes in cell adhesion, migration, cytoskeleton remodeling, and cell proliferation (Kos et al., 2015). When considering endothelial (HUVEC) and pancreatic cancer cells (PDA), the CTSX/integrin binding significantly changes the cell adhesion to ECM proteins (Lines et al., 2012) (Fig. 3). The integrin-binding motif Arg-Gly-Asp (RGD) of CTSX/Z propeptide (Nagler & Ménard, 1998; Sivaraman, Nagler, Zhang, Menard, & Cygler, 2000; Lechner et al., 2006) interacts with integrins, including αvβ3 (Kos et al., 2009) and regulate various immune processes, including dendritic cell maturation (Obermajer et al., 2008) and lymphocyte invasion and proliferation (Jevnikar, Obermajer, Bogyo, & Kos, 2008; Obermajer et al., 2008; Obermajer et al., 2009). The integrins mediating cell and ECM interactions trigger focal adhesion kinase (FAK) and Src kinase-mediated downstream signaling, thereby promoting cancer cell proliferation, survival, migration, and invasion (Desgrosellier & Cheresh, 2010; Moreno-Layseca & Streuli, 2014). Similarly, the majority of CTSX/Z mediated functions in RIP-Tag2 mice, including engagement of integrins and subsequent activation of FAK-Src signaling in cancer cells, are dependent on the RGD motif (Akkari et al., 2014). Recently, Li et al. (2018) observed that a natural compound deguelin effectively suppresses migration, invasion, and metastasis of NSCLC cells by inhibiting the CTSZ/FAK/Src/Paxillin signaling cascade. Because FAK/Src signaling is associated with integrin-mediated cell migration, so, CTSX/Z targeting can also dysregulate cellular migration (Fig. 3). A significant increase in B- and T-cell activators on CTSX/Z knockdown signifies its active participation in the suppression of lymphopoiesis (Bernhardt et al., 2010) (Fig. 3). On the other hand, loss of CTSX/Z has also been observed with advanced local invasion, distal metastasis, invasion, tumor budding and poorer overall survival of CRC patients (Jechorek et al., 2014), that proclaims the loss of CTSX/Z is required for tumor cell detachment, local invasion, and tumor progression in CRC. Interestingly, CTSX/Z expression increases up to two-folds in stomach tissue on CTSB silencing and *vice versa* that confers the compensatory role of CTSX/Z in CTSB-deficient cells including stomach cells and PymT mammary tumor cells. The synergistic decline in tumor growth, metastasis, and angiogenesis with the combined loss of CTSB and CTSX/Z (Buhler et al., 2013) underlie the compensatory role of these CTS.

Overexpression of CTSX/Z contributes to tumor metastasis by inducing epithelial to mesenchymal transition (EMT) in hepatocellular carcinoma (Wang et al., 2011). E-cadherin is a hallmark marker for epithelial cell phenotype (Son & Moon, 2010), while vimentin typically represents the mesenchymal phenotype (Satelli & Li, 2011). In hepatocellular carcinoma cells, overexpression of CTSX/Z is associated with upregulated mesenchymal markers such as N-cadherin and fibronectin, and downregulated epithelial markers such as E-cadherin and catenin (Wang et al., 2011). Recently, Mitrovic et al. (2017) observed that CTSB and CTSX/Z are associated with EMT in breast adenocarcinoma cells by inducing vimentin expression, while silencing CTSX/Z and CTSB in lung epithelial carcinoma cells (A549) attributed to the downregulation of vimentin and upregulation of E-cadherin, representing the suppression of EMT. CTSX/Z can also upregulates the matrix metalloproteases MMP2, MMP3, and MMP9 (common mesenchymal factors). Recently, Tuo et al. (2017) predicted that gene silencing of sorcin could downregulate the expression of CTSX and other regulatory molecules such as MMP2, MMP9, and p-STAT3 involved in tumor growth and metastasis of gastric cancer. Sorcin is a soluble resistance-related calcium-binding protein, and has a significant role in multidrug resistance related to the migration and invasion of cancer cells. However, the association of CTSX/Z and sorcin remains unclear, but downregulation of CTSX/Z and cell migration by sorcin gene silencing efficiently supports their upstream role in cancer progression. Thus, CTSX/Z is crucially involved in cell-to-cell interaction and EMT through its RGD motif, and understanding of its functioning in cancer

progression and drug resistance would therefore be fruitful for cancer therapeutics.

2.2. Aspartic cathepsins

2.2.1. CTSD

CTSD, a ubiquitously expressed aspartic endoprotease, contains a pepsin-like active site (Benes, Vetvicka, & Fusek, 2008). Expression of CTSD is significantly increased in various cancers including breast, ovarian, endometrial, head and neck, bladder, glioma, and melanoma (Berchem et al., 2002; reviewed in Liaudet-Coopman et al., 2006 and Benes et al., 2008). Numerous studies have found that pCTSD/CTSD levels are an independent prognostic factor in numerous types of cancers. CTSD stimulates cancer cell proliferation through fibroblast outgrowth, angiogenesis (Berchem et al., 2002; Hu, Roth, Brooks, Luty, & Karpatkin, 2008), and metastasis (Glondu et al., 2002; Vashishta, Ohri, Proctor, Fusek, & Vetvicka, 2007), with simultaneous inhibition of anti-tumor responses (Wolf et al., 2003). CTSD stimulates ERK1/2 and AKT pathways through non-proteolytic mechanisms, and consequently promotes cancer proliferation and migration of ovarian epithelial carcinoma (Pranjol, Gutowski, Hannemann, & Whatmore, 2018). Similar to CTSL, the protooncogenic transcription factor-like FOXM1 is also known to support CTSD mediated gastric cancer cell migration and invasion (Yang, Cui, Zhang, & Song, 2017). CTSD promotes cancer cell growth through binding with the IGF2 receptor, and facilitating the activation of mitogenic IGF1 receptor pathway (Faridi, Mohan, & De Leon, 2004). Zeleznik, Kadin, Turk, and Dolenc (2015) observed that CTSD degrades stefin B (a CTSB inhibitor), thereby substantiating its direct involvement in the activation of CTSB dependent enzymatic cascade responsible for cancer progression. Previous reports also elucidated the mitogenic activity of CTSD is due to the protein-protein interaction, but is independent of catalytic activity in fibroblasts and keratinocytes (Bazzett, Watkins, Gercel-Taylor, & Taylor, 1999; Berchem et al., 2002; Laurent-Matha et al., 2005).

Lysosomal CTSD is translocated to cytosol through lysosomal membrane permeabilization (LMP) (Roberg & Ollinger, 1998) where it induces the cancer cell growth by impairing secreted growth inhibitors such as heat shock cognate 70 protein (Nirde et al., 2010). Under stress conditions, CTSD protects the cancer cells through fostering of autophagy; upregulated CTSD inhibits H_2O_2-induced cell death in human malignant glioblastoma (M059 J) cells (lacking the catalytic subunit of DNA-dependent protein kinase by inducing autophagy (Hah et al., 2012). Moreover, heightened sensitivity of V-ATPase inhibitors such as bafilomycin A1 on CTSD targeting (Kitazawa et al., 2017) further supports the crucial role of CTSD in autophagy. Pro-CTSD (pCTSD) secreted from cancer cells stimulates pre-invasive and pro-metastatic functions in both cancer and stromal cells (Laurent-Matha et al., 2005; Liaudet-Coopman et al., 2006; reviewed in Benes et al., 2008). Laurent-Matha et al. (2005) have previously demonstrated that pCTSD secreted from cancer cells augments the proliferation of fibroblasts, consequently increasing the survival and invasive capacity in conjunction with activation of the RAS-MAPK pathway (Fig. 2).

A significant association between CTSD expression of host stromal cells and vascular density has been described in breast and ovarian cancers (Gonzalez-Vela, Garijo, Fernandez, Buelta, & Val-Bernal, 1999; Losch et al., 2004). Moreover, it has been shown that pCTSD stimulates tumor angiogenesis in xenografted athymic mice due to its signaling properties, and not due to enzymatic activity. It has also been observed that CTSD facilitates the release of pro-angiogenic βFGF from ECM (Takei, Higashira, Yamamoto, & Hayashi, 1997). Furthermore, CTSD is actively involved in the degradation of anti-angiogenic factors including angiostatin, 16 K prolactin (PRL), and endostatin (Morikawa et al., 2000; Ferreras, Felbor, Lenhard, Olsen, & Delaisse, 2000; Piwnica et al., 2004; Piwnica et al., 2006) (Fig. 3). Thus, extracellular CTSD promotes angiogenesis in both enzymatic and non-enzymatic dependent ways in cancers (Liaudet-Coopman et al., 2006; reviewed in Benes et al., 2008).

Similar to CTSB, cytosolic CTSD is also a key mediator of apoptosis through activation of pro-apoptotic and deactivation of anti-apoptotic or nuclear proteins. It triggers Bax insertion into the mitochondrial membrane either directly or indirectly through Bid cleavage (Bidere et al., 2003; Blomgran, Zheng, & Stendahl, 2007), conjunctively causing cytosolic release of mitochondrial cytochrome *c* and the activation of caspase 3 that leads to apoptosis (Johansson, Steen, Ollinger, & Roberg, 2003; Heinrich et al., 2004) (Fig. 4). CTSD also activates pro-caspase 3 by activating caspase-8. Overexpression of vacuolar protein sorting (VPS) 52 (a tumor suppressor gene) also induces CTSD dependent apoptosis in gastric cancer (Zhang, Lin, Hu, Wu, & Guo, 2017). Thus, CTSD possesses the ability to control cancer progression even in the absence of its activity that further increases the complexity of CTS-based cancer regulation. Moreover, the promotion of both tumor growth and apoptosis also demands more exploration to understand the functioning of cytosolic CTSD.

2.2.2. CTSE

CTSE, an aspartic protease, is highly expressed in premalignant cervical epithelium, lung carcinoma, pancreatic ductal adenocarcinoma, colorectal sessile serrated adenomas, bladder cancer, hepatocellular carcinoma, colorectal cancer, prostate cancer, and pancreatic ductal adenocarcinoma (reviewed in Kawakubo, Yasukochi, Nakamura, & Yamamoto, 2011; Fristrup, Ulhoi, Birkenkamp-Demtroder, et al., 2012; Konno-Shimizu et al., 2013; Navari, Prorok, & Castellino, 2014; Kawakubo et al., 2014; O'Donoghue et al., 2016; Atwa & Arafa, 2016). Upregulated CTSE is also demonstrated to be diagnostic of intestinal cancers; elevated CTSE levels in urine and intestinal tissue samples of mice and humans are proposed as a diagnostic marker for colorectal cancer (Navari et al., 2014). Paradoxically, Fisher et al. (2015) elucidated the significance of upregulated CTSE in the survival rate of patients with Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). However, a non-significant trend of higher CTSE protein levels in patients with esophageal adenocarcinoma suggests that CTSE is only a marker of Barrett's esophagus, since decreasing the CTSE expression reduces the differentiation of gastric tumors (Konno-Shimizu et al., 2013).

Recently, Dhawan et al. (2018) reported enrichment of the CTSE gene in addition to PPARG, LY6E, CTSE, CDK3, and TBX2 genes in a luminal subtype of invasive urothelial carcinoma, thereby establishing its significance in tumor regulations. Studies on serum levels of CTSE expression and clinicopathological parameters reveal that CTSE activity levels, and not its protein levels, are negatively associated with the stages and progression of breast cancers. Serum CTSE activity significantly correlated with favorable prognostic outcomes of patients. Multiparous CTSE−/− mice spontaneously developed mammary tumors, concomitant with morphological transformation and altered growth characteristics of mammary glands associated in part with the induction of epithelial-mesenchymal transition and the activation of the β-catenin-dependent pathway in mammary cells. On the other hand, CTSE contributes to normal growth and development of mammary glands through proper trafficking and Wnt5a (Kawakubo et al., 2014) mediated patterning during embryogenesis.

A remarkably higher level of CTSE is associated with improved survival in various cancers (Ullmann et al., 2004; Fristrup et al., 2012; Kawakubo et al., 2014). Loss of CTSE expression induces mammary gland neoplasia (Kawakubo et al., 2014). At 10 to 15 days post-inoculation, the growth of tumors in $CTSE^{-/-}$ mice is significantly higher than that in $CTSE^{+/+}$ and transgenic mice overexpressing CTSE. Moreover, numbers of apoptotic cells are increased in transgenic mice overexpressing CTSE, while fewer numbers are noted in $CTSE^{-/-}$ mice; this endorses the functional significance of CTSE in apoptosis (Kawakubo et al., 2007, reviewed in Kawakubo et al., 2011). For apoptosis, CTSE recruits the death-

inducing signaling complex (DISC) with death receptor DR4 or DR5 that promotes caspase cascade dependent programmed cell death (Yasukochi, Kawakubo, Nakamura, & Yamamoto, 2010) (Fig. 4). Therapeutic insertion of purified CTSE into human tumor xenograft facilitates apoptosis (Kawakubo et al., 2007). Tumor-infiltrated lymphocytes and macrophages in transgenic mice overexpressing CTSE reinforce both TRAIL-mediated apoptosis and the production of cytotoxic molecules such as various cytokines and reactive oxygen species that consequently suppress tumor development and metastasis (Andreesen, Hennemann, & Krause, 1998; Griffith et al., 1999; Kayagaki et al., 1999). This suppression of metastasis is also negatively associated with endogenous CTSE levels in lung cancer (Kawakubo et al., 2007). Besides apoptosis induction, CTSE also suppresses tumor growth through inhibition of angiogenesis by upregulating IL-12 and endostatin (antiangiogenic molecules) in prostate carcinoma (Shin et al., 2007). Contrarily, two CTSE genes or isozymic forms have been identified in normal and cancer cells in different proportions (Takeda-Ezaki & Yamamoto, 1993; Okamoto, Yu, Misumi, Ikehara, & Yamamoto, 1995), strongly suggesting that some CTSE proteins produced in cancer cells are nonfunctional. Besides, CTSE enhances the sensitivity of tumor cells to antitumor agents (Yasukochi et al., 2010). Thus, CTSE regulates malignancy and cancer progression by controlling apoptosis, immune responses, and angiogenesis, as well as sensitizes the cancer cells against anticancer drugs. Thus, CTSE showed tissue and tumor-specific functioning while its activity based cancer regulating efficiency is appealing for cancer therapeutics.

2.3. Serine cathepsins

2.3.1. CTSG

CTSG is a serine protease typically found in antigen presenting cells such as B-cells, myeloid dendritic cells, and microglia. CTSG is secreted by azurophilic granules of neutrophils and monocytes. It plays multiple roles in extracellular matrix degradation, apoptosis, chemotaxis, and other immune responses (Wiedow & Meyer-Hoffert, 2005; reviewed in Korkmaz, Horwitz, Jenne, & Gauthier, 2010 and Gregory & Houghton, 2011). CTSG is highly expressed in acute lymphoid leukemia cells and is an indicator of poor prognosis (Khan, Carmona et al., 2018). CTSG is also aberrantly expressed during early stages of myeloid leukemia cells. In acute myeloid leukemia (AML), CTSG expression is upregulated and localized outside the granules involved in antigen presentation, and is therefore associated with poorer outcomes in AML patients. However, *in vivo* studies reveal that CTSG targeting eliminates AML while sparing normal hematopoiesis. IL-20, a key regulator of proliferation and differentiation of keratinocytes during inflammation, also induces CTSG expression, which consequently enhances breast cancer progression (Hsu et al., 2012). Alatrash et al. (2017) have demonstrated that targeting CTSG with HLA-A2 restricted epitope containing leader sequence of CTSG-CTL reduces the leukemia burden in mice without affecting normal hematopoiesis. Clinically, CTSG-CTL may preferentially lead to the killing of high CTSG-expressing AML and acute lymphoid leukemia (ALL) cells which confers the involvement of CTSG in MHC processing and presentation within leukemic cells. This cell cytotoxicity might be due to the interaction of CTSG with oncogenic proteins, including expression/phosphorylation of members of the Hippo pathway such as TAZ and YAP1 in AML (Ogawa et al., 2015). Hence, CTSG is an immunotherapeutic target in myeloid leukemia and acute lymphoid leukemia.

