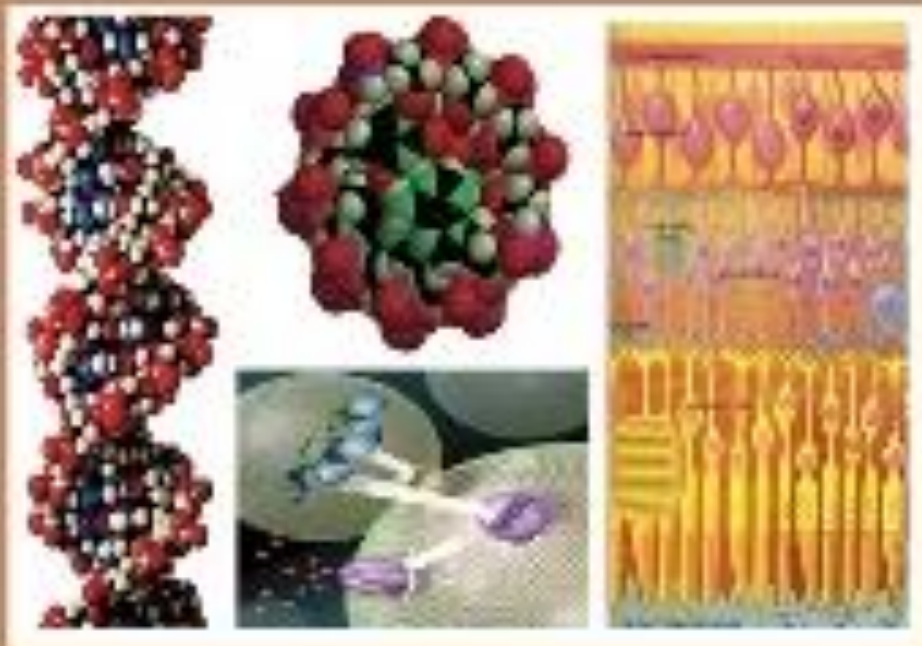




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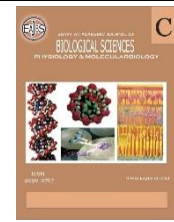
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Cysteine Cathepsins and Their Diagnostic Role in Breast Cancer

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ABSTRACT

Background: A large class of proteolytic enzymes known as cysteine cathepsins are created as pro-enzymes and are activated in slightly acidic conditions. They are crucial for both healthy cellular function and illness. Cysteine cathepsins are a family of proteases that play important roles in a variety of cellular processes, including protein turnover, cell adhesion, and migration. **Main body:** In breast cancer, cysteine cathepsins have been shown to be overexpressed in tumor cells and to be associated with poor prognosis. This review article discusses the role of cysteine cathepsins in breast cancer, focusing on their diagnostic potential. The article provides an overview of cysteine cathepsins, including their structure, function, and regulation in addition to the evidence for the overexpression of cysteine cathepsins in breast cancer and their association with a poor prognosis. **Conclusions:** The current review demonstrates the potential use of cysteine cathepsins as biomarkers for early detection and diagnosis of breast cancer.

INTRODUCTION

A large class of proteolytic enzymes known as cysteine cathepsins are created as pro-enzymes and are activated in slightly acidic conditions. They are crucial for both healthy cellular function and illness (Linders *et al.*, 2023). Cysteine proteases are divided into three subgroups, with cysteine cathepsins being the most prevalent of these, consisting of 11 related enzymes known as cathepsins B, C, F, H, K, L, O, S, V, W, and X, making up the papain subfamily of cysteine proteases (Watson and Kreuzaler 2009). This categorization is available at the sequence level, as proven by a bioinformatic analysis of the human genome's draft sequence (Rossi *et al.*, 2004). The cysteine cathepsins are primarily endopeptidases found inside cells in endo-lysosomal vesicles (Mohamed and Sloane 2006), where they are essential for the metabolism of proteins and lipids, autophagy, and antigen presentation (Linders *et al.*, 2023). Moreover, cathepsins have been discovered in the nucleus, where they are linked to a number of molecular processes (Biasizzo *et al.*, 2022). Under normal circumstances, cathepsins are largely involved in bone remodeling and plasma membrane repair, although cathepsin extracellular localization is more typically found under pathological circumstances (Yadati *et al.*, 2020). When cathepsins are extracellular or outside of lysosomes, they may be permanently inactivated at neutral pH. However, cathepsin S is an exception because it remains stable and retains much of its activity at neutral or slightly alkaline pH (Turk *et al.*, 2012). Moreover, the nucleus and mitochondrial matrix contain extra-lysosomal cathepsins that help regulate the cell cycle and initiate apoptosis (Linders *et al.*, 2023).

