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Review

Cathepsin B in urological tumors: unraveling its role and therapeutic potential

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Abstract
Cathepsin B(CTSB) is a key protease within the lysosomal protease family and is recognized as a tumor-promoting factor that exerts a substantial impact on cancer progression. It plays a critical role in the initiation, proliferation, metastasis, and angiogenesis of cancer, significantly advancing the disease. This review offers a concise overview of the structure and biological functions of CTSB, clarifying its relationship with cancer and the role it plays in the disease's progression. Additionally, we discuss the association between CTSB and several common malignant tumors of the urinary system, highlighting its potential role and clinical significance within these tumors, as well as the challenges that remain.

Keywords Cathepsin B · Prostate cancer · Bladder cancer · Renal cell carcinoma · Tumor drug resistance

Abbreviations

CTSB	Cathepsin B
ADT	Androgen deprivation therapy
RCC	Renal cell carcinoma
ECM	Extracellular matrix
CSPGs	Chondroitin sulfate proteoglycans
FLI1	Friend leukemia integration 1
ERG	Erythroblast transformation-specific
Cyt-C	Cytochrome C
TNF-α	Tumor necrosis factor-alpha
NLRP3	NOD-like receptor pyrin domain containing 3
BMDM	Bone marrow-derived macrophages
TFEB	Transcription factor EB
IGF-1	Insulin-like growth factor-1
CTS6	Cystatin 6
SPHK1	Sphingosine kinase 1
uPAR	Urokinase-type plasminogen activator receptor
MMPs	Matrix metalloproteinases

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HBSP	Hepatitis B splicing protein
VEGF	Vascular endothelial growth factor
MTA1	Metastasis-associated protein 1
AC	Acid ceramidase
BRCA1	Breast cancer 1 protein
FXR	Farnesoid X receptor
Evs	Extracellular vesicles
VEGFR TKI	Vascular endothelial growth factor receptor tyrosine kinase inhibitors
PSA	Prostate-specific antigen
ELISA	Enzyme-linked immunosorbent assay
TMZ	Temozolomide
miR-140	MicroRNA-140
TAMs	Tumor-associated macrophages
SAHA	Suberoylanilide hydroxamic acid
LMP	Lysosomal membrane permeabilization

1 Introduction

In recent years, there has been an increasing incidence of urological tumors, which has imposed a significant burden on society. According to the latest cancer statistics, prostate cancer is the most prevalent tumor in the male urinary system, accounting for 56% of cases, followed by bladder and kidney cancers. The incidence of these cancers is significantly higher in men than in women, with smoking identified as a major risk factor contributing to this marked disparity [1–3]. Currently, surgical treatment remains the most effective approach for urinary system cancers, but long-term survival rates are still suboptimal. Additionally, drug therapy is a prevalent treatment method for these cancers. For instance, in cases of locally advanced and metastatic prostate cancer, the combination of androgen deprivation therapy (ADT) and novel hormonal therapies is the standard clinical approach [4–6]. In advanced renal cell carcinoma (RCC) patients, apart from targeted drug therapy, a combination with immunotherapy enriches clinical treatment options [7]. Early-stage bladder cancer patients can benefit from bladder instillation therapy following transurethral resection, which generally yields satisfactory results. Furthermore, this therapy can be combined with immunotherapy or radiotherapy, and immunotherapy appears to hold great promise [8]. However, Bladder cancer frequently exhibits a high recurrence rate, and prognosis is typically poor upon distant metastasis [9]. Although numerous hypotheses have been proposed to elucidate the mechanisms underlying malignant tumors in the genitourinary system, and have provided theoretical guidance for clinical treatment, these hypotheses do not fully clarify the specific mechanisms involved.

Cathepsin B(CTSB) is a lysosomal cysteine protease that hydrolyzes various cellular structures and tissues to maintain the relative stability of intracellular protein component [10, 11]. It has been found to participate in various biological processes, including tumor invasion and metastasis, immune responses, tumor angiogenesis, and cell death [12–15]. Although the mechanisms by which CTSB contributes to cancer progression have been somewhat explored, research on its relevance in the field of urinary system tumors remains limited and warrants further investigation. Therefore, this review will focus on the critical role of CTSB in urinary system cancers, with the aim of contributing to the understanding of relevant mechanisms and enhancing clinical practice.

2 The structural and enzymatic properties of CTSB

CTSB is one of the significant members of the lysosome-dependent cysteine protease family. In humans, CTSB is encoded by the CTSB gene, which located on chromosome 8p22 and consists of 13 exons [16]. Similar to the synthesis process of most proteases, CTSB is initially synthesized as an inactive pro-peptide, which is subsequently processed into its mature form within the lysosome, ultimately yielding CTSB. CTSB typically exists in two distinct active forms: the 31 KDa single-chain form, which is distributed in endosomes, and the double-chain form, consisting of 25/26 KDa heavy chains and a 5 KDa light chain, distributed in lysosomes [17, 18]. Intracellular, CTSB predominantly exists in its mature form, whereas extracellular CTSB is primarily found in its proenzyme form [14] (Fig. 1.).

Currently, the prevailing view suggests that the function of CTSB is closely related to its subcellular localization and the pH environment. Previously, most studies have indicated that CTSB exhibits optimal activity under acidic conditions, with its activity diminishing or becoming inactive under slightly acidic conditions [19–21]. However, recent research have indicated that CTSB also exhibits significant activity in the cytoplasm at neutral pH values, implying a potentially broader range of functions for this enzyme [22]. Under normal physiological conditions, CTSB primarily maintains the dynamic balance of intracellular proteins by participating in the lysosomal degradation of various proteins [10]. Conversely, in pathological conditions, the expression and function of CTSB may be disrupted, leading to adverse consequences.