Regulation of MHC-I by CTSG supports its physiological function in immune system development (Palesch et al., 2016). In cancerous cells, upregulated CTSG endorses the transforming growth factor β (TGF-β)-mediated signaling and thereby promotes tumor vascularity. Hence, targeting CTSG can reduce VEGF and monocyte chemotactic protein (MCP)-1, leading to diminished micro-vessel density in breast cancer–bone interface (Morimoto-Kamata & Yui, 2017). Morimoto-Kamata, Mizoguchi, Ichisugi, and Yui (2012) and Wilson, Nannuru, Futakuchi, and Singh (2010) have disclosed that CTSG mediates MCF-7 cell aggregation through proteolytic cleavage of cell surface molecules, resulting in increased cell motility and switching of the cell-extracellular matrix adhesion to E-cadherin-mediated cell-cell adhesion (Yui, Tomita, Kudo, Ando, & Yamazaki, 2005; Yui et al., 2009; Yui, Osawa, Ichisugi, & Morimoto-Kamata, 2014) (Fig. 3). Recently, Woo et al. (2017) showed that CTSG targeting selectively enhances the TRAIL-mediated apoptosis in renal carcinoma, lung cancer, and cervical cancer through downregulation of survivin *via* 5-lipoxygenase mediated ROS production. Overall, it is well-established that CTSG regulates cell-cell interaction. Therefore, there is a high probability that it acts in the advanced stages of cancer progression.

3. Therapeutic potential of CTS regulation in cancer

3.1. Physiological CTS inhibitors

Under physiological conditions, CTS are tightly regulated by various distantly localized endogenous inhibitors including cystatins, thyropsin, propeptides, members of the serpin (serine peptidase inhibitors) family, and α2-macroglobulin inhibitors (reviewed in Dubin, 2005 and Janko, Ana, & Bojana, 2014). Cystatins are reversible competitive inhibitors of C1 cysteine proteases, classified into three families: type-I cystatins (stefins A and B) are expressed intracellularly, type-II cystatins contain the signal sequence for extracellular secretion (cystatins C, D, E/M, S, SA, and SN) (Turk & Bode, 1991), and type-III cystatins (kininogens) are multifunctional and multidomain glycoproteins having three family-2 cystatin domains, two of which (domains 2 and 3) encompass protease inhibitory activities. The cleaving ability of CTSD for cystatin C and inhibitory domains of kininogen support the significant role of CTSD in cysteine CTS regulation (reviewed in Turk et al., 2012). Association of CTS and cystatin can regulate malignancy. Likewise, higher levels of cystatin can promote the survival of cancer patients (Magister & Kos, 2013). For example, upregulated CTSB with downregulation of stefin A promotes brain tumor malignancy, while higher levels of stefins A and B in non-small cell lung tissues prevent tumor-associated proteolysis as evident by better survival of patients (Werle et al., 2006). Downregulation of cystatins C and E/M (type II cystatins) result in promoting malignancy in the breast, brain, and prostate carcinomas through enhanced proteolysis. Thus, cystatins C and E/M are also defensive in nature (Cox, Sexton, Green, & Darmani, 1999; Zhang et al., 2004; Ai et al., 2006; Qiu et al., 2008; Pulukuri, Gorantla, Knost, & Rao, 2009; Magister & Kos, 2013). Similarly, extracellular translocation of the cystatin II family also impairs ECM degradation, thereby regulating tumor cell invasion and metastasis. Implantation of cystatin E/M-expressing MDA-MB-435S breast cancer cells in SCID mice resulted in significant delay in primary tumor growth and diminished the lung and liver metastasis, further reinforcing that cystatin E/M suppresses tumor cell proliferation at the secondary site (Zhang et al., 2004; Shridhar et al., 2004).

Furthermore, cystatin C abrogates the binding of TGF-β by binding to the TGF-β type II receptors, thereby further regulating tumor progression. Unlike the other type II cystatins, cystatin F is present in endosomes and lysosomes. Its activation into monomer occurs in endosomal/lysosomal vesicles through proteolytic cleavage of its N-terminal portion, which is a potent inhibitor of CTSC, CTSH, and CTSL. In the tumor microenvironment, inactive dimeric cystatin F is secreted from tumor cells or immune cells and further taken up by cytotoxic cells. Subsequent monomerization and inhibition of cysteine CTS within the endosomal/lysosomal vesicles impairs the granzyme and perforin activation and provokes cell anergy. Therefore, cystatin F is an important mediator used by bystander cells to reduce NK and T-cell cytotoxicity. However, a higher level of cystatin F mRNA in the colorectal cancer tissues correlates with both liver metastasis and poor patient prognosis (Utsunomiya et al., 2002). Upregulated extracellular cystatins

such as cystatin C and stefins are also associated with higher risk of adverse outcomes in melanoma and colorectal cancer patients, demonstrating the involvement of type II cystatins in antitumor cellular mechanisms such as anti-tumor immune response, apoptosis, and protease mediated tumor regression (reviewed in Kos & Lah, 1998). Interestingly, down-regulation of tumorigenesis through a similar mechanism is also indicated for a family-3 cystatin (AHSG) which inhibits colon carcinogenesis by blocking the TGF-β1 binding to cell surface receptors and thereby suppressing TGF-β signal transduction (Swallow et al., 2004). Based on the available information, we speculate that besides concentration, the cell and tissue localization of cystatins make a critical switch for regulation of cysteine proteases after narrowing their broad specificity to enhanced CTS specificity, and promotes a checkpoint for specific stage of tumor progression.

3.2. Natural and chemical inhibitors

The multitude of roles played by different CTS in cancer progression is reflected in the use of various inhibitors for cancer treatment. Generally, natural compounds isolated from plants and microorganisms provide the base for new drug development. In the same way, leupeptin identified from *S. exfoliates* is a peptide aldehyde that possesses significant inhibitory activity against CTSD (in nanomolar range) and CTSB (in millimolar range) (Vidal-Albalat & Gonzalez, 2016). Contrarily, their non-selective inhibitory mechanism and contradictory outcomes on different tumors discouraged researchers for further exploring its antitumor function. Recent reports indicate that curcumin inhibits mammalian CTSB and CTSH with IC_{50} in the nanomolar range under *in vitro* conditions. However, various studies reveal the enhancement of CTSB and CTSL activities in curcumin-mediated apoptosis in different carcinoma cell lines (Chen et al., 2012; Terlikowska et al., 2014; Moustapha et al., 2015). To reach any conclusion, further *in vivo* studies are required to determine the utilization of curcumin as CTS inhibitor or enhancer of CTS cytotoxicity. Vidal-Albalat and Gonzalez (2016) have summarized additional details of few other natural compounds possessing significant inhibitory activity toward CTS with IC_{50} value from nanomolar to micromolar range, such as agathisflavone, tetrahydrobustaflavone, quercetin, Grassystatin B, Lichostatinal, cycloaltilisin 6, Miraziridine A, Tokaramide, Nikolaiodesin C, Guttiferone A, β-urosolic acid, *etc.* Although the exact inhibitory mechanism and clinical trials of these natural isolates are yet to be studied, natural flavonoids are known to control cancer cell progression through autophagy/apoptosis regulation (Paul, Jakhar, Bhardwaj, & Kang, 2015; Jakhar, Paul, Bhardwaj, & Kang, 2016; Singh, Park, Khaket, & Kang, 2017; Khan, Bahuguna, et al., 2018). So, exploration of natural flavonoids as anti-CTS agents might provide some invaluable tools as anti-cancerous agents.

Among the cysteine CTS inhibitors, epoxysuccinyl based E-64 isolated from *Aspergillus japonicas* is the most thoroughly studied covalent irreversible cysteine CTS inhibitor, except for its effect on CTSC (less sensitive as compared to CTSB, CTSL, and others) (Paulick & Bogyo, 2011; Turk et al., 2012). However, its broad specificity, less permeability, and irreversible inhibition are the main hurdles in its application, since targeted selectivity and delivery are required for targeted anticancer drug development. As alternatives, epoxysuccinyl based E-64 derivatives including E-64d with improved cellular permeability have been developed, while to enhance specificity, some other derivatives such as JPM-OEt and CTSB specific CA074 have been designed with more specific activity to CTS (Table 1). Although the pan-cathepsin inhibitor JPM-OEt has successfully been used in the treatment of pancreatic

Table 1
Cathepsins inhibitor showed anticancer properties in preclinical studies.

Cathepsin	Inhibitors	Cancer	References
CTSB	CA-074	Breast	Withana et al. (2012) Schurigt et al. (2008)
	Nitroxoline	Breast	Mirkovic et al. (2015)
CTSC	GFDMK	Colorectal	Khaket et al., Unpublished
CTSK	AFG495	Breast	Le Gall et al. (2007)
	L-235	Breast	Duong, Wesolowski, Leung, Oballa, & Pickarski (2014)
	odanacatib	Breast and Prostate	Jensen et al. (2010) Gauthier et al. (2008)
CTSL	miR-152	Gastrointestinal	Lu et al. (2018)
	CLIK148	Mandibular	Katunuma et al. (1999, 2002)
	CLIK195	Mandibular	Katunuma et al. (1999)
	nepsul-Ile-Trp-CHO	Neuroblastoma Osteosarcoma	Zheng et al. (2009)
	KGP94	Breast	Sudhan, Rabaglino, et al. (2016)
	(2Z)-2-[(3-bromophenyl)(2-fluorophenyl)methylidene]hydrazinecarbothioamide	Prostate	Kishore Kumar et al. (2010)
CTSS	*Z*-FL-COCHO	Renal	Seo et al. (2017) Huang, Lee, Lin, & Chang (2016)
	Fsn0503h	Colorectal	Burden et al. (2009); Zhang et al. (2015) Vazquez et al. (2015): Kwok et al. (2011)
	(*S*)-N-(1-cyanocyclopropyl)-3-(methylsulfonyl)-2-(((*S*)-2,2,2-trifluoro-1-(4-fluorophenyl) ethyl)amino) propanoate	Breast	Wilkinson, Young, Burden, Williams, & Scott (2016)
CTSX	d (1(2,3dihydrobenzo[b][1,4]dioxin6yl)2((4isopropyl4H1,2,4triazol3yl)thio)ethan1one)	Prostate	Fonovic et al. (2017)
CTSD	Pepstatin A	Breast	Johnson, Torri, Lippman, & Dickson (1993)
		Neuroblastoma	Soori, Lu, & Mason (2016)
		Colorectal	Trincheri, Nicotra, Follo, Castino, & Isidoro (2007)
CTSB/L/S	Fmoc-Tyr-Ala-CHN2 (FYAD)	Neuroblastoma	Colella et al. (2010), Cartledge, Colella, Glazewski, Lu, & Mason (2013)
	JPM-OEt	Breast and Pancreatic	Joyce et al. (2004) Schurigt et al. (2008)
	Z-Phe-Arg-fluoromethylketone	Pancreatic	Van Noorden, Jonges, Meade-Tollin, Smith, & Koehler (2000)
	VBP-825	Pancreatic	Elie et al. (2010)

neuroendocrine cancer in a mouse model, successive failures in the treatment of breast cancer, particularly breast-to-bone metastasis, have also demonstrated the poor bioavailability of this inhibitor (Withana et al., 2012); this can substantially be improved using liposome-targeted drug delivery of an acidic derivative of the same inhibitor (JPM-565), resulting in antitumor effects comparable to gene ablation studies in the same breast cancer model (Mikhaylov et al., 2011).

CA-074 is a specific inhibitor for CTSB capable of reducing cancer cell growth and promotion, including metastasis of a syngeneic mouse mammary tumor to bone (Withana et al., 2012). Owing to the poor cell permeability, off-target binding, and irreversible nature of inhibition, epoxy-succinyl inhibitors have not been introduced into clinical practice. However, reversible peptidyl inhibitors with carbonyl, nitriles, methylketones, trifluoromethylketones, α-ketoacids, α-ketoesters, α-ketoamides, α-keto-β-aldehydes, diketones, and dipeptide nitriles such as azapeptide nitriles, have been discovered as a new group of reversible covalent inhibitors of CTSB (Kos et al., 2015). Nitroxoline is an established antibiotic for treating urinary tract infections, and is found to regulate cancer progression by regulating the CTSB endopeptidase activity (Mirkovic et al., 2015). Hence, it can synergistically impair tumor progression, resulting in a significant reduction of tumor growth and metastasis in animal cancer models.

Dipeptide-derived diazoketones such as Gly-Phe-CHN2, acyloxymethyl ketones, vinyl sulfones, and nitrile warhead based peptidic inhibitors have also been developed for CTSC (Kam et al., 2004; reviewed in Guay et al., 2009 and Laine & Busch-Petersen, 2010). They have higher specificity for CTSC as compared to other CTS (Table 1). However, most have been terminated in preclinical testing possibly because high-level inhibition of enzyme activity is required to achieve therapeutically significant effects (Hunter et al., 2013), or due to the compensatory role of CTSH. Therefore, the field of investigation of CTSC inhibitors is still in its early stages for cancer regulation.

Katunuma, Tsuge, Nukatsuka, and Fukushima (2002) presented that exposure to epoxysuccinate-based CTSL inhibitors, namely CLIK-148 and CLIK-195, not only attenuate cancer-associated bone resorption and hypercalcemia, but also lead to a significant reduction in metastatic burden. Kishore Kumar, Chavarria, Charlton-Sevcik, Arispe, et al. (2010) generated and screened a library of functionalized benzophenone, thiophene, pyridine, and fluorene thiosemicarbazone derivatives as potent inhibitors of CTSL. Besides, CTSL inhibition by KGP94 significantly impairs the metastasis-associated tumor cell functions such as migration, invasion, and lung colonization (Sudhan & Siemann, 2013; Sudhan, Rabaglino, et al., 2016). In contrast, treatment with the CTSL specific inhibitor CLIK-148 resulted in decreased metastasis of human melanoma to the bone (Katunuma et al., 2002), and a partial decrease in the invasiveness of human glioblastoma *in vitro* (Zajc, Sever, Bervar, & Lah, 2002) (Table 1). Recently, Wilder et al. (2016) observed the reciprocal response of CTSL and S in the presence of E-64 and cystatin C in breast cancer cells, indicating cellular feedback to sustain the amount of active CTSS selectively.

Targeting of CTSS by specific inhibitors such as 4-Morpholineurea-Leu-HomoPhe-vinylsulphone (LHVS29) α-ketoamides, Fsn0503 and *Z*-FL-COCHO (ZFL) decreases the invasion efficiency and mobility of cancerous cells (Burden et al., 2009; Chen et al., 2010; Yang et al., 2010; Fan et al., 2012). Of these, LHVS is an irreversible inhibitor while ZFL is a reversible inhibitor of cathepsin S having preclinical efficacy in cancer models. ZFL induces autophagy-related apoptosis in nasopharyngeal carcinoma and glioblastoma cells. Synthetic α-ketoamide compound-mediated anticancer effects are also attributed to their effects on autophagy and apoptosis, paralleling with inhibiting angiogenesis, invasion, and migration (Chen, Chang, et al., 2012) (Table 1). Recently, Gautam et al. (2018) identified that BJ-2302, a novel 7-azaindolin-2-one derivative, possessing combinatorial inhibitory activity for CTSS and MMP-9.