Some cancer cells mistakenly relocate cathepsin to the cell surface from their usual intracellular compartments, allowing it to secrete itself outside the cell. Redistribution of cathepsin has been observed in normal cells; for example, CTSB escapes to the extracellular environment in cytotoxic T lymphocytes after lysis (Gocheva *et al.*, 2006). Immune cells of various kinds are the primary source of cysteine cathepsins in the extracellular environment. Because of its essential function in bone resorption, cathepsin K is the cysteine cathepsin that is most frequently seen in the extracellular space under physiological environments (Biasizzo *et al.*, 2022). Their absence is frequently caused by genetic anomalies, while the dysregulation of their inhibition or expression, or both, generally precedes their excessive activity. This results in inappropriate proteolytic processing, which contributes to the onset and progression of several pathologies, including cardiovascular disease, lung illness, arthritis, viral and bacterial infections, cancer, immunological disorders hereditary diseases, chronic pain conditions and others. The current review focuses on the relationship between cysteine cathepsin and the disease of cancer, particularly breast cancer.

Main text:

Types of Cysteine Cathepsins:

Cathepsin B (CTSB):

In human breast cancer tissue, cathepsin B has been discovered to be situated in the cytoplasm and on the cell membrane of cancer cells. In addition to being detected in lysosomes, it has also been observed that cancer cells also have CTSB on their surface (Yano *et al.*, 2001). In addition to being detected in lysosomes, it has also been observed that cancer cells also have CTSB on their surface. CTSB has a function of exopeptidase (carboxy-dipeptidase activity) and endopeptidase (Aggarwal and Sloane 2014). The papain family's most abundant lysosomal protease is essential for the lysosomes' regular maintenance function of turning over proteins (Pišlar and Kos 2014).

A recent study has shown an association between the invasive and metastatic characteristics of cancer and CTSB overexpression (Zamyatnin *et al.*, 2022). Tumor cells and macrophages are the main sources of CTSB in breast cancer, with stromal elements such as myofibroblasts, fibroblasts, myoepithelial cells and endothelial cells of the neo-vasculature playing a less significant role and belonging to the family of cysteine cathepsins and is more often expressed and has been the subject of many studies in breast cancer (Linders *et al.*, 2023). It is believed that CTSB, which has a variety of biological origins and is elevated in several breast cancer subtypes, plays a part in metastasis to the lung and bone. It might make a fantastic target for imaging applications (Linders *et al.*, 2023).

Cysteine Cathepsin C (CTSC):

Dipeptidyl peptidase I, commonly known as cathepsin C, belongs to the papain family of cysteine proteases and (encoded by CTSC) catalyzes the successive removal of dipeptides from free N-termini of peptides and proteins (Schneck *et al.*, 2008). In addition to exhibiting extracellular protease activity as secreted enzymes located at cell surfaces, CTSC is regarded as an endo-lysosomal component (Ruffell *et al.*, 2013). Inflammatory conditions like Wegener granulomatosis, pneumonia, and viral infections, rheumatoid arthritis are also linked to CTSC (Xiao *et al.*, 2021). Based mostly on experimental research in mice models of the development of organ-specific tumor cells and as biomarkers for risk prediction in human malignancies, a prominent role for the cysteine cathepsin family of proteases in cancer has arisen (Ruffell *et al.*, 2013) and many malignancies contain an overexpression of the CTSC gene (Cheng *et al.*, 2022). The enzyme CTSC has a unique function in the early stages of pulmonary colonization in breast cancer. By triggering a signaling cascade that activates and uses neutrophils, this enzyme promotes the development of lung cancer cells, making it a prospective target for lung metastasis imaging

(Linders *et al.*, 2023).