3 The functions of CTSB

Under physiological conditions, CTSB primarily facilitates the degradation and metabolism of substances within and outside the lysosomal environment. Furthermore, existing studies indicate that CTSB is involved in various processes such as immune responses, antigen processing and presentation, cellular stress signal transduction, and programmed cell death, demonstrating the diversity and complexity of its functions.

3.1 CTSB is involved in molecular degradation and metabolism

The enzymatic activity of CTSB is a critical factor in its involvement in both intracellular and extracellular protein hydrolysis. Within the acidic environment of lysosomes, CTSB effectively degrades proteins that are engulfed by cells and eliminates damaged organelles, thereby maintaining the balance of intracellular proteins to fulfill the physiological needs of the cell. CTSB exhibits dual functionality as both an endopeptidase and exopeptidase. Under the acidic conditions present in lysosomes, CTSB primarily exhibits endopeptidase activity, while in the relatively weakly acidic extracellular matrix (ECM), its exopeptidase activity is more pronounced. [22] CTSB's degradation of the ECM predominantly targets laminins, fibronectins, type I and type IV collagens, and proteoglycans, among other extracellular structural components [23], and this process also involves the activation of plasminogen [24], laying the foundation for its role in pathological processes. In neuronal cells, dopamine can induce the expression of CTSB by activating the cellular reactive oxygen species-sensitive mechanism, thereby mediating the degradation of amyloid precursor proteins. This process is closely associated with the homeostasis of catecholamines in the brain and the progression of Alzheimer's disease [25]. Additionally, still in neuronal cells, modulation of the receptor protein tyrosine phosphatase Sigma can enhance the expression of CTSB, which subsequently hydrolyzes chondroitin sulfate proteoglycans (CSPGs). The inhibitory effect of CSPGs on axonal growth is well-established, and by limiting this inhibition, the promotion of axonal regeneration and functional recovery following spinal cord injury is facilitated. Consequently, CTSB plays an indirect role in promoting recovery after spinal cord injury [26]. Furthermore, friend leukemia integration 1 (FLI1) and erythroblast transformation-specific (ERG) proteins

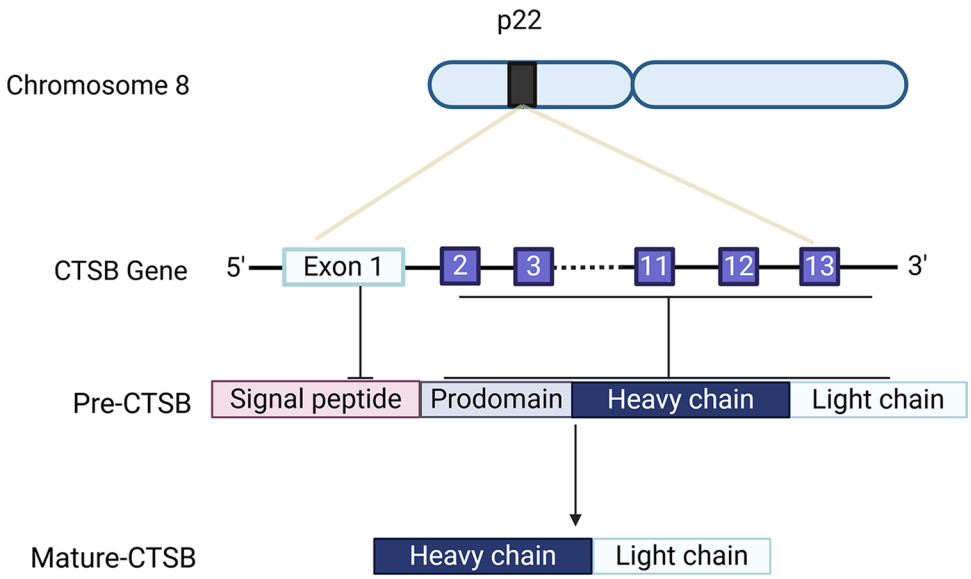

Fig. 1 Illustrates the chromosomal location of the CTSB gene and its trascription and tranlation

are expressed in human skin microvascular endothelial cells, and vascular lesions associated with systemic sclerosis are closely related. The degradation of FLI1 and ERG proteins primarily occurs through the lysosomal pathway of CTSB [27], indicating a protective role of CTSB in this process. These research findings suggest that CTSB may exert completely opposite biological functions in different temporal and spatial environments.

3.2 CTSB mediates inflammation and immune responses

CTSB plays a crucial role in the body's immune response, particularly in processes such as inflammation, antigen processing, and presentation. It mediates inflammation by regulating the activity of inflammatory cells and the production of associated inflammatory molecules. Under stress conditions, the expression and activity of CTSB in inflammatory cells, including neutrophils, lymphocytes, mast cells, and monocyte-macrophages, can change. Aberrant expression of CTSB can stimulate the production of inflammatory mediators, such as TNF-α and NLRP3 inflammasomes, thereby facilitating the inflammatory response [28, 29]. Studies have demonstrated that after application of NLRP3 inflammasome activators, the activation of Caspase-1 and the production of IL-1β in the supernatant of CTSB knockdown mouse bone marrow-derived macrophages (BMDM) are either partially or completely inhibited. Moreover, a deficiency in CTSB expression also hinders the formation of the NLRP3 inflammasome complex [29]. Additionally, CTSB is implicated in the NLRP3-mediated inflammasome secretion of IL-1β. In vitro studies on microvascular endothelial cells have revealed that CTSB mediates the formation of NLRP3 inflammasomes, the activation of caspase-1, and the production of IL-1β. These processes significantly enhance the permeability of endothelial cells, consequently promoting the release of inflammatory factors [30].