Considering all CTS, inhibition of CTSK has been intensively investigated by the pharmaceutical industry for osteoporosis and other bone mineralization-based diseases, though most have failed in clinical trials. However, scarce information is available regarding their implementation in controlling cancer. Among the numerous CTSK inhibitors, Odanacatib has especially been studied for breast and prostate cancer bone metastasis. However, similar to other CTSK inhibitors, it was discontinued after Phase III clinical trials. A few additional broad-spectrum inhibitors including VBY-825 (Elie et al., 2010) and GB111-NH2 (Salpeter et al., 2015) have also been developed (Table 1).

Till date, there are very few scaffolds reported for CTSD inhibition including hydroxyl ethyl isosteres with cyclic tertiary amines, synthetic oligopeptides, and non-peptidic acylguanidine. Ahmed et al. (2013) identified N-(3-chlorophenyl)-2-sulfamoylbenzamide as a potential CTSD inhibitor having micromolar IC_{50} value (1.25 μM). Pepstatin A is the most potent CTSD inhibitor having an IC_{50} of 0.1 nM. However, a low membrane penetration is the main hurdle in its implications for *in vivo* studies (Free, Hurley, Kageyama, Chain, & Tabor, 2006). To overcome this limitation, several pepstatins and cell penetrating peptide (CPP) conjugates were studied to enhance pepstatin bioavailability for lysosomal CTSD, but these conjugates were not successful in inhibiting lysosomal CTSD (Wender et al., 2000). Surprisingly, JMV4463, a conjugate of 2-aminomethyl-phenyl-acetic acid tetramer and pepstatin showed higher cellular penetration and CTSD inhibition. This conjugate exhibited significant anti-proliferative effect with altered cell cycle associated with apoptotic events in cancer cell lines in both *in vivo and in vitro* studies (Maynadier et al., 2013). Because ProCTSD is also involved in cancer progression, researchers need to consider cell to cell interactions when targeting CTSD enzyme activity.

Most efforts are now focused on the synthesis of reversible inhibitors including peptidyl aldehydes, amides, ketohetero-cycles, aliphatic ketones, and nitriles. In spite of CTS involvement in cancer progression, CTS could be a consequence of the action of drugs by triggering tumor cell apoptosis and prodrug processing. CTSB is known to activate various prodrugs such as doxorubicin, paclitaxel, and doxazolidine at the site of action (Shao et al., 2012). Though a large number of CTS inhibitors have been developed and screened, none has progressed into the clinic because of their accompanying moderate-to-severe side effects. Problems encountered are due to species variations and lysosomal accumulation of basic compounds (*i.e.*, lysosomotropism) that lead to off-target effects in cellular studies.

3.3. Combinatorial therapy of CTS targeting accompanied by conventional anticancer treatments

The E-64 based pan-cathepsin inhibitor JPM-OEt enhances chemotherapy regimens in a multistage cancer mouse model (Bell-McGuinn, Garfall, Bogyo, Hanahan, & Joyce, 2007). The majority of CTS are produced by tumor-associated macrophages, further arguing for the use of broad-spectrum non-cell-permeable inhibitors that would only block harmful extracellular CTS. This is further substantiated by the finding that combined treatment of conventional anti-cancerous compound and broad-spectrum CTS inhibitors significantly improves the treatment sensitivity (Roberg & Ollinger, 1998; Shree et al., 2011; Small et al., 2013). Consistent with these studies, CTSL targeting not only enhances the sensitivity of tumor cells against various chemotherapeutic agents (Zheng, Chou, Mirkin, & Rebbaa, 2004; Zheng et al., 2009), but also effectively reverses resistance to various cytotoxic and targeted agents including doxorubicin, paclitaxel, etoposide, imatinib, trichostatin A, and tamoxifen (Sui, Shi, Yan, & Wu, 2016; Zao et al., 2018). CTSC targeting by GFDMK in multidrug resistant cells also endorses the drug sensitivity (Khaket et al., unpublished). Indeed, CTSL suppression further alleviates the sensitivity of apoptotic agents such as staurosporine and anticas in glioblastoma (Levicar et al., 2003). Doxorubicin combined with a CTSL and CTSB-specific inhibitors induces senescence in human and murine drug-resistant cell lines (Zheng et al., 2004). Under *in vivo* conditions, a combination of

chemotherapeutics with both a broad-spectrum CTS inhibitor and a CTSL specific inhibitor (Zheng et al., 2009) has shown favorable results. Studies have also shown that CTSL inhibition improves the sensitivity of chemotherapeutic agents and effectively reverses the resistance to various cytotoxic agents including doxorubicin, etoposide, imatinib, trichostatin A, and tamoxifen (Katunuma et al., 2002; Zheng et al., 2004, 2009; reviewed in Sudhan & Siemann, 2015; Zhang et al., 2016). Wang et al. (2016) demonstrated that radio-resistance of glioblastoma stem-like cell is attributed to CTSL and CD133. Combined treatment with radiotherapy and CTSL inhibition significantly reduces the GSC growth and promotes apoptosis, consequently augmenting radiosensitivity (Wang et al., 2016). Recently, Fei et al. (2016) predicted that the activity of CTSL can be enhanced in curcumin-treated glioma cells, while CTSL knockdown significantly promoted the curcumin-induced cytotoxicity, apoptosis, cell cycle arrest, and inhibited invasion of glioma cells. Even, targeting of CTSL in X-ray irradiated human glioma U251 cells significantly increased the irradiation-induced DNA damage and G2/M phase cell cycle arrest and apoptosis (Zhang et al., 2015). The majority of anti-cancer drug therapy failures may be attributed to either inherent or acquired resistance. Hence, if drug sensitivity restoration by CTSL inhibition could be successfully translated to the clinic, such a strategy could have a significant impact on patient treatment outcome.

In addition to CTS targeting, co-treatment of CPT-11 with a neutralizing CTSS antibody enhanced the treatment outcome in colorectal carcinoma (Burden et al., 2009). Combinatorial treatment of CTSS inhibitor ZFL also enhances oxaliplatin-mediated apoptosis through ER stress-induced Bim upregulation in Caki cells (Seo et al., 2018). This concept extends beyond chemotherapy, as radiation therapy also induces CTSS expression in IFNγ-dependent manner, thus providing a rationale for combining CTSS inhibitors with radiotherapy (Navab et al., 2008). Intriguingly, simultaneous inhibition of CTSB, CTSL, and CTSS has recently been shown to induce tumor-associated macrophage-associated apoptosis that subsequently leads to the non-autonomous death of neighboring cancer cells (Kirschke et al., 2000). Recently, Gautam et al. (2018) identified a src inhibitor BJ-2302 which is a novel 7-azaindolin-2-one derivative. Since, Src is an upstream marker of cell growth pathways (including PI3K/Akt and Ras/Raf/ERK pathways), it might also be responsible for the expression of CTSS and MMP-9. Also, it effectively suppresses cell invasion and metastasis without any toxicity on normal cells. Hence, targeting of upstream regulators seems to be more promising for cancer regulation, as compared to CTS targeting.

Despite the inhibitory potential, the use of activity-based activatable fluorescent probes that are essentially irreversible active-site inhibitors equipped with appropriate fluorophores and fluorescent substrates (Biniossek, Nagler, Becker-Pauly, & Schilling, 2011; Zhang et al., 2015), also directs the therapeutic potential of CTS. Recently, Zhang et al. (2018) synthesized a novel prodrug GAM from gemcitabine with a CTSB-sensitive linker that provides hyper-selective tumor bioactivation with lower off-target toxicity, and is capable of bypassing acquired drug resistance. This synthesis enhances the prospects of specific CTS based conventional prodrug formation and their subsequent activation (Zhang et al., 2018). Similarly, CTSB cleavable valine-citrulline dipeptide linked with doxorubicin enhances the antitumor efficacy of doxorubicin, both in the *in vivo* and *in vitro* systems (Liang et al., 2018). CTSE specific prodrug 5-aminolevulinic acid (5-ALA) associated with photodynamic therapy can be selectively activated by endogenous CTSE within the pancreatic ductal adenocarcinoma (Abd-Elgaliel, Cruz-Monserrate, Wang, Logsdon, & Tung, 2013).

3.4. Limitations of CTS targeting

Contrary to the above researches, the proteolytic function of all CTS has not been deciphered. Given the critical normal tissue functions of some CTS, indiscriminate inhibition of all members of the CTS family could potentially entail the same negative consequences as reported for the application of broad-spectrum MMP inhibitors (reviewed in Turk, 2006). A likely factor underlying the failure of MMP inhibitors in a clinical trial is their lack of specificity. To date, no CTS inhibitor has passed clinical oncology trials. This likely reflects the complex roles that CTS play in tumor biology. Long-term administration of selective inhibitors of individual CTS poses a potential risk of therapeutic resistance through compensation by other CTS family members. Thus, the simultaneous inhibition of tumor-promoting CTS could potentially yield a better outcome. Pleiotropic functioning of individual CTS is the principle concern for researchers by individual targeting through either allosterically targeting of CTS, blocking substrate specific targeting, or by ameliorating three-dimensional structures of CTS (reviewed in Kramer, Turk, & Turk, 2017). However, similar to gene ablation studies, either broad spectrum or selective CTS inhibitors are able to cure cancer individually. Thus, CTS inhibition in combinational therapies with established chemotherapeutics would be a promising anticancer approach.

4. Conclusion

Upregulated levels of lysosomal and extracellular CTS with cancer progression are crucial for malignant tumor progression. However, cytosolic CTS induces both tumor growth and cell death; this localization-based CTS functioning and their compensatory roles further complicate CTS based anticancer drug development. Therefore, CTS based drug or synthetic inhibitors need to be designed by considering their extra-lysosomal activities during cancer progression. Moreover, a combination of conventional chemotherapies with CTS inhibition would provide additional secondary therapeutic benefits involving autophagy hindrance and diminished cancer recurrence. Since there are pros and cons for the use of either selective or broad-spectrum inhibitors in cancer, it is very likely that CTS inhibitors will not be used as a monotherapy, while combined therapy of CTS specific inhibitors in conjunction with other radiotherapy/chemotherapy will conceivably be a valuable approach for cancer treatment.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

This work was supported by the Korea Research Fellowship Program (KRF 2016H1D3A1938249) and National Research Foundation of Korea grants [NRF-2017R1D1A1B03036569, NRF-2016R1A2B4009227, (MSIP) NRF-2016R1A2B2013393 and (MSIP) NRF-2014R1A5A2010008].

References

Abd-Elgaliel, W. R., Cruz-Monserrate, Z., Wang, H., Logsdon, C. D., & Tung, C. H. (2013). Pancreatic cancer-associated Cathepsin E as a drug activator. *Journal of Controlled Release 167*, 221–227.

Adkison, A. M., Raptis, S. Z., Kelley, D. G., & Pham, C. T. (2002). Dipeptidyl peptidase I activates neutrophil-derived serine proteases and regulates the development of acute experimental arthritis. *The Journal of Clinical Investigation 109*, 363–371.

Aggarwal, N., & Sloane, B. F. (2014). Cathepsins B: Multiple roles in cancer. *Proteomics. Clinical Applications 8*, 427–437.

Ahmed, W., Khan, I. A., Arshad, M. N., Siddiqui, W. A., Haleem, M. A., & Azim, M. K. (2013). Identification of Sulfamoylbenzamide derivatives as selective Cathepsin D inhibitors. *Pakistan Journal of Pharmaceutical Sciences 26*, 687–690.

Ai, L., Kim, W. J., Kim, T. Y., Fields, C. R., Massoll, N. A., Robertson, K. D., et al. (2006). Epigenetic silencing of the tumor suppressor cystatin M occurs during breast cancer progression. *Cancer Research 66*, 7899–7909.

Akkari, L., Gocheva, V., Kester, J. C., Hunter, K. E., Quick, M. L., Sevenich, L., et al. (2014). Distinct functions of macrophage-derived and cancer cell-derived cathepsins Z combine to promote tumor malignancy via interactions with the extracellular matrix. *Genes & Development 28*, 2134–2150.

Alatrash, G., Garber, H. R., Zhang, M., Sukhumalchandra, P., Qiu, Y., Jakher, H., et al. (2017). Cathepsin G is broadly expressed in acute myeloid leukemia and is an effective immunotherapeutic target. *Leukemia 31*, 234–237.

Altorjay, A., Paal, B., Sohar, N., Kiss, J., Szanto, I., & Sohar, I. (2005). Significance and prognostic value of lysosomal enzyme activities measured in surgically operated