Cysteine Cathepsin K (CTSK):

Cathepsin K can break the triple helix of collagen molecules at many sites, making it one of a kind among human peptidases; Glycosaminoglycans (GAGs) regulate its collagenolytic activity in a complex concentration-dependent manner (Novinec *et al.*, 2014). Cathepsin K has the capacity to break collagen molecules outside of their helical region in addition to numerous places inside the helical region making it stand out from the crowd of other mammalian proteinases with collagenolytic function (Garnero *et al.*, 1999). It cannot function at neutral pH since it is an acidic endopeptidase one which can efficiently degrade collagen at pH (4.5-6) (Konttinen *et al.*, 2002). The primary cysteine protease in osteoclast-mediated bone remodeling is CTSK, which was linked to the pathophysiology of conditions characterized by abnormally high rates of cartilage and bone resorption (Li, Hou, and Brömme 2000). Arthritis, metabolic function, osteoporosis and even breast cancer have all been linked to this enzyme (Andrade *et al.*, 2016). Currently, CTSK is linked to several malignancies, including bone cancer, renal carcinoma, breast cancer, prostate cancer, and lung cancer (Qian *et al.*, 2022). Because cathepsin K immunopositivity was seen in healthy breast tissue, it appears likely that the source of the tissue and the sensitivity of the detection method utilized may affect the capacity to identify cathepsin K in healthy tissue (Littlewood-Evans *et al.*, 1997).

Although adipocytes have been implicated in a variety of tumor-supporting activities, recent research suggests that inhibiting adipocyte development may provide a novel treatment strategy for combating fatal metastatic breast tumors (Vashum and Khashim 2020). Despite the fact that cathepsin K's function in breast cancer cells is still unclear, compared to the expression shown in the patient's primary tumor and soft tissue metastases, breast cancer cells in bone metastases overproduced cathepsin K (Le Gall *et al.*, 2007). Breast cancer cells that reside in the bone exhibit

increased enzymatic activity and upregulation, and this protease may be useful for imaging bone metastases due to its extracellular location. This suggests that cathepsin K is essential for the metastatic spread of breast cancer cells to the bone (Linders *et al.*, 2023).

Cathepsin L (CTSL):

Cathepsin L is a lysosomal endopeptidase that is significant in the proteolytic cleavage of intracellular and endocytosed proteins and is produced everywhere (Sudhan and Siemann 2015). CTSL was discovered to be considerably elevated and linked with poor prognosis in breast cancer patients and it is normally engaged in protein turnover in lysosomes (Caserman *et al.*, 2006). There is some evidence that CTSL expression is related to cancer histology and progression. There was a favorable correlation between tumor grade, growth-regulating genes such as Ki-67, cyclin B1, and p21, and HER2 receptor status, and a 50-fold rise in CTSL levels in endometrial cancer patients (Sudhan and Siemann 2015). Patients having breast cancer who have a high CTSL level have a much higher risk of experiencing a tumor recurrence and a shorter overall survival time than those who do not (Sudhan and Siemann 2015). Tumor cells can upregulate CTSL mRNA via increased transcription or epigenetic regulation; as shown in ErbB2-positive breast cancer (Tholen *et al.*, 2015). As a key enzyme in the proteolysis of intracellular and secreted proteins involved in growth regulation, such as transforming growth factor- β (TGF- β), basic fibroblast growth factor (bFGF), and epidermal growth factor receptors (EGFR), CTSL is essential for tumor invasion, antigen processing, bone resorption and metastasis and other processes (Lee and Song 2013).

In addition to being found in the cytoplasm, In breast cancer cells, CTSL is strongly expressed in the nucleus, especially in individuals with triple-negative disease (Burton *et al.*, 2015). Tissue-specific roles for CTSL in breast cancer homeostasis, survival, and proliferation were shown by conditional deletion of CTSL in malignancy cells and the

mammary epithelium produced therefrom or, alternatively, in myeloid cells that are able to invade breast cancers (Parigiani *et al.*, 2020). Patients with high amounts of CTSS and CTSL in their original tumors were more likely to experience a recurrence than those whose tumors contained lower levels of these proteins (Lah *et al.*, 2000).

Cathepsin O (CTSO):

While it is known that BRCA1 deficit contributes to the development of breast cancer, and that low BRCA1 expression leads to tamoxifen resistance through modifying ER co-regulator interaction in breast cancer cells, it is not apparent how CTSO controls BRCA1 (Cairns *et al.*, 2017). The fact that CTSO is expressed in ER-positive breast cancer cells makes it a promising target for tumor imaging. Nevertheless, further research into all breast cancer subtypes is required to fully understand the differences in the Expression and activity of CTSO, its cellular origins, and its location in tumor cells and healthy breast tissue (Linders *et al.*, 2023).