Furthermore, research has indicated that CTSB can mediate the translocation of TNF-α-containing vesicles from macrophages to the plasma membrane. The disruption or inhibition of CTSB expression obstructs the translocation of these vesicles, leading to their accumulation in the cytoplasm and directly or indirectly affecting the occurrence of inflammation [15]. Furthermore, CTSB is known to cleave relevant enzymes and chemokines, hereby maintaining cellular homeostasis and contributing to antigen processing [31, 32]. Marissa et al. pointed out that CTSB prevent the activation of autoreactive B cells and enhances the peripheral tolerance of B lymphocytes by directly or indirectly inhibiting the activity of the CD40L-CD40 pathway, which in turn prevents excessive immune responses [13]. CTSB is also involved in immune cell infiltration and immune suppression processes, and it can promote the generation and proliferation of tumor stem cells through the Ras pathway in gliomas, regulating their self-renewal [33]. In conclusion, CTSB is involved in the intricate immune processes of the body, exerting both beneficial and detrimental effects.

3.3 CTSB mediates cell death

CTSB also mediates and regulates various forms of cell death, including pyroptosis, ferroptosis, and autophagy [34], playing a unique role in maintaining the balance of cell death [35]. Under normal physiological conditions, mature CTSB is typically localized within lysosomes. However, under stress conditions, it can be released from lysosomes. This process primarily involves an increase in lysosomal permeability leading to the leakage of CTSB, which mediates cell death by participating in multiple signaling pathways. For instance, in this state, activated caspase-8 can induce the release of CTSB into the cytosol [36], where CTSB not only directly triggers apoptosis but also acts on mitochondria, promoting the release of cytochrome C (Cyt-C). This event lead to the cleavage of caspase-3 and caspase-9, thereby initiating an apoptotic cascade reaction, that ultimately results in cell death [37, 38]. A study on apoptosis in mouse liver cells found that CTSB can also promote TNF-α-mediated apoptosis in liver cells by mediating the release of Cyt-C [39]. Another study demonstrated that silencing CTSB expression can downregulate apoptotic regulators such as TNF-α, caspase-8, and caspase-3, while upregulating Bcl-2, thus reducing the early apoptosis rate of mouse granulosa cells [40]. This indicates that TNF-α is one of the important pathways through which CTSB mediates cell apoptosis. Under oxidative stress conditions, intracellular reactive oxygen species (ROS) accumulate significantly. ROS promote the release and activation of CTSB by inducing an increase in lysosomal membrane permeability. Similarly, this process ultimately mediates pyroptosis by activating caspase pathways such as caspase-1 and caspase-11 [41]. Besides, CTSB is involved in the process of ferroptosis, which is described as a form of non-apoptotic cell death characterized by excessive lipid peroxidation and iron dependency [42]. The activation of STAT3 can upregulate the transcriptional levels of CTSB. Subsequently, the activated CTSB mediate ferroptosis through autophagy or lysosome-dependent cell death pathways [43, 44]. Pandian et al. confirmed that pre-treatment of HT22 cells with CA074-me, an irreversible inhibitor of CTSB, significantly reduced glutamate-induced cell death, thereby preventing ferroptosis [45].

Autophagy is a lysosomes-associated degradation system, which is responsible for the degradation and recycling of macromolecules and organelles [46]. The components that are engulfed are transported to lysosomes by autophagosomes, where they are degraded by specific enzymes. In this process, CTSB plays a crucial role [47, 48]. Under homeostatic conditions, CTSB maintains the suppression of the transcription factor TFEB by cleaving MCOLN1/TRPML1, a calcium ion channel in lysosomes. This action effectively reduces the expression of lysosomal and autophagic proteins, thereby regulating the quantity of lysosomes and autophagosomes within cells. Ming et al. demonstrated through genome-wide expression analysis that absence of CTSB led to increased expression levels of the gene encoding TFEB in bone marrow-derived macrophages (BMDM) of mice [12]. The Bcl-2/Beclin1 complex is a key protein complex involved in both cell apoptosis and autophagy [49]. Studies have shown that the Bcl-2 protein exerts an inhibitory effect on the autophagic process [50, 51]. Interestingly, anti-apoptotic members of the Bcl-2 family are also substrates of CTSB [52], suggesting that CTSB may play a role in autophagy-related cell apoptosis. Furthermore, CTSB, Which located within lysosomes can transport vesicles containing TNF-α to the plasma membrane of macrophages, thereby promoting cellular autophagy and immune responses [15]. Thus, it can be posited that CTSB acts as a 'high-speed train' that mediates the pathway of cells towards death (Fig. 2.).

4 Several pathways by which CTSB influences cancer progression

As a multifunctional hydrolase, CTSB exhibits abnormal expression in various cancers and plays a "pioneer" role in cancer progression [53–57]. Under normal circumstances, CTSB maintains a delicate dynamic balance with endogenous inhibitors. Once this balance is disrupted, it frequently leads to a series of detrimental consequences, particularly in promoting cancer cell proliferation, tissue invasion and metastasis, as well as angiogenesis. The following section outline several critical roles that CTSB plays in the progression of cancer.