adenocarcinomas of the gastroesophageal junction and squamous cell carcinomas of the lower third of esophagus. *World Journal of Gastroenterology 11*, 5751–5756.
Andreesen, R., Hennemann, B., & Krause, S. W. (1998). Adoptive immunotherapy of cancer using monocyte derived macrophages:Rationale, current status, and perspectives. *Journal of Leukocyte Biology 64*, 419–426.
Andreu, P., Johansson, M., Affara, N. I., Pucci, F., Tan, T., Junankar, S., et al. (2010). FcRγ activation regulates inflammation associated squamous carcinogenesis. *Cancer Cell 17*, 121–134.
Asagiri, M., Hirai, T., Kunigami, T., Kamano, S., Gober, H. J., Okamoto, K., et al. (2008). Cathepsin K-dependent toll-like receptor 9 signaling revealed in experimental arthritis. *Science 319*, 624–627.
Atwa, H. A., & Arafa, S. A. (2016). Significance of TGF-β1 and Cathepsin E expression in gastric adenocarcinoma and precancerous lesions. *Journal of American Science 12*, 59–67.
Barbarin, A., & Frade, R. (2011). Procathepsins L secretion, which triggers tumor progression, is regulated by Rab4a in human melanoma cells. *The Biochemical Journal 437*, 97–107.
Bazzett, L. B., Watkins, C. S., Gercel-Taylor, C., & Taylor, D. D. (1999). Modulation of proliferation and chemosensitivity by procathepsin D and its peptides in ovarian cancer. *Gynecologic Oncology 74*, 181–187.
Bell-McGuinn, K. M., Garfall, A. L., Bogyo, M., Hanahan, D., & Joyce, J. A. (2007). Inhibition of cysteine cathepsin protease activity enhances chemotherapy regimens by decreasing tumor growth and invasiveness in a mouse model of multistage cancer. *Cancer Research 67*, 7378–7385.
Benes, P., Vetvicka, V., & Fusek, M. (2008). Cathepsin D-many functions of one aspartic protease. *Critical Reviews in Oncology/Hematology 68*, 12–28.
Bengsch, R., Buck, A., Gunther, S. C., Seiz, J. R., Tacke, M., Pfeifer, D., et al. (2014). Cell type-dependent pathogenic functions of overexpressed human cathepsinB in murine breast cancer progression. *Oncogene 33*, 4474–4484.
Berchem, G., Glondu, M., Gleizes, M., Brouillet, J. P., Vignon, F., Garcia, M., & Liaudet-Coopman, E. (2002). Cathepsin D affects multiple tumor progression steps in vivo: Proliferation, angiogenesis and apoptosis. *Oncogene 21*, 5951–5955.
Bernhardt, A., Kuester, D., Roessner, A., Reinheckel, T., & Krueger, S. (2010). Cathepsin X-deficient gastric epithelial cells in co-culture with macrophages: Characterization of cytokine response and migration capability after helicobacter pylori infection. *The Journal of Biological Chemistry 285*, 33691–33700.
Bian, B., Mongrain, S., Cagnol, S., Langlois, M. J., Boulanger, J., Bernatchez, G., et al. (2016). Cathepsin B promotes colorectal tumorigenesis, cell invasion, and metastasis. *Molecular Carcinogenesis 55*, 671–687.
Bidere, N., Lorenzo, H. K., Carmona, S., Laforge, M., Harper, F., Dumont, C., et al. (2003). Cathepsin D triggers Bax activation, resulting in selective apoptosis-inducing factor (AIF) relocation in T lymphocytes entering the early commitment phase to apoptosis. *The Journal of Biological Chemistry 278*, 31401–31411.
Biniossek, M. L., Nagler, D. K., Becker-Pauly, C., & Schilling, O. (2011). Proteomic identification of protease cleavage sites characterizes prime and non-prime specificity of cysteine cathepsins B, L, and S. *Journal of Proteome Research 10*, 5363–5373.
Biswas, S. K., Allavena, P., & Mantovani, A. (2013). Tumor-associated macrophages: Functional diversity, clinical significance, and open questions. *Seminars in Immunopathology 35*, 585–600.
Blomgran, R., Zheng, L., & Stendahl, O. (2007). Cathepsin-cleaved bid promotes apoptosis in human neutrophils via oxidative stress-induced lysosomal membrane permeabilization. *Journal of Leukocyte Biology 81*, 1213–1223.
Bossard, M. J., Tomaszek, T. A., Thompson, S. K., Amegadzie, B. Y., Hanning, C. R., Jones, C., et al. (1996). Proteolytic activity of human osteoclast cathepsin K. Expression, purification, activation, and substrate identification. *The Journal of Biological Chemistry 271*, 12517–12524.
Bromme, D., Okamoto, K., Wang, B. B., & Biroc, S. (1996). Human cathepsin O2, a matrix protein-degrading cysteine protease expressed in osteoclasts. Functional expression of human cathepsin O_2 in *Spodoptera frugiperda* and characterization of the enzyme. *The Journal of Biological Chemistry 271*, 2126–2132.
Brubaker, K. D., Vessella, R. L., True, L. D., Thomas, R., & Corey, E. (2003). Cathepsin K mRNA and protein expression in prostate cancer progression. *Journal of Bone and Mineral Research 18*, 222–230.
Bruchard, M., Mignot, G., Derangère, V., Chalmin, F., Chevriaux, A., Vegran, F., et al. (2013). Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. *Nature Medicine 19*, 57–64.
Buck, M. R., Karustis, D. G., Day, N. A., Honn, K. V., & Sloane, B. F. (1992). Degradation of extracellular-matrix proteins by human cathepsin B from normal and tumour tissues. *The Biochemical Journal 282*, 273–278.
Buhler, A., Berger, S., Bengsch, F., Martin, G., Han, H., Vierkotten, S., et al. (2013). Cathepsins proteases promote angiogenic sprouting and laser-induced choroidal neovascularisation in mice. *Experimental Eye Research 115*, 73–78.
Bullon, P., Castejon-Vega, B., Roman-Malo, L., Jimenez-Guerrero, M. P., Cotan, D., et al. (2018). Autophagic dysfunction in patients with Papillon-Lefèvre syndrome is restored by recombinant cathepsin C treatment. *The Journal of Allergy and Clinical Immunology 142* (1131-1143.e7).
Burden, R. E., Gormley, J. A., Jaquin, T. J., Small, D. M., Quinn, D. J., et al. (2009). Antibody-mediated inhibition of cathepsin S blocks colorectal tumor invasion and angiogenesis. *Clinical Cancer Research 15*, 6042–6051.
Burton, L. J., Dougan, J., Jones, J., Smith, B. N., Randle, D., Henderson, V., et al. (2017). Targeting the nuclear cathepsin L CCAAT displacement protein/cut Homeobox transcription factor-epithelial mesenchymal transition pathway in prostate and breast cancer cells with the Z-FY-CHO inhibitor. *Molecular and Cellular Biology 37* e00297.
Cartledge, D. M., Colella, R., Glazewski, L., Lu, G., & Mason, R. W. (2013). Inhibitors of cathepsins B and L induce autophagy and cell death in neuroblastoma cells. *Investigational New Drugs 31*, 20–29.
Chang, S. H., Kanasaki, K., Gocheva, V., Blum, G., Harper, J., Moses, M. A., et al. (2009). VEGF-A induces angiogenesis by perturbing the cathepsin-cysteine protease inhibitor balance in venules, causing basement membrane degradation and mother vessel formation. *Cancer Research 69*, 4537–4544.
Chen, B., & Platt, M. O. (2011). Multiplex zymography captures stage-specific activity profiles of cathepsins K, L, and S in human breast, lung, and cervical cancer. *Journal of Translational Medicine 9*, 109.
Chen, J. C., Uang, B. J., Lyu, P. C., Chang, J. Y., Liu, K. J., et al. (2010). Design and synthesis of alpha-ketoamides as cathepsin S inhibitors with potential applications against tumor invasion and angiogenesis. *Journal of Medicinal Chemistry 53*, 4545–4549.
Chen, K. L., Chang, W. S., Cheung, C. H., Lin, C. C., Huang, C. C., Yang, Y. N., et al. (2012). Targeting cathepsin S induces tumor cell autophagy via the EGFR-ERK signaling pathway. *Cancer Letters 317*, 89–98.
Chen, Q. Y., Shi, J. G., Yao, Q. H., Jiao, D. M., Wang, Y. Y., Hu, H. Z., et al. (2012). Lysosomal membrane permeabilization is involved in curcumin-induced apoptosis of A549 lung carcinoma cells. *Molecular and Cellular Biochemistry 359*, 389–398.
Cirman, T., Oresic, K., Mazovec, G. D., Turk, V., et al. (2004). Selective disruption of lysosomes in HeLa cells triggers apoptosis mediated by cleavage of bid by multiple papain-like lysosomal cathepsins. *The Journal of Biological Chemistry 279*, 3578–3587.
Colella, R., Lu, G., Glazewski, L., Korant, B., Matlapudi, A., England, M. R., ... Mason, R. W. (2010). Induction of cell death in neuroblastoma by inhibition of cathepsins B and L. *Cancer Letters 294*, 195–203.
Cox, J. L., Sexton, P. S., Green, T. J., & Darmani, N. A. (1999). Inhibition of B16 melanoma metastasis by overexpression of the cysteine proteinase inhibitor cystatin C. *Melanoma Research 9*, 369–374.
De Marco, C., Laudanna, C., Rinaldo, N., Oliveira, D. M., Ravo, M., Weisz, A., et al. (2017). Specific gene expression signatures induced by the multiple oncogenic alterations that occur within the PTEN/PI3K/AKT pathway in lung cancer. *PLoS One 12* e0178865.
Dean, R. A., & Overall, C. M. (2007). Proteomics discovery of metalloproteinase substrates in the cellular context by iTRAQ labeling reveals a diverse MMP-2 substrate degradome. *Molecular & Cellular Proteomics 6*, 611–623.
DeNardo, D. G., Brennan, D. J., Rexhepaj, E., Ruffell, B., Shiao, S. L., Madden, S. F., et al. (2011). Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discovery 1*, 54–67.
Dennemarker, J., Lohmüller, T., Mayerle, J., Tacke, M., Lerch, M. M., Coussens, L. M., et al. (2010). Deficiency for the cysteine protease cathepsin L promotes tumor progression in mouse epidermis. *Oncogene 29*, 1611–1621.
Desgrosellier, J. S., & Cheresh, D. A. (2010). Integrins in cancer: Biological implications and therapeutic opportunities. *Nature Reviews. Cancer 10*, 9–22.
Dhawan, D., Hahn, N. M., Ramos-Vara, J. A., & Knapp, D. W. (2018). Naturally-occurring canine invasive urothelial carcinoma harbors luminal and basal transcriptional subtypes found in human muscle invasive bladder cancer. *PLoS Genetics 14*, e1007571.
Drake, F. H., Dodds, R. A., James, I. E., Connor, J. R., Debouck, C., Richardson, S., et al. (1996). Cathepsin K, but not Cathepsins B, L, or S, is abundantly expressed in human osteoclasts. *The Journal of Biological Chemistry 271*, 12511–12516.
Droga-Mazovec, G., Bojic, L., Petelin, A., Ivanova, S., et al. (2008). Cysteine cathepsins trigger caspase dependent cell death through cleavage of bid and antiapoptotic Bcl-2 homologues. *The Journal of Biological Chemistry 283*, 19140–19150.
Dubin, G. (2005). Proteinaceous cysteine protease inhibitors. *Cellular and Molecular Life Sciences 62*, 653–669.
Duong, L. T., Wesolowski, G. A., Leung, P., Oballa, R., & Pickarski, M. (2014). Efficacy of a cathepsin K inhibitor in a preclinical model for prevention and treatment of breast cancer bone metastasis. *Molecular Cancer Therapeutics 13*, 2898–2909.
Ebert, M. R., Kruger, S., Fogeron, M. L., Lamer, S., et al. (2005). Overexpression of cathepsin B in gastric cancer identified by proteome analysis. *Proteomics 5*, 1693–1704.
Elie, B. T., Gocheva, V., Shree, T., Dalrymple, S. A., Holsinger, L. J., & Joyce, J. A. (2010). Identification and pre-clinical testing of a reversible cathepsin protease inhibitor reveals anti-tumor efficacy in a pancreatic cancer model. *Biochimie 92*, 1618–1624.
Fan, Q., Wang, X., Zhang, H., Li, C., Fan, J., et al. (2012). Silencing cathepsin S gene expression inhibits growth, invasion and angiogenesis of human hepatocellular carcinoma in vitro. *Biochemical and Biophysical Research Communications 425*, 703–710.
Faridi, J. S., Mohan, S., & De Leon, D. D. (2004). Modulation of cathepsin D routing by IGF-II involves IGF-II binding to IGF-II/M6P receptor in MCF-7 breast cancer cells. *Growth Factors 22*, 169–177.
Fei, X., Qin, Z., & Liang, Z. (2007). Contribution of CDP/Cux, a transcription factor, to cell cycle progression. *Acta Biochimica et Biophysica Sinica Shanghai 39*, 923–930.
Fei, Y., Xiong, Y., Zhao, Y., Wang, W., Han, M., Wang, L., et al. (2016). Cathepsin L knockdown enhances curcumin-mediated inhibition of growth, migration, and invasion of glioma cells. *Brain Research 1646*, 580–588.
Ferreras, M., Felbor, U., Lenhard, T., Olsen, B. R., & Delaisse, J. (2000). Generation and degradation of human endostatin proteins by various proteinases. *FEBS Letters 486*, 247–251.
Fisher, O. M., Levert-Mignon, A. J., Lord, S. J., Botelho, N. K., Freeman, A. K., Thomas, M. L., et al. (2015). High expression of Cathepsin E in tissues but not blood of patients with Barrett's Esophagus and adenocarcinoma. *Annals of Surgical Oncology 22*, 2431–2438.
Fonovic, U. P., Mitrovic, A., Knez, D., Jakos, T., Pislar, A., & Brus, B. (2017). Identification and characterization of the novel reversible and selective cathepsin X inhibitors. *Scientific Reports 7*, 11459.
Free, P., Hurley, C. A., Kageyama, T., Chain, B. M., & Tabor, A. B. (2006). Mannose–pepstatin conjugates as targeted inhibitors of antigen processing. *Organic & Biomolecular Chemistry 4*, 1817–1830.

Fristrup, N., Ulhoi, B. P., Birkenkamp-Demtroder, K., et al. (2012). Cathepsin E, maspin, Plk1, and survivin are promising prognostic protein markers for progression in non-muscle invasive bladder cancer. *The American Journal of Pathology 180*, 1824–1834.

Garcia-Cattaneo, A., Gobert, F. X., Müller, M., Toscano, F., Flores, M., Lescure, A., et al. (2012). Cleavage of toll-like receptor 3 by cathepsins B and H is essential for signaling. *Proceedings of the National Academy of Sciences of the United States of America 109*, 9053–9058.

Gautam, J., Banskota, S., Lee, H., Lee, Y. J., Jeon, Y. H., Kim, J. A., & Jeong, B. S. (2018). Down-regulation of cathepsin S and matrix metalloproteinase-9 via Src, a non-receptor tyrosine kinase, suppresses triple-negative breast cancer growth and metastasis. *Experimental & Molecular Medicine 50*, 118.

Gauthier, J. Y., Chauret, N., Cromlish, W., Desmarais, S., Duong, L. T., Falgueyret, J. P., et al. (2008). The discovery of odanacatib (MK-0822), a selective inhibitor of cathepsin K. *Bioorganic & Medicinal Chemistry Letters 18*, 923–928.

Girotti, M. R., Rernandez, M., Lopez, J. A., Camafeita, E., et al. (2011). SPARC promotes cathepsin B-mediated melanoma invasiveness through a collagen I/alpha2beta1 integrin axis. *The Journal of Investigative Dermatology 737*, 2438–2447.

Glondu, M., Liaudet-Coopman, E., Derocq, E., Platet, N., Rochefort, H., & Garcia, M. (2002). Down-regulation of cathepsin-D expression by antisense gene transfer inhibits tumor growth and experimental lung metastasis of human breast cancer cells. *Oncogene 21*, 5127–5134.

Gocheva, V., & Joyce, J. A. (2007). Cysteine cathepsins and the cutting edge of cancer invasion. *Cell Cycle 6*, 60–64.

Gocheva, V., Wang, H. W., Gadea, B. B., Shree, T., Hunter, K. E., Garfall, A. L., Berman, T., Joyce, J. A., et al. (2010). IL-4 induces cathepsin protease activity in tumor-associated macrophages to promote cancer growth and invasion. *Genes & Development 24*, 241–255.

Gocheva, V., Zeng, W., Ke, D., Klimstra, D., Reinheckel, T., Peters, C., et al. (2006). Distinct roles for cysteine cathepsin genes in multistage tumorigenesis. *Genes & Development 20*, 543–556.

Gole, B., Duran Alonso, M. B., Dolenc, V., & Lah, T. (2009). Post-translational regulation of cathepsin B, but not of other cysteine cathepsins, contributes to increased glioblastoma cell invasiveness in vitro. *Pathology Oncology Research 15*, 711–723.

Gonzalez-Vela, M. C., Garijo, M. F., Fernandez, F., Buelta, L., & Val-Bernal, J. F. (1999). Cathepsin D in host stromal cells is associated with more highly vascular and aggressive invasive breast carcinoma. *Histopathology 34*, 35–42.

Gopinathan, A., Denicola, G. M., Frese, K. K., Cook, N., Karreth, F. A., Mayerle, J., et al. (2012). Cathepsin B promotes the progression of pancreatic ductal adenocarcinoma in mice. *Gut 61*, 877–884.

Gregory, A. D., & Houghton, A. M. (2011). Tumor-associated neutrophils: New targets for cancer therapy. *Cancer Research 71*, 2411–2416.

Griffith, T. S., Wiley, S. R., Kubin, M. Z., Sedger, L. M., Maliszewski, C. R., & Fanger, N. A. (1999). Monocyte mediated tumoricidal activity via the tumor necrosis factor related cytokine, TRAIL. *The Journal of Experimental Medicine 189*, 1343–1354.

Grotsky, D. A., Gonzalez-Suarez, I., Novell, A., Neumann, M. A., Yaddanapudi, S. C., Croke, M., et al. (2013). BRCA1 loss activates cathepsin L-mediated degradation of 53BP1 in breast cancer cells. *The Journal of Cell Biology 200*, 187–202.

Guay, D., Beaulieu, C., Truchon, J. F., Jagadeeswar Reddy, T., Zamboni, R., Bayly, C. I., et al. (2009). Design and synthesis of dipeptidyl nitriles as potent, selective, and reversible inhibitors of cathepsin C. *Bioorganic & Medicinal Chemistry Letters 19*, 5392–5396.

Guo, B., Fu, S., Zhang, J., Liu, B., & Li, Z. (2016). Targeting inflammasome/IL-1 pathways for cancer immunotherapy. *Scientific Reports 6*, 36107.

Hah, Y. S., Noh, H. S., Ha, J. H., Ahn, J. S., Hahm, J. R., Cho, H. Y., et al. (2012). Cathepsin D inhibits oxidative stress-induced cell death via activation of autophagy in cancer cells. *Cancer Letters 323*, 208–214.