Cathepsin S (CTSS):

Cathepsin S's fibrinogen-degrading endo-protease activity suggests a potential function in an extracellular matrix collapse when pH is low (Sun *et al.*, 2017). CTSS has been found in several types of cancer, including hepatocellular, prostate, and gastric cancers. Furthermore, there was a correlation between high levels of CTSS expression and poor outcomes in grade IV astrocytoma, and colorectal, and gastric carcinomas (Wilkinson *et al.*, 2019). Unfortunately, knowledge of CTSS's regulation mechanism and its significance in the development of breast cancer is limited (Gautam, Bae, and Kim 2017). It has been determined that greater cathepsin S levels correlate with the production of auto-reactive cells through prolonged major histocompatibility complex class II (MHC II) presentation time, suggesting a function for cathepsin S in autoimmunity (Yu *et al.*, 2022).

Moreover, it has been suggested that CTSS is a therapeutic target that doesn't interfere with MHC II activity, which would

be advantageous not only in the treatment of cancer but also in the control of autoimmune illnesses that cause tissue degeneration, such as rheumatoid arthritis (Gautam *et al.*, 2018). CTSS activity in tear fluid appears to be a meaningful biomarker for disease activity in pSS (Primary Sjögren syndrome), and as CTSS inhibition reduces T cell and associated monokine responses towards important autoantigens in pSS, CTSS inhibition may offer a viable innovative therapy option in pSS, (Hargreaves *et al.*, 2019). By applying the specific inhibitor RO5459072, the T-cell response to autoantigens was significantly reduced (Senjor, Kos, and Nanut 2023). It has also been established that Cathepsin S plays a significant role in coordinating breast cancer metastases to the brain (Linders *et al.*, 2023).

Cathepsin V (CTSV):

Cathepsin V is a versatile endopeptidase that plays a role in elastin fibril turnover, peptide release, MHC II molecule maturation, and the cleavage of intra- and extracellular substrates (Lecaille *et al.*, 2022). Inhibitors of CTSV have recently been developed and found to be effective in boosting the immunological response to tumors that reduced tumor-cell proliferation and elastin breakdown and blocking cystatin F (CysF) activation (Senjor, Kos, and Nanut 2023). While cathepsins V and L share a genetic locus on the human chromosome, 9q22.2, their tissue distribution, binding site architecture, substrate selectivity, and functions are distinct (Mitrović *et al.*, 2022). Due to its ability to facilitate GATA3's turnover via the proteasome, cathepsin V can reduce GATA3 expression in ER-positive breast cancers, restoring GATA3 protein expression, which is associated with a better prognosis, and making cathepsin V targeting a practical treatment option in ER-positive breast tumors (Sereesongsaeng *et al.*, 2020).

Cathepsin F (CTSF):

Lysosomal cathepsin F is a papain-family cysteine protease and it has been hypothesized that cathepsin F activity will hinder MHC II processing in macrophages, suggesting that inhibitors of this enzyme may be effective in treating illnesses characterized

by an improper or overactive immune response (Somoza, Palmer, and Ho 2002). The expression of CTSF was significantly downregulated in a wide variety of malignant tissues, including breast invasive carcinoma, bladder urothelial carcinoma, and endocervical adenocarcinoma (Song *et al.*, 2021).

Cathepsin H (CTSH):

Like other members of the family, cathepsin H is a cysteine protease found in lysosomes, where it catalyzes the breakdown of proteins. Nevertheless, cathepsin H is clearly recognized from other endo-lysosomal cysteine proteases by its distinct aminopeptidase function (Waghray *et al.*, 2002). Higher protein levels of CTSH were identified in breast cancer, glioblastoma, and anaplastic astrocytoma when compared to normal tissues, however, lower levels of CTSH were assessed in melanocyte lesions, head, neck, and lung tumors, demonstrating significantly diverse behavior amongst tumor types (Schweiger *et al.*, 2004). Higher CTSH expression was discovered in THCA (thyroid carcinoma), which resulted in a favorable prognosis for patients. Breast cancer, prostate cancer, and colorectal cancer have all been linked to abnormal CTSH expression (Peng *et al.*, 2021).

Cathepsin X (CTSIX):

Cathepsin X is a carboxy-mono-peptidase-active cysteine cathepsin (U. P. Fonović and Kos 2015). CTSIX expression has been shown to be highly expressed in the lung, spleen, kidney, pancreas, placenta, ovary, colon, peripheral blood leukocytes, small intestine, prostate, and liver, although it is expressed everywhere (Puzer *et al.*, 2005). Human glioblastoma (GBM) tissues were found to have high levels of cathepsin X expression and activity, in contrast to low-grade gliomas and healthy brain tissues. Additionally, tumor-associated macrophages and microglia contained this enzyme (Majc *et al.*, 2022). Both and their proteolytic activity have been found to be significantly elevated in the mouse brain, with a preference towards glial cells and old neurons. (Pišlar *et al.*, 2020).