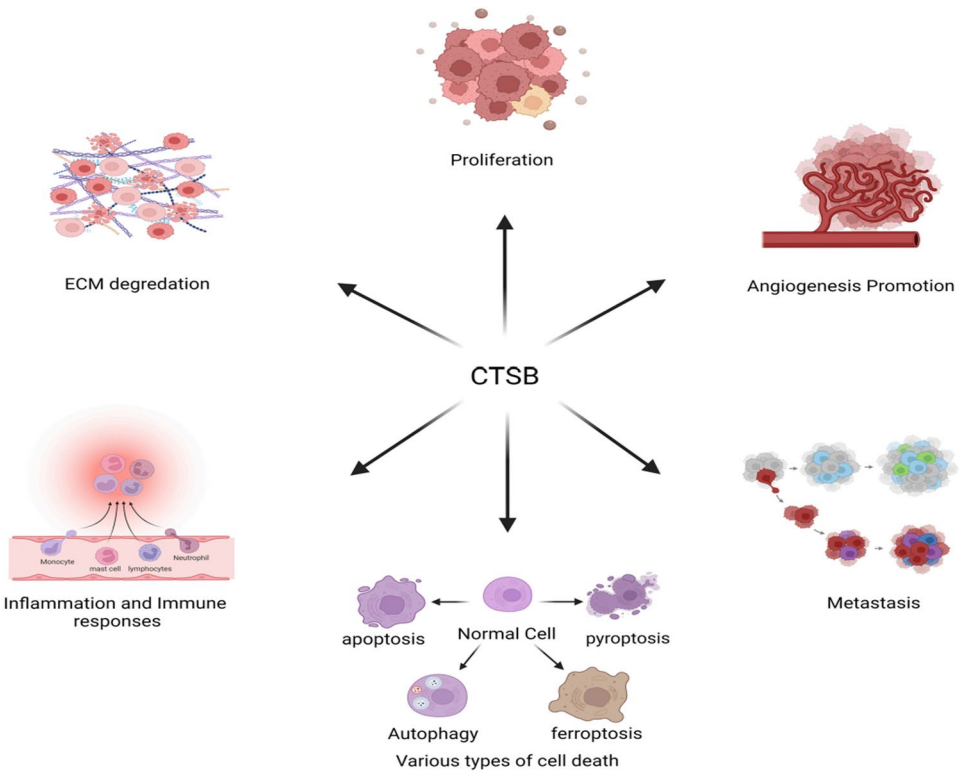

Fig. 2 Illustrates the main functions of CTSB, including promoting cell proliferation, tumor angiogenesis, tumor metastasis, inflammatory responses, immune responses, and programmed cell death

4.1 Promoting cell proliferation

Although CTSB is involved in various cell death pathways under stress, research has shown that it also promotes the proliferation of different cancer cells [34], which may lead to poor prognoses in cancer patients. CTSB participates in multiple signaling pathways that promote cancer cell proliferation. Its expression levels and activity may peak in early-stage cancer, but could decline as the disease progresses to advanced stages [58, 59]. For instance, significant inhibition of cell proliferation has been reported in endometrial cancer cells, meningioma cells, and human T lymphocytes when CTSB was silenced or inhibited using plasmids or lentiviral tools [60–62]. Furthermore, Sida et al. silenced CTSB mRNA in HL-60 (an acute myeloid leukemia cell line) using shRNA, resulting in a significant inhibition of HL-60 cell proliferation. They suggested that this inhibition may be associated with CTSB-mediated inactivation of the AKT signaling pathway [63]. In hepatocellular carcinoma, depleting CTSB can counteract the tumor-promoting effects of insulin-like growth factor-1(IGF-1), thereby limiting cancer cell proliferation [64]. Similarly, in cholangiocarcinoma cells, CTSB expression is suppressed under the interference of miR-637, leading to decreased cell proliferation, migration, and invasion capabilities [65], indicating a close association between CTSB and tumor development.

Additionally, a study involving a CTSB-deficient mouse model of breast cancer found that tumor cell proliferation was inhibited in these mice, and the progression of high-grade breast cancer was also delayed [66]. The CTS6 protein can inhibit bone metastasis in breast cancer by upregulating SPHK1 through the inhibition of CTSB activity. SPHK1, in turn, inhibits osteoclast maturation by suppressing RANKL-induced p38 activation, thus further suppressing breast cancer cell proliferation and bone metastasis [67]. However, it is worth noting that an in vitro cell experiment, which showed that inhibiting CTSB expression actually increased the proliferation and quantity of primary mouse granule cells. This finding contrasts with the prevailing conclusion in the literature, which posits that high CTSB expression promotes cell proliferation [40]. Consequently, these results suggest that the role of CTSB may differ under various physiological conditions, thereby generating further interest for researchers to explore these distinctions.

4.2 Involved in tissue invasion and metastasis

Invasion and metastasis of cancer primarily involve the degradation of the ECM, which is one of the characteristics of many advanced malignant tumors. Cancer cells degrade ECM by producing and releasing various proteases, a critical step for cancers to achieve distant metastasis. CTSB is typically released extracellularly via exocytosis, where it exerts its peptidase activity [19], which can directly or indirectly hydrolyze the primary components of the ECM, thereby facilitating tumor invasion and distant metastasis [24]. In glioblastoma, CTSB is initially released from lysosomes and subsequently translocated to the cell membrane, where it binds to and activates the urokinase-type plasminogen activator receptor (uPAR). This activation leads to the conversion of plasminogen into the serine protease plasmin by activated uPA, which can degrade ECM structural proteins and activate matrix metalloproteinases (MMPs) for ECM degradation. Studies have shown that both uPAR and CTSB are abnormally elevated in gliomas [24, 68]. Additionally, research on inflammatory breast cancer indicates that inhibiting the expression or activity of CTSB and uPAR can effectively reduce cancer cell migration and invasion [69]. This finding suggests that the activation of the CTSB/uPAR pathway is a key mechanism promoting tumor invasion. Furthermore, CTSB is closely associated with the onset and invasiveness of hepatocellular carcinoma, and can directly interact with the hepatitis B splicing protein (HBSP). In liver cancer cells with HBSP overexpression, there is a notable increase in uPA expression and MMP-9 activity, paralleling the role of CTSB in gliomas [70].