Hamon, Y., Legowska, M., Herve, V., Dallet-Choisy, S., Marchand-Adam, S., Vanderlynden, L., et al. (2016). Neutrophilic Cathepsin C is maturated by a multistep Proteolytic process and secreted by activated cells during inflammatory lung diseases. *The Journal of Biological Chemistry 291*, 8486–8499.

Han, M. A., Min, K. J., Woo, S. M., Seo, B. R., & Kwon, T. K. (2016). Eupafolin enhances TRAIL-mediated apoptosis through cathepsin S-induced down-regulation of Mcl-1 expression and AMPK-mediated Bim up-regulation in renal carcinoma Caki cells. *Oncotarget 7*, 65707–65720.

Heinrich, M., Neumeyer, J., Jakob, M., Hallas, C., Tchikov, V., Winoto-Morbach, S., et al. (2004). Cathepsin D links TNF-induced acid sphingomyelinase to bid-mediated caspase-9 and -3 activation. *Cell Death and Differentiation 11*, 550–563.

Herroon, M. K., Rajagurubandara, E., Rudy, D. L., Chalasani, A., Hardaway, A. L., & Podgorski, I. (2013). Macrophage cathepsin K promotes prostate tumor progression in bone. *Oncogene 32*, 1580–1593.

Hira, V. V. V., Ploegmakers, K. J., Verbovsek, U., Roing, C. S., Aronica, E. M. A., Tigchelaar, W., et al. (2015). CD133+ and nestin+ glioma stem-like cells reside around CD31+ arterioles in niches that express SDF-1. CXCR4, osteopontin and cathepsin K. *The Journal of Histochemistry and Cytochemistry 63*, 481–493.

Hsu, Y. H., Hsing, C. H., Li, C. F., Chan, C. H., Chang, M. C., Yan, J. J., et al. (2012). Anti-IL-20 monoclonal antibody suppresses breast cancer progression and bone osteolysis in murine models. *Journal of Immunology 15*, 1981–1991.

Hu, L., Roth, J. M., Brooks, P., Luty, J., & Karpatkin, S. (2008). Thrombin up-regulates cathepsin D which enhances angiogenesis, growth, and metastasis. *Cancer Research 68*, 4666–4673.

Huang, C. C., Lee, C. C., Lin, H. H., & Chang, J. Y. (2016). Cathepsin S attenuates endosomal EGFR signalling: A mechanical rationale for the combination of cathepsin S and EGFR tyrosine kinase inhibitors. *Scientific Reports 6*, 29256.

Hunter, K. E., Palermo, C., Kester, J. C., Simpson, K., Li, J. P., Tang, L. H., et al. (2013). Heparanase promotes lymphangiogenesis and tumor invasion in pancreatic neuroendocrine tumors. *Oncogene 33*, 1799–1808.

Husi, H., MacDonald, A., Skipworth, R. J. E., Miller, J., Cronshaw, A., Fearon, K. C. H., et al. (2018). Proteomic identification of potential markers of myosteatosis in human urine. *Biomedical Reports 8*, 557–564.

Illy, C., Quraishi, O., Wang, J., Purisima, E., Vernet, T., & Mort, J. S. (1997). Role of the occluding loop in cathepsin B activity. *The Journal of Biological Chemistry 272*, 1197–1202.

Ishida, M., Kojima, F., & Okabe, H. (2013). Cathepsin K expression in basal cell carcinoma. *Journal of the European Academy of Dermatology and Venereology 27*, e128–e130.

Ishidoh, K., & Kominami, E. (1995). Procathepsin L degrades extracellular matrix proteins in the presence of glycosaminoglycans *in vitro*. *Biochemical and Biophysical Research Communications 217*(624–63), 1.

Jain, M., Bakhshi, S., Shukla, A. A., & Chauhan, S. S. (2010). Cathepsins B and L in peripheral blood mononuclear cells of pediatric acute myeloid leukemia: Potential poor prognostic markers. *Annals of Hematology 89*, 1223–1232.

Jakhar, R., Paul, S., Bhardwaj, M., & Kang, S. C. (2016). Astemizole-histamine induces Beclin-1-independent autophagy by targeting p53-dependent crosstalk between autophagy and apoptosis. *Cancer Letters 372*, 89–100.

Janko, K., Ana, M., & Bojana, M. (2014). The current stage of cathepsin B inhibitors as potential anticancer agents. *Future Medicinal Chemistry 6*, 1355–1371.

Jechorek, D., Votapek, J., Meyer, F., Kandulski, A., Roessner, A., & Franke, S. (2014). Characterization of cathepsin X in colorectal cancer development and progression. *Pathology, Research and Practice 210*, 822–829.

Jensen, A. B., Wynne, C., Ramirez, G., He, W., Song, Y., Berd, Y., et al. (2010). The cathepsin K inhibitor odanacatib suppresses bone resorption in women with breast cancer and established bone metastases: Results of a 4-week, double-blind, randomized, controlled trial. *Clinical Breast Cancer 10*, 452–458.

Jevnikar, Z., Obermajer, N., Bogyo, M., & Kos, J. (2008). The role of cathepsin X in the migration and invasiveness of T lymphocytes. *Journal of Cell Science 121*, 2652–2661.

Jia, R. J., Lan, C. G., Wang, X. C., & Gao, C. T. (2018). Integrated analysis of gene expression and copy number variations in MET proto-oncogene-transformed human primary osteoblasts. *Molecular Medicine Reports 17*, 2543–2548.

Jiang, H., Cheng, X. W., Shi, G. P., Hu, L., Inoue, A., Yamamura, Y., et al. (2014). Cathepsin K-mediated Notch1 activation contributes to neovascularization in response to hypoxia. *Nature Communications 5*, 3838.

Johansson, A. C., Steen, H., Ollinger, K., & Roberg, K. (2003). Cathepsin D mediates cytochrome c release and caspase activation in human fibroblast apoptosis induced by staurosporine. *Cell Death and Differentiation 10*, 1253–1259.

Johnson, M. D., Torri, J. A., Lippman, M. E., & Dickson, R. B. (1993). The role of cathepsin D in the invasiveness of human breast cancer cells. *Cancer Research 53*, 873–877.

Joyce, J. A., Baruch, A., Chehade, K., Meyer-Morse, N., Giraudo, E., Tsai, F. Y., et al. (2004). Cathepsin cysteine proteases are effectors of invasive growth and angiogenesis during multistage tumorigenesis. *Cancer Cell 5*, 443–453.

Joyce, J. A., & Pollard, J. W. (2009). Microenvironmental regulation of metastasis. *Nature Reviews. Cancer 9*, 239–252.

Kam, C. M., Gotz, M. G., Koot, G., McGuire, M., Thiele, D., Hudig, D., & Powers, J. C. (2004). Designand evaluation of inhibitors for dipeptidyl peptidase I (cathepsin C). *Archives of Biochemistry and Biophysics 427*, 123–134.

Katunuma, N., Murata, E., Kakegawa, H., Matsui, A., Tsuzuki, H., Tsuge, H., et al. (1999). Structure based development of novel specific inhibitors for cathepsin L and cathepsin S in vitro and in vivo. *FEBS Letters 458*, 6–10.

Katunuma, N., Tsuge, H., Nukatsuka, M., & Fukushima, M. (2002). Structure-based development of cathepsin L inhibitors and therapeutic applications for prevention of cancer metastasis and cancer-induced osteoporosis. *Advances in Enzyme Regulation 42*, 159–172.

Kawakubo, T., Okamoto, K., Iwata, J., Shin, M., Okamoto, Y., Yasukochi, A., et al. (2007). Cathepsin E prevents tumor growth and metastasis by catalyzing the proteolytic release of soluble TRAIL from tumor cell surface. *Cancer Research 67*, 10869–10878.

Kawakubo, T., Yasukochi, A., Nakamura, S., & Yamamoto, K. (2011). Cathepsin E as a potent anticancer protease. *Journal of Oral Biosciences 53*, 128–136.

Kawakubo, T., Yasukochi, A., Toyama, T., Takahashi, S., Okamoto, K., Tsukuba, T., et al. (2014). Repression of cathepsin E expression increases the risk of mammary carcinogenesis and links to poor prognosis in breast cancer. *Carcinogenesis 35*, 714–726.

Kayagaki, N., Yamaguchi, N., Nakayama, M., Takeda, K., Akiba, H., Tsutsui, H., et al. (1999). Expression and function of TNF related apoptosis-inducing ligand on murine activated NK cells. *Journal of Immunology 163*, 1906–1913.

Keerthivasan, S., Keerthivasan, S., Keerthivasan, G., Mittal, S., & Chauhan, S. S. (2007). Transcriptional upregulation of human cathepsin L by VEGF in glioblastoma cells. *Gene 399*, 129–136.

Khaket, T. P., Dhanda, S., Jodha, D., & Singh, J. (2016). Biochemical studies on dipeptidyl peptidase I (cathepsin C) from germinated *Vigna radiata* seeds. *Process Biochemistry 51*, 1015–1027.

Khaket, T. P., & Singh, J. (2017). Potential of plant's dipeptidyl peptidase I & II homologs in generation of ACE inhibitory peptides. *International Journal of Peptide Research and Therapeutics 23*, 81.

Khaket, T. P., Singh, M. P., Khan, I., Bhardwaj, M., & Kang, S. C. (2018). Targeting of cathepsin C induces autophagic dysregulation that directs ER stress mediated cellular cytotoxicity in colorectal cancer cells. *Cellular Signalling 46*, 92–102.

Khan, I., Bahuguna, A., Bhardwaj, M., Khaket, T. P., & Kang, S. C. (2018). Carvacrol nanoemulsion evokes cell cycle arrest, apoptosis induction and autophagy inhibition in doxorubicin resistant-A549 cell line. *Artificial Cells Nanomedicine Biotechnology 6*, 1–12.

Khan, M., Carmona, S., Sukhumalchandra, P., Roszik, J., Philips, A., Perakis, A. A., et al. (2018). Cathepsin G is expressed by acute lymphoblastic leukemia and is a potential immunotherapeutic target. *Frontiers in Immunology 8*, 1975.

Kirschke, H., Eerola, R., Hopsu-Havu, V. K., Bromme, D., & Vuorio, E. (2000). Antisense RNA inhibition of CTS L expression reduces tumorigenicity of malignant cells. *Eur. J. Cancer 36*, 787–795.

Kishore Kumar, G. D., Chavarria, G. E., Charlton-Sevcik, A. K., Arispe, W. M., et al. (2010). Design, synthesis, and biological evaluation of potent thiosemicarbazone based cathepsin L inhibitors. *Bioorganic & Medicinal Chemistry Letters 20*, 1415–1419.

Kitazawa, S., Nishizawa, S., Nakagawa, H., Funata, M., Nishimura, K., Soga, T., et al. (2017). Cancer with low cathepsin D levels is susceptible to vacuolar (H+)-ATPase inhibition. *Cancer Science 108*, 1185–1193.

Klose, A., Wilbrand-Hennes, A., Zigrino, P., Weber, E., Krieg, T., Mauch, C., & Hunzelmann, N. (2006). Contact of high-invasive, but not low-invasive, melanoma cells to native collagen I induces the release of mature cathepsin B. *International Journal of Cancer 118*, 2735–2743.

Kobayashi, H., Schmitt, M., Goretzki, L., Chucholowski, N., Calvete, J., Kramer, M., et al. (1991). Cathepsin B. Efficiently activates the soluble and the tumor cell receptor-bound form of the proenzyme urokinase-type plasminogen activator (pro-uPA). *The Journal of Biological Chemistry 266*, 5147–5152.

Kolwijck, E., Massuger, L. F., Thomas, C. M., Span, P. N., Krasovec, M., Kos, J., & Sweep, F. C. (2010). Cathepsins B, L and cystatin C in cyst fluid of ovarian tumors. *Journal of Cancer Research and Clinical Oncology 136*, 771–778.

Kominami, E., Tsukahara, T., Hara, K., & Katunuma, N. (1988). Biosyntheses and processing of lysosomal cysteine proteinases in rat macrophages. *FEBS Letters 231*, 225–228.

Konno-Shimizu, M., Yamamichi, N., Inada, K., Kageyama Yahara, N., Shiogama, K., Takahashi, Y., et al. (2013). Cathepsin E is a marker of gastric differentiation and signet-ring cell carcinoma of stomach: A novel suggestion on gastric tumorigenesis. *PLoS One 8* e56766.

Korenc, M., Lenarcic, B., & Novinec, M. (2015). Human cathepsin L, a papain-like collagenase without proline specificity. *The FEBS Journal 282*, 4328–4340.

Korkmaz, B., Caughey, G. H., Chapple, I., Gauthier, F., Hirschfeld, J., Jenne, D. E., & Kettritz, R. (2018). Therapeutic targeting of cathepsin C: From pathophysiology to treatment. *Pharmacology & Therapeutics 190*, 202–236.

Korkmaz, B., Horwitz, M. S., Jenne, D. E., & Gauthier, F. (2010). Neutrophil elastase, proteinase 3, and cathepsin G as therapeutic targets in human diseases. *Pharmacological Reviews 62*, 726–759.

Kos, J., & Lah, T. T. (1998). Cysteine proteases and their endogenous inhibitors: Target proteins for prognosis, diagnosis and therapy in cancer (review). *Oncology Reports 5*, 1349–13461.

Kos, J., Vizin, T., Fonovic, U. P., & Pislar, A. (2015). Intracellular signaling by cathepsin X: Molecular mechanisms and diagnostic and therapeutic opportunities in cancer. *Seminars in Cancer Biology 31*, 76–83.

Kostoulas, G., Lang, A., Nagase, H., & Baici, A. (1999). Stimulation of angiogenesis through cathepsin B inactivation of the tissue inhibitors of matrix metalloproteinases. *FEBS Letters 455*, 286–290.

Kos, J., Jevnikar, Z., & Obermajer, N. (2009). The role of cathepsin X in cell signaling. *Cell Adhes Migr 3*, 164–166.

Kramer, L., Turk, D., & Turk, B. (2017). The future of cysteine cathepsins in disease management. *Trends in Pharmacological Sciences 38*, 873–898.

Kraus, S., Bunsen, T., Schuster, S., Cichoń, M. A., Tacke, M., Reinheckel, T., et al. (2011). Cellular senescence induced by cathepsin X downregulation. *European Journal of Cell Biology 90*, 678–686.

Kraus, S., Fruth, M., Bunsen, T., & Nagler, D. K. (2012). IGF-I receptor phosphorylation is impaired in cathepsin X-deficient prostate cancer cells. *Biological Chemistry 393*, 1457–1462.

Krepela, E., Kasafirek, E., Novak, K., & Viklicky, J. (1990). Increased cathepsin B activity in human lung tumors. *Neoplasma 37*, 61–70.

Krepela, E., Vicar, J., & Cernoch, M. (1989). Cathepsin B in human breast tumor tissue and cancer cells. *Neoplasma 36*, 41–52.

Krueger, S., Haeckel, C., Buehling, F., & Roessner, A. (1999). Inhibitory effects of antisense cathepsin B cDNA transfection on invasion and motility in a human osteosarcoma cell line. *Cancer Res 59*, 6010–6014.

Krueger, S., Kalinski, T., Hundertmark, T., Wex, T., Küster, D., Peitz, U., et al. (2005). Up-regulation of cathepsin X in helicobacter pylori gastritis and gastric cancer. *The Journal of Pathology 207*, 32–42.

Kwok, H. F., Buick, R. J., Kuehn, D., Gormley, J. A., Doherty, D., & Jaquin, T. J. (2011). Antibody targeting of Cathepsin S induces antibody-dependent cellular cytotoxicity. *Molecular Cancer 10*, 147.

Lah, T. T., Kalman, E., Najjar, D., Gorodetsky, E., Brennan, P., Somers, R., et al. (2000). Cells producing cathepsin s D, B, and L in human breast carcinoma and their association with prognosis. *Human Pathology 31*, 149–160.