Finally, researchers have identified that Netrin-1 (a layer-specific adhesion glycoprotein secreted by axon-target cells) can enhance the invasiveness of glioblastoma by activating CTSB. This suggests that direct intervention in the netrin-1/CTSB pathway may offer potential therapeutic efficacy for brain tumor treatment [71]. The role of CTSB in cancer invasion and metastasis is critical and serves as a key factor in promoting these processes (Fig. 3.).

4.3 Mediating tumor angiogenesis

The progression of tumors is typically accompanied by high metabolism, which is an energy-intensive process. To meet their own growth demands, tumors can promote the production of angiogenesis-related factors, thereby mediating angiogenesis. Among the many members of the cathepsin family, CTSB is considered to be involved in the complex process of tumor angiogenesis. Although the majority of current literature indicates that CTSB has a promoting effect

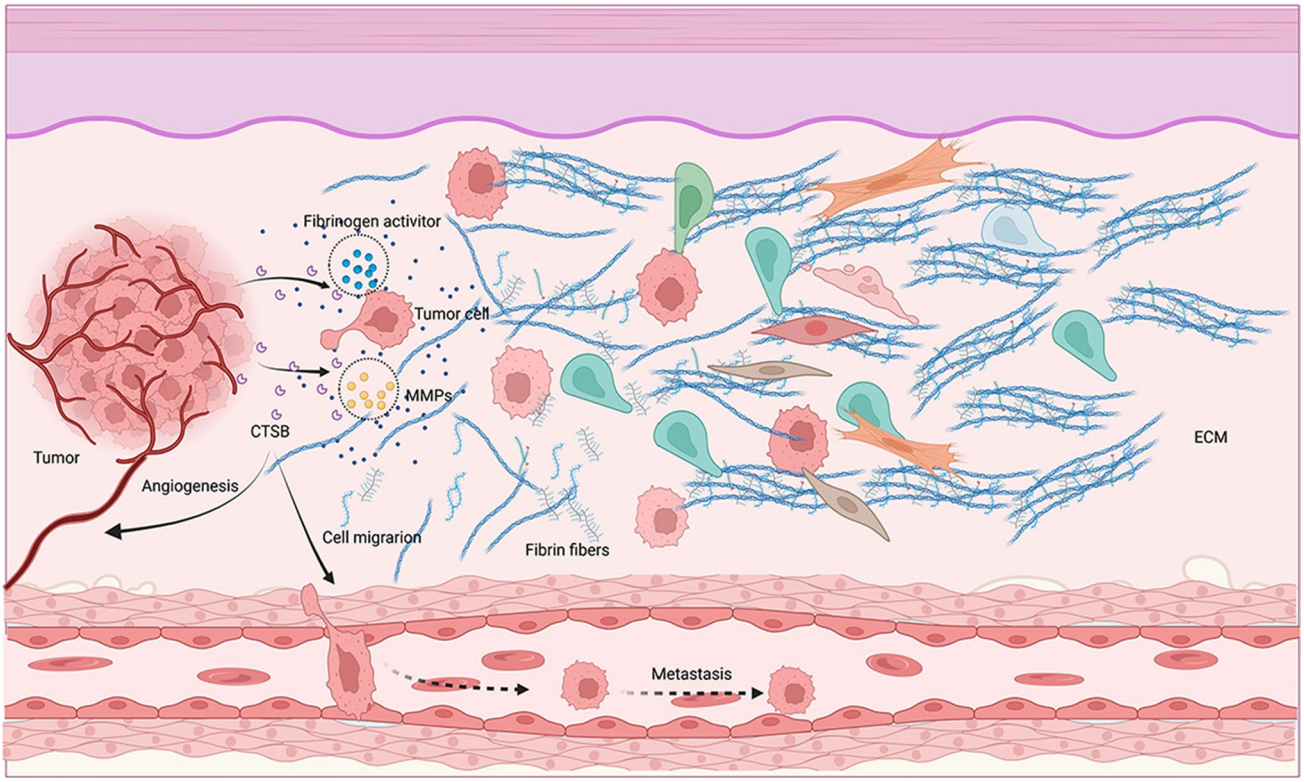

Fig. 3 CTSB promotes the processes of tumor infiltration, metastasis, and angiogenesis. Tumor cells synthesize and secrete CTSB into the ECM. CTSB directly degrades ECM components or indirectly degrades the ECM by activating fibrinogen activators and MMPs, thereby facilitating tumor infiltration, metastasis, and angiogenesis

on tumor angiogenesis, its role in non-tumor angiogenesis is appears to be opposite, exhibiting a 'double-edged sword' effect. In most cancers, the overexpression of CTSB can facilitates angiogenesis. However, in normal vascular endothelial cells, this overexpression can inhibit angiogenesis by downregulating vascular endothelial growth factor (VEGF), thereby avoiding pathological vascular growth [72].

VEGF serves as the ultimate regulatory factor of angiogenesis. A study investing angiogenesis in bladder cancer demonstrated that increased CTSB activity significantly activates the TPX2-mediated AURKA-PI3K-AKT axis phosphorylation, increasing VEGF expression and promoting angiogenesis [73]. In prostate cancer, it was observed that the inhibition of CTSB, MMP-9, and uPAR collectively suppresses angiogenesis [74]. Additionally, the inhibition of these factors in prostate cancer has been corroborated by further studies [75, 76]. This angiogenic process may also involve the activation of the RAS/RAF/MEK/ERK pathway, where ERK activation influences the expression of CTSB and MMP-9 through the transcription factor AP-1, ultimately targeting VEGF [77]. As previously mentioned, the direct interaction between CTSB and HBSP in hepatocellular carcinoma can promote tumor invasion; indeed, their interaction is closely related to tumor angiogenesis. HBSP significantly enhances tumor-induced endothelial cell vascular formation, a mechanism that may involve the secretion and activation of CTSB, as well as the activation of the MAPK/AKT signaling pathway [70]. In glioblastoma, the use of the CTSB-specific inhibitor CA-074Me resulted in significant inhibition of netrin-1-mediated blood vessel sprouting and formation [71]. Collectively, these studies suggest that targeting CTSB inhibitors may be a promising strategy to restrain tumor growth and achieve favorable outcomes in clinical treatment.

5 The role of CTSB in urological tumors

Despite extensive research on CTSB in numerous human diseases, particularly in various malignant tumors where it influences cancer progression, studies focusing on CTSB in urological cancers remain relatively limited. Given the significant role that CTSB plays in other types of cancer, and considering the existing literature on CTSB in urological cancers, we hypothesize that CTSB may be critical in the progression of urological tumors.

5.1 In prostate cancer

In prostate cancer, the overexpression of CTSB primarily contributes to critical processes such as invasion, angiogenesis, and bone metastasis, serving as a significant factor associated with poor prognosis in this disease [78–81]. An early literature has demonstrated that during the angiogenesis of human prostate cancer, the microvessel density in cancerous tissue is significantly increased compared to non-cancerous tissue, suggesting that CTSB may be play a role in the early stages of angiogenesis [82]. In the context of prostate cancer bone metastasis, studies have shown that the interaction between tumor-stroma in the bone microenvironment can regulate CTSB expression. Although in vitro cell experiments indicated increased expression and secretion levels of CTSB only in the DU145 cell line, high levels of CTSB expression and activity have been observed in bone lesions [79] Furthermore, CTSB is also found in the extracellular resorption lacunae of osteoclasts, which is related to bone resorption by these cells [83–85]. This indicates a crucial role for CTSB in the bone metastasis of prostate cancer.

Additionally, studies have shown that metastasis-associated protein 1(MTA1) is highly expressed in metastatic tumors and bone metastatic lesions. After silencing MTA1 expression, there was a significant decrease in CTSB expression. This decrease corresponded with reduced colony formation, invasiveness, and migratory capabilities of prostate cancer cells, suggesting that targeting the MTA1/CTSB signaling pathway may help prevent prostate cancer bone metastasis [86]. Research conducted by Thomas et al. suggests a strong correlation between CTSB overexpression and acid ceramidase (AC), whereby AC promotes Ets1 nuclear expression through the generation of S1P (Sphingosine-1-Phosphate). The binding of Ets1 to the promoter region of CTSB induces its expression and release, thereby enhancing the invasiveness of prostate cancer. This mechanism may be related to AC overexpression,which promotes the pericellular localization and externalization of CTSB [87]. Additionally, both in vitro and in vivo experiments have demonstrated that targeting CTSB, MMP-9, and uPAR can effectively inhibit the invasion, migration, and tumor angiogenesis associated with prostate cancer, which promotes apoptosis in prostate cancer cells, and effectively inhibit the progression of the cancer [74]. RD-N is an aminomethylated derivative that can enhance lysosomal membrane permeability and trigger CTSB-dependent apoptosis in prostate cancer cells. This mechanism involves the translocation of CTSB from lysosomes to the nucleus, where it inhibits breast cancer 1 protein (BRCA1), leading to DNA damage that promotes cell apoptosis [88].

In conclusion, CTSB plays a crucial role in the progression of prostate cancer, contributing to poor prognosis, while also offering new insights for potential treatment strategies.

5.2 In bladder cancer

Although research on CTSB in bladder cancer is insufficient, existing literature suggests that CTSB plays a significant role in the progression of this disease, impacting its development. For instance, a study indicated that after implanting invasive transitional cell carcinoma in the bladders of nude mice, the results indicated enhanced expression and activity of CTSB in the membranes of invading tumor cells. This promoting the degradation of the tumor-adjacent ECM, thereby increasing the tumor invasiveness [89]. Research by Ana et al. demonstrates that CTSB is highly expressed in metastatic bladder cancer and significantly correlates with tumor infiltration. Furthermore, the results also indicate differences in the molecular weight forms of CTSB expression between tumors and surrounding tissues (although immunohistochemical results do not show changes in CTSB localization), they point out that the progression of bladder tumors seems to be associated with changes in the quantity and form of CTSB expression [90].Additionally, recent studies indicate that the farnesoid X receptor(FXR) agonist GW4064 can inhibit the migration and invasion of bladder cancer cells. This inhibitory effect is achieved by downregulating the expression of CTSB and MMP2 [91]. CTSB can promote angiogenesis in bladder cancer, further facilitating the disease's progression [73]. Furthermore, CTSB has potential applications in the diagnosis and prognosis of bladder cancer. Evaluating the concentration of CTSB in the urine and serum of patients with bladder metastatic cell carcinoma aids in tumor grading and assessing patient prognosis [92]. The overexpression or heightened activity of CTSB indicates an unfavorable prognosis for bladder cancer patients. Li et al. demonstrated that CTSB expression is upregulated in both tumor tissues and serum extracellular vesicles (EVs) of bladder cancer patients, showing a significant correlation with poor prognostic outcomes [73].