Laine, D. I., & Busch-Petersen, J. (2010). Inhibitors of cathepsin C (dipeptidyl peptidase I). *Expert Opinion on Therapeutic Patents 20*, 497–506.

Laurent-Matha, V., Derocq, D., Prebois, C., Katunuma, N., & Liaudet-Coopman, E. (2006). Processing of human cathepsin D is independent of its catalytic function and autoactivation: Involvement of cathepsin s L and B. *Journal of Biochemistry 139*, 363–371.

Laurent-Matha, V., Maruani-Herrmann, S., Prebois, C., Beaujouin, M., Glondu, M., Noel, A., et al. (2005). Catalytically inactive human cathepsin D triggers fibroblast invasive growth. *The Journal of Cell Biology 168*, 489–499.

Le Gall, C., Bellahcène, A., Bonnelye, E., Gasser, J. A., Castronovo, V., Green, J., ... Clezardin, P. (2007). A cathepsin K inhibitor reduces breast cancer induced osteolysis and skeletal tumor burden. *Cancer Research 67*, 9894–9902.

Lechner, A. M., Assfalg-Machleidt, I., Zahler, S., Stoeckelhuber, M., Machleidt, W., Jochum, M., & Nagler, D. K. (2006). RGD-dependent binding of procathepsin X to integrin αvβ3 mediates cell-adhesive properties. *The Journal of Biological Chemistry 281*, 39588–39597.

Leto, G., Sepporta, M. V., Crescimanno, M., Flandina, C., & Tumminello, F. M. (2010). Cathepsin L in metastatic bone disease: Therapeutic implications. *Biological Chemistry 391*, 655–664.

Leusink, F. K., Koudounarakis, E., Frank, M. H., Koole, R., van Diest, P. J., & Willems, S. M. (2018). Cathepsin K associates with lymph node metastasis and poor prognosis in oral squamous cell carcinoma. *BMC Cancer 18*, 385.

Levicar, N., Dewey, R. A., Daley, E., Bates, T. E., Davies, D., Kos, J., et al. (2003). Selective suppression of cathepsin L by antisense cDNA impairs human brain tumor cell invasion in vitro and promotes apoptosis. *Cancer Gene Therapy 10*, 141–151.

Li, W., Yu, X., Ma, X., Xie, L., Xia, Z., Liu, L., ... Liu, H. (2018). Deguelin attenuates non-small cell lung cancer cell metastasis through inhibiting the cathepsin Z/FAK signaling pathway. *Cellular Signalling 50*, 131–141.

Li, Z. Y., Yang, Y., Ming, M., & Liu, B. (2011). Mitochondrial ROS generation for regulation of autophagic pathways in cancer. *Biochemical and Biophysical Research Communications 414*, 5–8.

Liang, Q., Ouyang, X., Schneider, L., & Zhang, J. (2011). Reduction of mutant huntingtin accumulation and toxicity by lysosomal cathepsin s D and B in neurons. *Molecular Neurodegeneration 6*, 37.

Liang, Y., Li, S., Wang, X., Zhang, Y., Sun, Y., Wang, Y., et al. (2018). A comparative study of the antitumor efficacy of peptide-doxorubicin conjugates with different linkers. *Journal of Controlled Release 275*, 129–141.

Liaudet-Coopman, E., Beaujouin, M., Derocq, D., Garcia, M., Glondu-Lassis, M., Laurent-Matha, V., et al. (2006). Cathepsin D: Newly discovered functions of a long-standing aspartic protease in cancer and apoptosis. *Cancer Letters 237*, 167–179.

Lilla, J. N., & Werb, Z. (2010). Mast cells contribute to the stromal microenvironment in mammary gland branching morphogenesis. *Developmental Biology 337*, 124–133.

Lindeman, J. H., Hanemaaijer, R., Mulder, A., Dijkstra, P. D., Szuhai, K., Bromme, D., ... Hogendoorn, P. C. (2004). Cathepsin K is the principal protease in giant cell tumor of bone. *The American Journal of Pathology 165*, 593–600.

Lines, K. E., Chelala, C., Dmitrovic, B., Wijesuriya, N., Kocher, H. M., Marshall, J. F., et al. (2012). S100P-binding protein, S100PBP, mediates adhesion through regulation of cathepsin Z in pancreatic cancer cells. *The American Journal of Pathology 180*, 1485–1494.

Losch, A., Schindl, M., Kohlberger, P., Lahodny, J., Breitenecker, G., Horvat, R., Birner, P., et al. (2004). Cathepsin D in ovarian cancer: Prognostic value and correlation with p53 expression and microvessel density. *Gynecologic Oncology 92*, 545–552.

Lu, H. J., Yan, J., Jin, P. Y., Zheng, G. H., Qin, S. M., Wu, D. M., et al. (2018). MicroRNA-152 inhibits tumor cell growth while inducing apoptosis via the transcriptional repression of cathepsin L in gastrointestinal stromal tumor. *Cancer Biomarkers 21*, 711–722.

Luan, H., Mohapatra, B., Bielecki, T. A., Mushtaq, I., Mirza, S., Jennings, T. A., et al. (2018). Loss of the nuclear Pool of ubiquitin ligase CHIP/STUB1 in breast Cancer unleashes the MZF1-Cathepsin pro-oncogenic program. *Cancer Research 78*, 2524–2535.

Magister, S., & Kos, J. (2013). Cystatins in immune system. *Journal of Cancer 4*, 45–56.

Martignoni, G., Bonetti, F., Chilosi, M., Brunelli, M., Segala, D., Amin, M. B., et al. (2012). Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. *Modern Pathology 25*, 100–111.

Mason, S. D., & Joyce, J. A. (2011). Proteolytic networks in cancer. *Trends in Cell Biology 21*, 228–237.

Matas, N., Thygesen, P., Stacey, M., Risch, A., & Sim, E. (1997). Mapping AAC1, AAC2 and AACP, the genes for arylamine N-acetyltransferases, carcinogen metabolising enzymes on human chromosome 8p22, a region frequently deleted in tumors. *Cytogenetics and Cell Genetics 77*, 290–295.

Maynadier, M., Vezenkov, L. L., Amblard, M., Martin, V., Gandreuil, C., et al. (2013). Dipeptide mimic oligomer transporter mediates intracellular delivery of Cathepsin D inhibitors: A potential target for cancer therapy. *Journal of Controlled Release 171*, 251–257.

McGuire, M. J., Lipsky, P. E., & Thiele, D. L. (1993). Generation of active myeloid and lymphoid granule serine proteases requires processing by the granule thiol protease dipeptidyl peptidase I. *The Journal of Biological Chemistry 268*, 2458–2467.

McKerrow, J. H., Bhargava, V., Hansell, E., Huling, S., Kuwahara, T., Matley, M., et al. (2000). A functional proteomics screen of proteases in colorectal carcinoma. *Molecular Medicine 6*, 160–450.

Mi, S., Qin, X. W., Lin, Y. F., He, J., Chen, N. N., Liu, C., et al. (2016). Budding of Tiger frog virus (an Iridovirus) from HepG2 cells via three ways recruits the ESCRT pathway. *Scientific Reports 6*, 26581.

Mikhaylov, G., Mikac, U., Magaeva, A. A., Itin, V. I., Naiden, E. P., Psakhye, I., et al. (2011). Ferri-liposomes as an MRI-visible drug-delivery system for targeting tumors and their microenvironment. *Nature Nanotechnology 6*, 594–602.

Mikosch, P., Kerschan-Schindl, K., Woloszczuk, W., Stettner, H., Kudlacek, S., Kresnik, E., ... Pietschmann, P. (2008). High cathepsin K levels in men with differentiated thyroid cancer on suppressive L-thyroxine therapy. *Thyroid 18*, 27–33.

Mirkovic, B., Markelc, B., Butinar, M., Mitrovic, A., Sosic, I., Gobec, S., et al. (2015). Nitroxoline impairs tumor progression in vitro and in vivo by regulating cathepsin B activity. *Oncotarget 6*, 19027–19042.

Mitrovic, A., Pecar Fonovic, U., & Kos, J. (2017). Cysteine cathepsins B and X promote epithelial-mesenchymal transition of tumor cells. *European Journal of Cell Biology 96*, 622–631.

Moreno-Layseca, P., & Streuli, C. H. (2014). Signalling pathways linking integrins with cell cycle progression. *Matrix Biology 34*, 144–153.

Morikawa, W., Yamamoto, K., Ishikawa, S., Takemoto, S., Ono, M., Fukushi, J., et al. (2000). Angiostatin generation by cathepsin D secreted by human prostate carcinoma cells. *The Journal of Biological Chemistry 275*, 38912–38920.

Morimoto-Kamata, R., Mizoguchi, S., Ichisugi, T., & Yui, S. (2012). Cathepsin G induces cell aggregation of human breast cancer MCF-7 cells via a 2-step mechanism: Catalytic site-independent binding to the cell surface and enzymatic activity-dependent induction of the cell aggregation. *Mediators of Inflammation 2012*, 456462.

Morimoto-Kamata, R., & Yui, S. (2017). Insulin-like growth factor-1 signaling is responsible for cathepsin G-induced aggregation of breast cancer MCF-7 cells. *Cancer Science 108*, 1574–1583.

Moustapha, A., Peretout, P. A., Rainey, N. E., Sureau, F., Geze, M., Petit, J. M., ... Petit, P. X. (2015). Curcumin induces crosstalk between autophagy and apoptosis mediated by calcium release from the endoplasmic reticulum, lysosomal destabilization and mitochondrial events. *Cell Death Discovery 1*, 15017.

Mueller-Steiner, S., Zhou, Y., Arai, H., Roberson, E. D., Sun, B., Chen, J., et al. (2006). Antiamyloidogenic and neuroprotective functions of cathepsin B: Implications for Alzheimer's disease. *Neuron 51*, 703–714.

Musil, D., Zucic, D., Turk, D., Engh, R. A., Mayr, I., Huber, R., Popovic, T., et al. (1991). The refined 2.15 a X-ray crystal structure of human liver cathepsin B: The structural basis for its specificity. *The EMBO Journal 10*, 2321–2330.

Nagler, D. K., Kraus, S., Feierler, J., Mentele, R., Lottspeich, F., Jochum, M., et al. (2010). Acysteine-type carboxypeptidase, cathepsin X, generates peptide receptor agonists. *International Immunopharmacology 10*, 134–139.

Nagler, D. K., & Ménard, R. (1998). Human cathepsin X: A novel cysteine protease of the papain family with very short proregion and unique insertions. *FEBS Letters 434*, 135–139.

Navab, R., Pedraza, C., Fallavollita, L., Wang, N., Chevet, E., Auguste, P., et al. (2008). Loss of responsiveness to IGF-I in cells with reduced cathepsin L expression levels. *Oncogene 27*, 4973–4985.

Navari, R. M., Prorok, M., & Castellino, F. J. (2014). Cathepsin E as a marker of colon cancer. Patent No.US 8,637,265 B2 (45).

Nirde, P., Derocq, D., Maynadier, M., Chambon, M., Basile, I., Gary-Bobo, M., & Garcia, M. (2010). Heat shock cognate 70 protein secretion as a new growth arrest signal for cancer cells. *Oncogene 29*, 117–127.

Nishimura, Y., Kawabata, T., & Kato, K. (1988). Identification of latent procathepsins B and L in microsomal lumen: Characterization of enzymatic activation and proteolytic processing in vitro. *Archives of Biochemistry and Biophysics 261*, 64–71.

Novinec, M., Grass, R. N., Stark, W. J., Turk, V., Baici, A., & Lenarcic, B. (2007). Interaction between human cathepsins K, L, and S and elastins: Mechanism of elastinolysis and inhibition by macromolecular inhibitors. *The Journal of Biological Chemistry 282*, 7893–7902.

Obermajer, N., Magister, S., Kopitar, A. N., Tepes, B., Ihan, A., & Kos, J. (2009). Cathepsin X prevents an effective immune response against helicobacter pylori infection. *European Journal of Cell Biology 88*, 461–471.

Obermajer, N., Repnik, U., Jevnikar, Z., Turk, B., Kreft, M., & Kos, J. (2008). Cysteine protease cathepsin X modulates immune response via activation of beta2 integrins. *Immunology 124*, 76–88.

O'Donoghue, A. J., Ivry, S. L., Chaudhury, C., Hostetter, D. R., Hanahan, D., & Craik, C. S. (2016). Procathepsin E is highly abundant but minimally active in pancreatic ductal adenocarcinoma tumors. *Biological Chemistry 397*, 871–881.

Ogawa, S., Yokoyama, Y., Suzukawa, K., Nanmoku, T., Kurita, N., Seki, M., et al. (2015). Identification of a fusion gene composed of a hippo pathway gene MST2 and a common translocation partner ETV6 in a recurrent translocation t(8,12)(q22;p13) in acute myeloid leukemia. *Annals of Hematology 94*, 1431–1433.

Okamoto, K., Yu, H., Misumi, Y., Ikehara, Y., & Yamamoto, K. (1995). Isolation and sequencing of two cDNA clones encoding rat spleen cathepsin E and analysis of the activation of purified procathepsin E. *Archives of Biochemistry and Biophysics 322*, 103–111.

Olson, O. C., & Joyce, J. A. (2015). Cysteine cathepsin proteases: Regulators of cancer progression and therapeutic response. *Nature Reviews. Cancer 15*, 712–729.

Palesch, D., Wagner, J., Meid, A., Molenda, N., Sienczyk, M., Burkhardt, J., et al. (2016). Cathepsin G-mediated proteolytic degradation of MHC class I molecules to facilitate immune detection of human glioblastoma cells. *Cancer Immunology Immunotherapy 65*, 283–291.

Pandey, G., Bakhshi, S., Thakur, B., Jain, P., & Chauhan, S. S. (2018). Prognostic significance of cathepsin L expression in pediatric acute myeloid leukemia. *Leukemia & Lymphoma 59*, 2175–2187.

Paul, S., Jakhar, R., Bhardwaj, M., & Kang, S. C. (2015). Glutathione-S-transferase omega 1 (GSTO1-1) acts as mediator of signaling pathways involved in aflatoxin B1-induced apoptosis-autophagy crosstalk in macrophages. *Free Radical Biology & Medicine 89*, 1218–1230.

Paulick, M. G., & Bogyo, M. (2011). Development of activity-based probes for cathepsin X. *ACS Chemical Biology 6*, 563–572.

Pecar Fonovic, U., Jevnikar, Z., Rojnik, M., Doljak, B., Fonovic, M., Jamnik, P., et al. (2013). Profilin 1 as a target for cathepsin X activity in tumor cells. *PLoS One 8* e53918.

Pham, C. T., & Ley, T. J. (1999). Dipeptidyl peptidase I is required for the processing and activation of granzymes a and B *in vivo*. *Proceedings of the National Academy of Sciences of the United States of America 96*, 8627–8632.

Piwnica, D., Fernandez, I., Binart, N., Touraine, P., Kelly, P. A., & Goffin, V. (2006). A new mechanism for prolactin processing into 16K PRL by secreted cathepsin D. *Molecular Endocrinology 20*, 3263–3278.

Piwnica, D., Touraine, P., Struman, I., Tabruyn, S., Bolbach, G., Clapp, C., et al. (2004). Cathepsin D processes human prolactin into multiple 16K-like N-terminal fragments: Study of their antiangiogenic properties and physiological relevance. *Molecular Endocrinology 18*, 2522–2542.

Pranjol, M. Z. I., Gutowski, N. J., Hannemann, M., & Whatmore, J. L. (2018). Cathepsin D non-proteolytically induces proliferation and migration in human omental microvascular endothelial cells via activation of the ERK1/2 and PI3K/AKT pathways. *Biochimica et Biophysica Acta 1865*, 25–33.