To a certain extent, evaluating the concentration of CTSB can enhance tumor grading and prognosis assessment, suggesting that the use of CTSB-related inhibitors may help to mitigate the progression of bladder cancer and potentially extend survival duration for patients.

5.3 In renal cell carcinoma

CTSB is abnormally expressed in renal cell carcinoma, typically at elevated levels [93, 94]. Chen et al. investigated the role of CTSB in the progression of renal cell carcinoma by establishing a model of clear cell renal cell carcinoma. Their in vitro and in vivo experiments demonstrated that knocking down CTSB inhibited the growth of renal cell carcinoma, while overexpression of CTSB negated the therapeutic effects of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKI) on renal cell carcinoma, leading to disease progression [93]. For instance, CTSB may be linked to resistance against sunitinib treatment in renal cell carcinoma. Sunitinib accumulates continuously in lysosomes, inhibiting CTSB activity and resulting in incomplete autophagic flux. Additionally, sunitinib can promote the release of CTSB into the ECM, where it degrades the ECM through its enzymatic activity, thereby enhancing the invasive and metastatic capabilities of renal cell carcinoma cells [95]. A recent study indicated that overexpression of CTSB in renal cell carcinoma cells correlates with increased cancer cell proliferation. Further analysis revealed a positive correlation between CTSB overexpression and factors such as patient age, tumor size, lymph node infiltration, occurrence of metastasis, and survival rate in renal cell carcinoma patients [94]. This suggests that CTSB plays a significant role in the progression of renal cell carcinoma and is helpful in assisting clinical assessment of patient prognosis.

6 The clinical potential of Cathepsin B in urological tumors

CTSB is abnormally expressed in various cancers, and current research indicates that this phenomenon is also observed in tumors of the urogenital system. Consequently, CTSB may function as a significant biomarker or regulatory factor in these tumors. Future comprehensive research on CTSB could have substantial implications for the early diagnosis, prognosis assessment, and clinical treatment of malignant tumors in the urogenital system.

6.1 Serving as a tumor marker

CTSB exhibits elevated levels in the early stages of various cancers and is recognized as an effective tumor biomarker. Evaluating the expression levels of CTSB in patients can facilitate early cancer screening and diagnosis, as well as assist in prognosis assessment for advanced-stage patients. Currently, biomarker screening is categorized into non-invasive and invasive techniques. For tumors of urogenital system, non-invasive detection technologies may offer more promising applications, particularly during the early screening phase. For instance, a study focused on urogenital system tumors, analyzed protein differences in the urine of various patient groups using proteomics, revealing specific changes in CTSB levels in the prostate cancer group, which were strongly correlated with the disease [96]. Invasive testing techniques also provide advantages in cancer diagnosis and prognosis assessment. In prostate cancer biopsies, the ratio of CTSB to the prostate-specific antigen (PSA) is significantly higher than in benign prostatic tissues, and the combination of CTSB with PSA and MIB-1 can accurately evaluate the nature of prostate cancer [97].

The discovery of tumor biomarkers is contingent upon advancements in detection technologies. Currently, methods for detecting CTSB include enzyme-linked immunosorbent assay (ELISA), fluorescence quantitative detection, bioluminescence detection, and photoacoustic imaging, which can be employed for both in vivo and in vitro CTSB detection. A common approach involves designing highly selective activity probes that specifically bind to CTSB, followed by luminescence measurement at designated wavelengths. Numerous researchers have developed various types of CTSB activity probes with exceptional detection performance. Chen et al. designed and developed two CTSB-activated FL/PA (fluorescence/photoacoustic) probes: HCy-Cit-Val and HCy-Gly-Leu-Phe-Gly, which can accurately identify CTSB in tissues. Furthermore, cellular imaging results demonstrate that these probes effectively detect endogenous CTSB in lysosomes, showing a more than threefold enhancement in FL/PA signal compared to the control group, which indicates excellent detection performance [98]. These continuously evolving detection technologies significantly enhance the potential role of CTSB as a tumor biomarker.

6.2 The potential and challenges of CTSB serving as a drug therapy target

Currently, systemic cancer treatment primarily encounters two significant challenges: tumor drug resistance and cytotoxicity. CTSB has been identified as a target for drug action and has undergone preliminary validation in clinical practice, suggesting its substantial potential in the research and application of clinical drugs.

CTSB is closely associated with tumor drug resistance, which is mediated by several mechanisms, including alterations in cell death pathways, the influence of the tumor microenvironment, the enhancement of DNA repair mechanisms, and modifications in drug target sites [35, 99, 100]. In a clinical context, temozolomide (TMZ) is widely utilized for the treatment of glioblastoma, while microRNA-140(miR-140) can directly modulate the expression of CTSB. In glioblastoma, the overexpression of miR-140 inhibits CTSB expression, thereby enhancing the activity of TMZ, promoting cell death, and inhibiting epithelial-mesenchymal transition. Conversely, the overexpression of CTSB effectively mitigates cell death induced by TMZ in glioblastoma cells and promotes epithelial-mesenchymal transition, consequently diminishing the cytotoxic effects of TMZ that are amplified by miR-140 [101]. Furthermore, glucose metabolism plays a crucial role in reshaping the pro-tumor functions of tumor-associated macrophages (TAMs), where the O-GlcNAc modification of CTSB at serine 210 in lysosomes is recognized as one of the primary mechanisms. This modification elevates the levels of mature CTSB in macrophages and enhances its secretion within the tumor microenvironment, thereby facilitating cancer metastasis and chemotherapy resistance [102]. Earlier, we noted that lysosomal membrane permeabilization (LMP) results in the release of CTSB, which can induce cell death. In the context of chemotherapy resistance in osteosarcoma, this process can be triggered by palladacycle-like compounds, potentially aiding in the prevention of chemotherapy resistance [103]. Additionally, CTSB is also implicated in the development of resistance to sunitinib therapy in renal cell carcinoma [88].

CTSB plays a crucial role in the activation of cytotoxic drugs and serves as an effective prodrug-activating enzyme. In the tumor microenvironment, CTSB is present at elevated levels, making it a potential therapeutic target. By selectively releasing active drugs from prodrugs, the safety of chemotherapy can be significantly enhanced which reducing side effects [104]. In normal tissues, CTSB is typically found at low levels or in an inactive state, which can greatly diminish the systemic toxicity of chemotherapy drugs. For instance, CTSB has demonstrated efficacy as a targeted activation tool for albumin-bound doxorubicin prodrugs. Through CTSB cleavage activation, these prodrugs can be released within tumor cells, exerting targeted cytotoxic effects and promoting effective anti-tumor responses [105]. PNP is a CTSB-specific nanoparticle prodrug of doxorubicin, which selectively releases free doxorubicin in peritoneal cancer cells that exhibit high CTSB expression, while remaining inactivated in normal cells with low or defective CTSB expression. This characteristic significantly reduces systemic toxicity [106]. In glioblastoma, the CTSB-responsive brain-targeted delivery system aids in overcoming the blood–brain barrier, thereby enhancing the effectiveness of TAM-targeted therapy in conjunction with conventional chemotherapy [107].Furthermore, drugs such as suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, can activate CTSB, promoting cytotoxic autophagy. Studies indicate that in the presence of anti-CTSB or cystatin C interference, breast cancer cells display reduced apoptosis and increased viability following SAHA treatment, underscoring the significant role of CTSB in SAHA-induced cytotoxicity [108]. HCPT-FF-GFLG-EEYSA is a bladder tumor-specific convertible peptide prodrug that targets bladder tumors and is activated through the catalysis of CTSB. Compared to the standalone chemotherapy drug HCPT, it offers advantages such as prolonged drug concentration maintenance, reduced dosing frequency, and fewer side effects [109]. A functional polymer-lipid, PEG-GLFG-K(C16)2, has been developed to facilitate the controlled delivery of anticancer drugs. Elevated levels of CTSB degrade this polymer-lipid within cancer tissues, leading to the release of the encapsulated anticancer drugs and significantly reducing their toxicity to healthy tissues. In a zebrafish model, GLFG liposomes loaded with doxorubicin (Dox) (GLFG/Dox) demonstrate effective anticancer activity against Hep G2 cells, inhibiting cancer cell proliferation [110].

A comprehensive understanding of the specific mechanisms by which CTSB contributes to tumor drug resistance is crucial for its potential application as a target in clinical drug therapy.

7 Conclusions and prospects

As research on CTSB in urological tumors continues to advance, our understanding of its role has significantly deepened. Current studies have demonstrated a close association between CTSB and the occurrence and progression of urological tumors; however, the precise mechanisms remain to be fully elucidated. This review provides a comprehensive overview of the roles and mechanisms of CTSB in cancer, specifically focusing on its effects on cell proliferation, metastasis, and angiogenesis. It further clarifies the relationship between CTSB and urological tumors based on existing research, highlighting its clinical potential and offering new perspectives for the study of these tumors. The review encompasses various physiological functions and impacts of CTSB, its prominent roles in cancer progression, and its influence on the invasiveness and angiogenesis of urological tumors. Additionally, the review discusses the clinical potential of CTSB based on current findings, suggesting that it may hold significant value for the diagnosis and treatment of urological tumors.

While this review provides initial insights into the role of CTSB in urological tumors, several key issues remain to be addressed. First, existing studies have predominantly focused on the roles of CTSB in other cancers, leaving a gap in evidence regarding its tumorigenic effects and underlying mechanisms in urological tumors. Further exploration of these mechanisms is warranted. Second, the functions of CTSB extend beyond cancer to encompass normal physiological processes in cells, and the significant differences between these roles necessitate in-depth elucidation. Additionally, this review highlights the clinical potential of CTSB, discussing its promise as a tumor biomarker and therapeutic target. However, we also acknowledge the limitations of current research. For instance, the evidence supporting CTSB as a tumor biomarker in urological tumors is not yet conclusive, and related detection technologies remain in their infancy. Future studies may leverage single-cell sequencing technologies to further analyze and provide theoretical support for CTSB as a tumor biomarker. Moreover, although CTSB holds promise as a therapeutic target, research and clinical evidence specifically addressing urological tumors are markedly insufficient, indicating that considerable work remains before it can be considered an effective target. Currently, while there are established standards for treating urological tumors, the outcomes remain unsatisfactory. For example, the standard treatment for prostate cancer involves surgery combined with anti-androgen therapy, which often progresses to castration-resistant prostate cancer in the later stages. Similarly, renal cell carcinoma frequently develops resistance to sunitinib, leading to reduced sensitivity and poor therapeutic outcomes. Considering the clinical potential of CTSB discussed earlier, we propose that future research should investigate targeted drugs or inhibitors aimed at CTSB. For instance, the combination of CTSB-targeted drugs or inhibitors with anti-androgen therapies may effectively suppress tumor progression and delay the onset of castration resistance in prostate cancer, ultimately enhancing patient survival rates.

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Declarations

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