Pulukuri, S. M., Gorantla, B., Knost, J. A., & Rao, J. S. (2009). Frequent loss of cystatin E/M expression implicated in the progression of prostate cancer. *Oncogene 28*, 2829–2838.

Qiu, J., Ai, L., Ramachandran, C., Yao, B., Gopalakrishnan, S., Fields, C. R., et al. (2008). Invasion suppressor cystatin E/M (CST6): High-level cell type-specific expression in normal brain and epigenetic silencing in gliomas. *Laboratory Investigation 88*, 910–925.

Quraishi, O., Nagler, D. K., Fox, T., Sivaraman, J., Cygler, M., Mort, J. S., Storer, A. C., et al. (1999). The occluding loop in cathepsin B defines the pH dependence of inhibition by its propeptide. *Biochemistry 38*, 5017–5023.

Rao Malla, R., Gopinath, S., Alapati, K., Gorantla, B., Gondi, C. S., & Rao, J. S. (2013). Knockdown of cathepsin B and uPAR inhibits CD151 and alpha3beta1 integrin-mediated cell adhesion and invasion in glioma. *Molecular Carcinogenesis 52*, 777–790.

Rao, Q., Cheng, L., Xia, Q. Y., Liu, B., Li, L., Shi, Q. L., et al. (2013). Cathepsin K expression in a wide spectrum of perivascular epithelioid cell neoplasms (PEComas): A clinicopathological study emphasizing extrarenal PEComas. *Histopathology 62*, 642–650.

Rao, Q., Wang, Y., Xia, Q. Y., Shi, S. S., Shen, Q., Tu, P., et al. (2014). Cathepsin K in the immunohistochemical diagnosis of melanocytic lesions. *International Journal of Clinical and Experimental Pathology 7*, 1132–1139.

Ratovitski, T., Chighladze, E., Waldron, E., Hirschhorn, R. R., & Ross, C. A. (2011). Cysteine proteases bleomycin hydrolase and cathepsin Z mediate N-terminal proteolysis and toxicity of mutant huntingtin. *The Journal of Biological Chemistry 286*, 12578–12589.

Reinheckel, T., Hagemann, S., Dollwet-Mack, S., Martinez, E., Lohmüller, T., Zlatkovic, G., et al. (2005). The lysosomal cysteine protease cathepsin L regulates keratinocyte proliferation by control of growth factor recycling. *Journal of Cell Science 118*, 3387–3395.

Reisenauer, A., Eickelberg, O., Wille, A., Heimburg, A., Reinhold, A., Sloane, B. F., ... Bühling, F. (2007). Increased carcinogenic potential of myeloid tumor cells induced by aberrant TGR-beta1-signaling and upregulation of cathepsin B. *Biological Chemistry 388*, 639–650.

Rempel, S. A., Rosenblum, M. L., Mikkelsen, T., Yan, P. S., Ellis, K. D., Golembieski, W. A., et al. (1994). Cathepsin B expression and localization in glioma progression and invasion. *Cancer Research 54*, 6027–6031.

Ren, G., Tian, Q., An, Y., Feng, B., Lu, Y., Liang, J., et al. (2012). Coronin 3 promotes gastric cancer metastasis via the up-regulation of MMP-9 and cathepsin K. *Molecular Cancer 11*, 67.

Roberg, K., & Ollinger, K. (1998). Oxidative stress causes relocation of the lysosomal enzyme cathepsin D with ensuing apoptosis in neonatal rat cardiomyocytes. *The American Journal of Pathology 152*, 1151–1156.

Ruffell, B., Affara, N. I., Cottone, L., Junankar, S., Johansson, M., DeNardo, et al. (2013). Cathepsin C is a tissue-specific regulator of squamous carcinogenesis. *Genes & Development 27*, 2086–2098.

Salpeter, S. J., Pozniak, Y., Merquiol, E., Ben-Nun, Y., Geiger, T., & Blum, G. (2015). A novel cysteine cathepsin inhibitor yields macrophage cell death and mammary tumor regression. *Oncogene 34*, 6066–6078.

Samaiya, M., Bakhshi, S., Shukla, A. A., Kumar, L., & Chauhan, S. S. (2011). Epigenetic regulation of cathepsin L expression in chronic myeloid leukaemia. *Journal of Cellular and Molecular Medicine 15*, 2189–2199.

Satelli, A., & Li, S. (2011). Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cellular and Molecular Life Sciences 68*, 3033–3046.

Schraufstatter, I. U., Trieu, K., Zhao, M., Rose, D. M., Terkeltaub, R. A., & Burger, M. (2003). IL-8-mediated cell migration in endothelial cells depends on cathepsin B activity and transactivation of the epidermal growth factor receptor. *Journal of Immunology 171*, 6714–6722.

Schurigt, U., Hummel, K. M., Petrow, P. K., Gajda, M., Stockigt, R., Middel, P., et al. (2008). Cathepsin K deficiency partially inhibits, but does not prevent, bone destruction in human tumor necrosis factor-transgenic mice. *Arthritis and Rheumatism 58*, 422–434.

Seo, B. R., Min, K. J., Woo, S. M., Choe, M., Choi, K. S., Lee, Y. K., et al. (2017). Inhibition of Cathepsin S induces mitochondrial ROS that sensitizes TRAIL-mediated apoptosis through p53-mediated Downregulation of Bcl-2 and c-FLIP. *Antioxidants & Redox Signaling 27*, 215–233.

Seo, S. U., Woo, S. M., Min, K. J., & Kwon, T. K. (2018). Z-FL-COCHO, a cathepsin S inhibitor, enhances oxaliplatin-induced apoptosis through upregulation of Bim expression. *Biochemical and Biophysical Research Communications 498*, 849–854.

Sevenich, L., Bowman, R. L., Mason, S. D., Quail, D. F., Rapaport, F., Elie, B. T., et al. (2014). Analysis of tumor- and stroma-supplied proteolytic networks reveals a brain-metastasis-promoting role for cathepsin S. *Nature Cell Biology 16*, 876–888.

Sevenich, L., Schurigt, U., Sachse, K., Gajda, M., Werner, F., Muller, S., et al. (2010). Synergistic antitumor effects of combined cathepsin B and cathepsin Z deficiencies on breast cancer progression and metastasis in mice. *Proceedings of the National Academy of Sciences of the United States of America 107*, 2497–2502.

Sevenich, L., Werner, R., Gajda, M., Schurigt, U., Sieber, C., Muller, S., et al. (2011). Transgenic expression of human cathepsin B promotes progression and metastasis of polyoma-middle-T-induced breast cancer in mice. *Oncogene 30*, 54–64.

Shao, G., Wang, R., Sun, A., Wei, J., Peng, K., Dai, Q., et al. (2018). The E3 ubiquitin ligase NEDD4 mediates cell migration signaling of EGFR in lung cancer cells. *Molecular Cancer 17*, 24.

Shao, L. H., Liu, S. P., Hou, J. X., Zhang, Y. H., Peng, C. W., Zhong, Y. J., et al. (2012). Cathepsin B cleavable novel prodrug ac-Phe-Lys-PABC-ADM enhances efficacy at reduced toxicity in treating gastric cancer peritoneal carcinomatosis: An experimental study. *Cancer 118*, 2986–2996.

Shin, M., Kadowaki, T., Iwata, J., Kawakubo, T., Yamaguchi, N., Takii, R., et al. (2007). Association of cathepsin E with tumor growth arrest through angiogenesis inhibition and enhanced immune responses. *Biological Chemistry 388*, 1173–1181.

Shree, T., Olson, O. C., Elie, B. T., Kester, J. C., Garfall, A. L., Simpson, K., et al. (2011). Macrophages and cathepsin proteases blunt chemotherapeutic response in breast cancer. *Genes & Development 25*, 2465–2479.

Shridhar, R., Zhang, J., Song, J., Booth, B. A., Kevil, C. G., Sotiropoulou, G., et al. (2004). Cystatin M suppresses the malignant phenotype of human MDA-MB-435S cells. *Oncogene 23*, 2206–2215.

Singh, M. P., Park, K. H., Khaket, T. P., & Kang, S. C. (2017). CJK-7, a novel flavonoid from Paulownia tomentosa, triggers cell death cascades in HCT-116 human colon carcinoma cells via redox signaling. *Anti-Cancer Agents in Medicinal Chemistry*. https://doi.org/10.2174/1871520617666171026170009.

Singh, N., Das, P., Gupta, S., Sachdev, V., Srivasatava, S., Datta Gupta, S., et al. (2014). Plasma cathepsin L: A prognostic marker for pancreatic cancer. *World Journal of Gastroenterology 20*, 17532–17540.

Sinha, A. A., Morgan, J. L., Buus, R. J., Ewing, S. L., Fernandes, E. T., Le, C., Wilson, M. J., et al. (2007). Cathepsin B expression is similar in African-American and Caucasian prostate cancer patients. *Anticancer Research 27*, 3135–3141.

Sivaraman, J., Nagler, D. K., Zhang, R., Menard, R., & Cygler, M. (2000). Crystal structure of human procathepsin X: A cysteine protease with the proregion covalently linked to the active site cysteine. *Journal of Molecular Biology 295*, 939–951.

Small, D. M., Burden, R. E., Jaworski, J., Hegarty, S. M., Spence, S., et al. (2013). Cathepsin S from both tumor and tumor-as-sociated cells promote cancer growth and neovascularization. *International Journal of Cancer 133*, 2102–2112.

Soderstrom, M., Ekfors, T., Bohling, T., Aho, A., Aro, H. T., & Vuorio, E. (2001). Cysteine proteinases in chondrosarcomas. *Matrix Biology 19*, 717–725.

Son, H., & Moon, A. (2010). Epithelial-mesenchymal transition and cell invasion. *Toxicology Research 26*, 245–252.

Soori, M., Lu, G., & Mason, R. W. (2016). Cathepsin inhibition prevents Autophagic protein turnover and Downregulates insulin growth Factor-1 receptor-mediated Signaling in Neuroblastoma. *The Journal of Pharmacology and Experimental Therapeutics 356*, 375–386.

Srisomsap, C., Subhasitanont, P., Otto, A., Mueller, E. C., Punyarit, P., Wittmann-Liebold, B., & Svasti, J. (2002). Detection of cathepsin B up-regulation in neoplastic thyroid tissues by proteomic analysis. *Proteomics 2*, 706–712.

Staudt, N. D., Aicher, W. K., Kalbacher, H., Stevanovic, S., Carmona, A. K., Bogyo, M., et al. (2010). Cathepsin X is secreted by human osteoblasts, digests CXCL-12 and impairs adhesion of hematopoietic stem and progenitor cells to osteoblasts. *Haematologica 95*, 1452–1460.

Stoka, V., Turk, B., Schendel, S. L., Kim, T. H., Cirman, T., Snipas, S. J., et al. (2001). Lysosomal protease pathways to apoptosis. Cleavage of bid, not pro-caspases, is themost likely route. *Journal of Biological Chemistry 276*, 3149–3157.

Sudhan, D. R., Pampo, C., Rice, L., & Siemann, D. W. (2016). Cathepsin L inactivation leads to multimodal inhibition of prostate cancer cell dissemination in a preclinical bone metastasis model. *International Journal of Cancer 138*, 2665–2677.

Sudhan, D. R., Rabaglino, M. B., Wood, C. E., & Siemann, D. W. (2016). Cathepsin L in tumor angiogenesis and its therapeutic intervention by the small molecule inhibitor KGP94. *Clinical & Experimental Metastasis 33*, 461–473.

Sudhan, D. R., & Siemann, D. W. (2013). Cathepsin L inhibition by the small molecule KGP94 suppresses tumor microenvironment enhanced metastasis associated cell functions of prostate and breast cancer cells. *Clinical & Experimental Metastasis 30*, 891–902.

Sudhan, D. R., & Siemann, D. W. (2015). Cathepsin L targeting in cancer treatment. *Pharmacology & Therapeutics 155*, 105–116.

Sui, H., Shi, C., Yan, Z., & Wu, M. (2016). Overexpression of Cathepsin L is associated with chemoresistance and invasion of epithelial ovarian cancer. *Oncotarget 7*, 45995–46001.

Sun, J., Sukhova, G. K., Zhang, J., Chen, H., Sjöberg, S., Libby, P., Xiang, M., Wang, J., Peters, C., Reinheckel, T., Shi, G. P., et al. (2011). Cathepsin L activity is essential to elastase perfusion-induced abdominal aortic aneurysms in mice. *Arteriosclerosis, Thrombosis, and Vascular Biology 31*, 2500–2508.

Svatek, R. S., Karam, J., Karakiewicz, P. I., Gallina, A., Casella, R., Roehrborn, C. G., et al. (2008). Role of urinary cathepsin B and L in the detection of bladder urothelial cell carcinoma. *The Journal of Urology 179*, 478–484.

Swallow, C. J., Partridge, E. A., Macmillan, J. C., Tajirian, T., DiGuglielmo, G. M., Hay, K., et al. (2004). alpha2HS-glycoprotein, an antagonist of transforming growth factor beta in vivo, inhibits intestinal tumor progression. *Cancer Research 64*, 6402–6409.

Takeda-Ezaki, M., & Yamamoto, K. (1993). Isolation and biochemical characterization of procathepsin E from human erythrocyte membranes. *Archives of Biochemistry and Biophysics 304*, 352–358.

Takei, Y., Higashira, H., Yamamoto, T., & Hayashi, K. (1997). Mitogenic activity toward human breast cancer cell line MCF-7 of two bFGFs purified from sera of breast cancer patients: Co-operative role of cathepsin D. *Breast Cancer Research and Treatment 43*, 53–63.

Teller, A., Jechorek, D., Hartig, R., Adolf, D., Reibig, K., Roessner, A., et al. (2015). Dysregulation of apoptotic signaling pathways by interaction of RPLP0 and cathepsin X/Z in gastric cancer. *Pathology, Research and Practice 211*, 62–70.

Terlikowska, K. M., Witkowska, A. M., Zujko, M. E., Dobrzycka, B., & Terlikowski, S. J. (2014). Potential application of curcumin and its analogues in the treatment strategy of patients with primary epithelial ovarian cancer. *International Journal of Molecular Sciences 15*, 21703–21722.

Tholen, M., Wolanski, J., Stolze, B., Chiabudini, M., Gajda, M., Bronsert, P., et al. (2015). Stress-resistant translation of Cathepsin L mRNA in breast Cancer progression. *The Journal of Biological Chemistry 290*, 15758–15769.

Tobin, D. J., Foitzik, K., Reinheckel, T., Mecklenburg, L., Botchkarev, V. A., Peters, C., & Paus, R. (2002). The lysosomal protease cathepsin L is an important regulator of keratinocyte and melanocyte differentiation during hair follicle morphogenesis and cycling. *The American Journal of Pathology 160*, 1807–1821.

Tomita, A., Kasaoka, T., Inui, T., Toyoshima, M., Nishiyama, H., Saiki, H., et al. (2008). Human breast adenocarcinoma (MDA-231) and human lung squamous cell carcinoma (Hara) do not have the ability to cause bone resorption by themselves during the establishment of bone metastasis. *Clinical & Experimental Metastasis 25*, 437–444.

Trincheri, N. F., Nicotra, G., Follo, C., Castino, R., & Isidoro, C. (2007). Resveratrol induces cell death in colorectal cancer cells by a novel pathway involving lysosomal cathepsin D. *Carcinogenesis 28*, 922–931.

Tripathi, R., Fiore, L. S., Richards, D. L., Yang, Y., Liu, J., Wang, C., et al. (2018). Abl and Arg mediate cysteine cathepsin secretion to facilitate melanoma invasion and metastasis. *Sci. Signal. 11* eaao0422.

Tuo, H., Shu, F., She, S., Yang, M., Zou, X. Q., Huang, J., et al. (2017). Sorcin induces gastric cancer cell migration and invasion contributing to STAT3 activation. *Oncotarget 8*, 104258–104271.

Turk, B. (2006). Targeting proteases: Successes, failures and future prospects. *Nature Reviews. Drug Discovery 5*, 785–799.

Turk, B., Dolenc, I., & Turk, V. (1998). Dipeptidyl-peptidase I. In A. J. Barrett, N. D. Rawlings, & J. F. Woessner (Eds.), *Handbook of Proteolytic enzymes* (pp. 631–634). London, UK: Academic Press.

Turk, D., Janjić, V., Stern, I., Podobnik, M., Lamba, D., & Dahl, et al. (2001). Structure of human dipeptidyl peptidase I (cathepsin C): Exclusion domain added to an endopeptidase framework creates the machine for activation of granular serine proteases. *The EMBO Journal 20*, 6570–6582.

Turk, V., & Bode, W. (1991). The cystatins: Protein inhibitors of cysteine proteinases. *FEBS Letters 285*, 213–219.

Turk, V., Stoka, V., Vasiljeva, O., Renko, M., Sun, T., Turk, B., & Turk, D. (2012). Cysteine cathepsins: From structure, function and regulation to new frontiers. *Biochimica et Biophysica Acta 1824*, 68–88.

Ugarova, T. P., Ljubimov, A. V., Deng, L., & Plow, E. F. (1996). Proteolysis regulates exposure of the IIICS-1 adhesive sequence in plasma fibronectin. *Biochemistry 35*, 10913–10921.

Ullmann, R., Morbini, P., Halbwedl, I., Bongiovanni, M., Gogg-Kammerer, M., Papotti, M., et al. (2004). Protein expression profiles in adenocarcinomas and squamous cell carcinomas of the lung generated using tissue microarrays. *The Journal of Pathology 203*, 798–807.

Urbich, C., Heeschen, C., Aicher, A., Sasaki, K., Bruhl, T., Farhadi, M. R., et al. (2005). Cathepsin L is required for endothelial progenitor cell-induced neovascularization. *Nature Medicine 11*, 206–213.

Utsunomiya, T., Hara, Y., Kataoka, A., Morita, M., Arakawa, H., Mori, M., et al. (2002). Cystatin-like metastasis-associated protein mRNA expression in human colorectal cancer is associated with both liver metastasis and patient survival. *Clinical Cancer Research 8*, 2591–2594.

Van Noorden, C. J., Jonges, T. G., Meade-Tollin, L. C., Smith, R. E., & Koehler, A. (2000). In vivo inhibition of cysteine proteinases delays the onset of growth of human pancreatic cancer explants. *British Journal of Cancer 82*, 931–936.

Vashishta, A., Ohri, S. S., Proctor, M., Fusek, M., & Vetvicka, V. (2007). Ribozyme-targeting procathepsin D and its effect on invasion and growth of breast cancer cells: An implication in breast cancer therapy. *International Journal of Oncology 30*, 1223–1230.

Vasiljeva, O., Korovin, M., Gajda, M., Brodoefel, H., Bojic, L., Krüger, A., Schurigt, U., et al. (2008). Reduced tumor cell proliferation and delayed development of high-grade mammary carcinomas in cathepsin B deficient mice. *Oncogene 27*, 4191–4199.

Vasiljeva, O., Papazoglou, A., Krüger, A., Brodoefel, H., Korovin, M., Deussing, J., et al. (2006). Tumor cell-derived and macrophage-derived cathepsin B promotes progression and lung metastasis of mammary cancer. *Cancer Research 66*, 5242–5250.

Vazquez, R., Astorgues-Xerri, L., Bekradda, M., Gormley, J., Buick, R., & Kerr, P. (2015). Fsn0503h antibody-mediated blockade of cathepsin S as a potential therapeutic strategy for the treatment of solid tumors. *Biochimie 108*, 101–107.

Verbovsek, U., Motaln, H., Rotter, A., Atai, N. A., Gruden, K., Van Noorden, C. J. F., et al. (2014). Expression analysis of all protease genes reveals cathepsin K to beoverexpressed in glioblastoma. *PLoS One 9* e111819.

Vidal-Albalat, A., & Gonzalez, F. V. (2016). Natural products as Cathepsin inhibitors. Studies in natural product chemistry. In Atta-ur-Rahman (Ed.), *Studies in Natural Products Chemistry* (pp. 179–213).

Wang, B., Sun, J., Kitamoto, S., Yang, M., Grubb, A., & Chapman, H. A. (2006). Cathepsin S controls angiogenesis and tumor growth via matrix-derived angiogenic factors. *The Journal of Biological Chemistry 281*, 6020–6029.

Wang, J., Chen, L., Li, Y., & Guan, X. Y. (2011). Overexpression of cathepsin Z contributes to tumor metastasis by inducing epithelial-mesenchymal transition in hepatocellular carcinoma. *PLoS One 6* e24967.

Wang, L., Zhao, Y., Xiong, Y., Wang, W., Fei, Y., Tan, C., et al. (2018). K-ras mutation promotes ionizing radiation-induced invasion and migration of lung cancer in part via the Cathepsin L/CUX1 pathway. *Experimental Cell Research 362*, 424–435.

Wang, W., Long, L., Wang, L., Tan, C., Fei, X., Chen, L., ... Liang, Z. (2016). Knockdown of cathepsin L promotes radiosensitivity of glioma stemcells both in vivo and in vitro. *Cancer Letters 371*, 274–284.

Ward, C., Kuehn, D., Burden, R. E., Gormley, J. A., Jaquin, T. J., et al. (2010). Antibody targeting of cathepsin S inhibits angiogenesis and synergistically enhances anti-VEGF. *PLoS One 5* pii: e12543.

Wender, P. A., Mitchell, D. J., Pattabiraman, K., Pelkey, E. T., Steinman, L., & Rothbard, J. B. (2000). The design, synthesis, and evaluation of molecules that enable or enhance cellular uptake: Peptoid molecular transporters. *Proceedings of the National Academy of Sciences of the United States of America 97*, 13003–13008.

Werle, B., Schanzenbacher, U., Lah, T. T., Ebert, E., Jülke, B., Ebert, W., et al. (2006). Cystatins in non-small cell lung cancer: Tissue levels, localization and relation to prognosis. *Oncology Reports 16*, 647–655.

Wiedow, O., & Meyer-Hoffert, U. (2005). Neutrophil serine pro-teases: Potential key regulators of cell signalling during inflammation. *Journal of Internal Medicine 257*, 319–328.

Wilder, C. L., Walton, C., Watson, V., Stewart, F. A., Johnson, J., Peyton, S. R., et al. (2016). Differential cathepsin responses to inhibitor-induced feedback: E-64 and cystatin C

elevate active cathepsin S and suppress active cathepsin L in breast cancer cells. *The International Journal of Biochemistry & Cell Biology 79*, 199–208.
Wilkinson, R. D., Young, A., Burden, R. E., Williams, R., & Scott, C. J. (2016). A bioavailable cathepsin S nitrile inhibitor abrogates tumor development. *Molecular Cancer 15*, 29.
Wilson, T. J., Nannuru, K. C., Futakuchi, M., & Singh, R. K. (2010). Cathepsin G-mediated enhanced TGF-beta signaling promotes angiogenesis via upregulation of VEGF and MCP-1. *Cancer Letters 288*, 162–169.
Withana, N. R., Blum, G., Sameni, M., Slaney, C., Anbalagan, A., Olive, M. B., et al. (2012). Cathepsin B inhibition limits bone metastasis in breast cancer. *Cancer Research 72*, 1199–1209.
Wolf, M., Clark-Lewis, I., Buri, C., Langen, H., Lis, M., & Mazzucchelli, L. (2003). Cathepsin D specifically cleaves the chemokines macrophage inflammatory protein-1 alpha, macrophage inflammatory protein-1 beta, and SLC that are expressed in human breast cancer. *The American Journal of Pathology 162*, 1183–1190.
Wolters, P. J., Pham, C. T., Muilenburg, D. J., Ley, T. J., & Caughey, G. H. (2001). Dipeptidyl peptidase 1 is essential for activation of mast cell chymases, but not tryptases in mice. *The Journal of Biological Chemistry 276*, 18551–18556.
Woo, S. M., Min, K. J., Seo, B. R., & Kwon, T. K. (2016). YM155 sensitizes TRAIL-induced apoptosis through cathepsin S-dependent down-regulation of Mcl-1 and NF-κB-mediated down-regulation of c-FLIP expression in human renal carcinoma Caki cells. *Oncotarget 7*, 61520–61532.
Woo, S. M., Min, K. J., Seo, S. U., Kim, S., Park, J. W., Song, D. K., Lee, H. S., Kim, S. H., & Kwon, T. K. (2017). Up-regulation of 5-lipoxygenase by inhibition of cathepsin G enhances TRAIL-induced apoptosis through down-regulation of survivin. *Oncotarget 8*, 106672–106684.
Wulfkuhle, J. D., Sgroi, D. C., Krutzsch, H., McLean, K., McGarvey, K., Knowlton, M., et al. (2002). Proteomics of human breast ductal carcinoma in situ. *Cancer Research 62*, 6740–6749.
Xie, L., Moroi, Y., Hayashida, S., Tsuji, G., Takeuchi, S., Shan, B., et al. (2011). Cathepsin K upregulation in fibroblass propotes matrigel invasive ability of squamous cell carcinoma cells via tumor-derived IL-1α. *Journal of Dermatological Science 61*, 45–50.
Xiong, Y., Ji, W., Fei, Y., Zhao, Y., Wang, L., Wang, W., et al. (2017). Cathepsin L is involved in X-ray induced invasion and migration of human glioma U251cells. *Cellular Signalling 29*, 181–191.
Yan, S., Berquin, I. M., Troen, B. R., & Sloane, B. F. (2000). Transcription of human cathepsin B is mediated by Sp1 and Ets family factors in glioma DNA. *Cell Biol. 19*, 79–91.
Yan, X., Takahara, M., Xie, L., Oda, Y., Nakahara, T., Uchi, H., et al. (2011). Stromal expression of cathepsin K in squamous cell carcinoma. *Journal of the European Academy of Dermatology and Venereology 25*, 362–365.
Yang, L., Cui, M., Zhang, L., & Song, L. (2017). FOXM1 facilitates gastric cancer cell migration and invasion by inducing cathepsin D. *Oncotarget 8*, 68180–68190.
Yang, M., Liu, J., Shao, J., Qin, Y., Ji, Q., et al. (2014). Cathepsin S-mediated autophagic flux in tumor-associated macrophages accelerates tumor development by promoting M2 polarization. *Molecular Cancer 13*, 43.
Yang, W. E., Ho, C. C., Yang, S. F., Lin, S. H., Yeh, K. T., Lin, C. W., et al. (2016). Cathepsin B expression and the correlation with clinical aspects of Oral squamous cell carcinoma. *PLoS One 11* e0152165.
Yang, Y., Lim, S. K., Choong, L. Y., Lee, H., Chen, Y., et al. (2010). Cathepsin S mediates gastric cancer cell migration and invasion via a putative network of metastasis-associated proteins. *Journal of Proteome Research 9*, 4767–4778.
Yasukochi, A., Kawakubo, T., Nakamura, S., & Yamamoto, K. (2010). Cathepsin E enhances anticancer activity of doxorubicin on human prostate cancer cells showing resistance to TRAIL-mediated apoptosis. *Biological Chemistry 391*, 947–958.
Yin, M., Soikkeli, J., Jahkola, T., Virolainen, S., Saksela, O., Holtta, E., et al. (2012). TGF-beta signaling, activated stromal fibroblasts, and cysteine cathepsins B and L drive the invasive growth of human melanoma cells. *The American Journal of Pathology 181*, 2202–2216.
Yu, S., Yu, Y., Zhang, W., Yuan, W., Zhao, N., Li, Q., et al. (2016). FOXO3a promotes gastric cancer cell migration and invasion through the induction of cathepsin L. *Oncotarget 7*, 34773–34784.
Yuan, Y., Xue, L., & Fan, H. (2014). Screening of differentially expressed genes related to esophageal squamous cell carcinoma and functional analysis with DNA microarrays. *International Journal of Oncology 44*, 1163–1170.
Yui, S., Kudo, T., Kigoshi, H., Hagiwara, T., Takino, T., & Yamazaki, M. (2009). Cathepsin G, a neutrophil protease, induces compact cell-cell adhesion in MCF- 7 human breast cancer cells. *Mediators of Inflammation 2009*, 850940.
Yui, S., Osawa, Y., Ichisugi, T., & Morimoto-Kamata, R. (2014). Neutrophil cathepsin G, but not elastase, induces aggregation of MCF-7 mammary carcinoma cells by a protease activity-dependent cell-oriented mechanism. *Mediators of Inflammation 2014*, 971409.
Yui, S., Tomita, K., Kudo, T., Ando, S., & Yamazaki, M. (2005). Induction of multicellular 3-D spheroids of MCF-7 breast carcinoma cells by neutrophil-derived cathepsin G and elastase. *Cancer Science 96*, 560–570.
Zajc, I., Sever, N., Bervar, A., & Lah, T. T. (2002). Expression of cysteine peptidase cathepsin L and its inhibitors stefins a and B in relation to tumorigenicity of breast cancer cell lines. *Cancer Letters 187*, 185–190.
Zao, Y. F., Han, M. L., Xiong, Y. J., Wang, L., Fei, Y., Shen, X., et al. (2018). A miRNA-200c/cathepsin L feedback loop determines paclitaxel resistance in human lung cancer A549 cells in vitro through regulating epithelial-mesenchymal transition. *Acta Pharmacologica Sinica 39*, 1034–1047.
Zeleznik, T. Z., Kadin, A., Turk, V., & Dolenc, I. (2015). Aspartic cathepsin D degrades the cytosolic cysteine cathepsin inhibitor stefin B in the cells. *Biochemical and Biophysical Research Communications 465*, 213–217.
Zhang, H., Sun, Z., Wang, K., Li, N., Chen, H., Tan, X., et al. (2018). Multifunctional tumor-targeting cathepsin B-sensitive gemcitabine prodrug covalently targets albumin in situ and improves cancer therapy. *Bioconjugate Chemistry 29*, 1852–1858.
Zhang, H., Zhang, L., Wei, L., Gao, X., Tang, L. I., Gong, W., et al. (2016). Knockdown of cathepsin L sensitizes ovarian cancer cells to chemotherapy. *Oncology Letters 11*, 4235–4239.
Zhang, J., Lin, Y., Hu, X., Wu, Z., & Guo, W. (2017). VPS52 induces apoptosis via cathepsin D in gastric cancer. *Journal of Molecular Medicine (Berlin) 95*, 1107–1116.
Zhang, J., Shridhar, R., Dai, Q., Song, J., Barlow, S. C., Yin, L., et al. (2004). Cystatin M: A novel candidate tumor suppressor gene for breast cancer. *Cancer Research 64*, 6957–6964.
Zhang, L., Wang, H., & Xu, J. (2015). Cathepsin S as a cancer target. *Neoplasma 62*, 16–26.
Zheng, G., Martignoni, G., Antonescu, C., Montgomery, E., Eberhart, C., Netto, G., et al. (2013). A broad survey of cathepsin K immunoreactivity in human neoplasms. *American Journal of Clinical Pathology 139*, 151–159.
Zheng, X., Chou, P. M., Mirkin, B. L., & Rebbaa, A. (2004). Senescence-initiated reversal of drug resistance: Specific role of cathepsin L. *Cancer Research 64*, 1773–1780.
Zheng, X., Chu, F., Chou, P. M., Gallati, C., Dier, U., Mirkin, B. L., et al. (2009). Cathepsin L inhibition suppresses drug resistance in vitro and in vivo: A putative mechanism. *American Journal of Physiology. Cell Physiology 296*, C65–C74.