Cathepsin W (CTSW):

The cysteine protease human cathepsin W (CTSW) was discovered in a genome-wide RNA interference (RNAi) screen to be essential for influenza A virus (IAV) proliferation (Edinger *et al.*, 2015). Although CTSW has been identified as a host component necessary for IAV entrance, more particularly for IAV escape from late endosomes, its substrate specificity and the proviral mechanism remain unclear (Günther *et al.*, 2022). In addition, cathepsin W and other metastasis-specific indicators are demonstrated to be among the 348 changed proteins detected in breast cancer (Shen *et al.*, 2023).

Role of Cysteine Cathepsins In Breast Cancer:

Low expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) distinguishes triple-negative breast cancer (TNBC), the most aggressive subtype of breast cancer, and makes it resistant to endocrine therapy and HER2 targeted drugs (Wang *et al.*, 2020). Cathepsin B is just one example of numerous cysteine cathepsins that are expressed in breast cancer cells and that have been demonstrated to correlate positively with the number of positive metastatic lymph nodes in inflammatory breast cancer, as discussed before in this study (Swisher *et al.*, 2015). The tumor-secreted protein CTSC promotes breast-to-lung metastasis by controlling neutrophil recruitment and the development of neutrophil extracellular traps (NETs) (Xiao *et al.*, 2021). In human disorders like breast cancer, cathepsin K enhances the dysfunction of platelets and promotes its aggregation (Andrade *et al.*, 2016). The presence of cathepsins B and L in human breast cancer was linked to worse survival rates (Harbeck *et al.*, 2001) also CTSS in colorectal and breast cancer metastasis (Gautam *et al.*, 2018). CTSS expression was found to be correlated with 5-hydroxy-tryptamine receptor 7 (5-HT7) signaling in TNBC tumors, and CTSS levels were found to vary according to the Lehmann subtype, which includes six

subtypes (basal-like 1 (BL -1), basal-like 2 (BL -2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR), and other types of cathepsins have roles in breast cancer (McDowell *et al.*, 2020).

Cysteine Cathepsin Types As A Breast Cancer Biomarker For Prognosis:

Biomarkers are observable indications that may be tested and analyzed to provide insight into physiological processes, disease states, and drug reactions. In the period of developing molecular profiling techniques, novel findings in the field of breast cancer proteases as diagnostic and/or prognostic biomarkers have been made (Suaifan *et al.*, 2016) and breast cancer has been at the forefront of the use of therapeutic predictive biomarkers among the most prevalent malignancies (Nicolini, Ferrari, and Duffy 2018). Cathepsin activity and levels are often observed to be elevated in the blood and tumors of people. CTSB and CTSL, for instance, were found to have an inverse relationship between expression and activity and the development of breast cancer, and B and L cathepsins linked with recurrence rate in primary breast tumors following therapy (Yadati *et al.*, 2020). There is a significant potential for cysteine cathepsins to be employed as biomarkers for early illness diagnosis or as prognostic biomarkers, allowing for the selection of the most effective medication based on the patient's condition and expected course of treatment (Fonović and Turk 2014b).

CTSB:

Patients with inflammatory breast cancer had higher levels of this protease than healthy controls, and there was a significant connection between cathepsin B expression and nodal metastasis, indicating that nodal metastasis may be aided by this proteolytic enzyme (Pulz and Strefezzi 2017). With regards to disease-free and overall survival, total tissue CTSB protein was a more potent predictive predictor than CTSL, especially in lymph node-negative individuals (Lah *et al.*, 2008). Nonetheless, CTSB was the cathepsin

most typically linked to tumor growth, followed by CTSL (Fonović and Turk 2014a). According to numerous genomic and proteomic studies, high levels of CTSB have also been associated with a worse prognosis in a wide range of cancers, including thyroid, breast, ovarian, gastric, and colorectal tumors (Yan *et al.*, 2017). Hence, its higher expression by tumor cells is associated with poor outcomes in breast cancer and serves as a prognostic marker in several cancer types as well (Chakraborti and Dhalla 2017). CTSB expression levels have been validated as useful diagnostic indicators in part because of their co-detection with cystatin proteins, whose diagnostic value was additionally investigated (Zamyatnin *et al.*, 2022).

CTSS:

The increased M1 polarization of macrophages in patients with high epithelial CTSS expression, its role as a biomarker, and the finding that differential CTSS expression had compartmental and sub-type effects on patient outcome are a few examples of the evidence that CTSS has a novel function in TNBC (Wilkinson *et al.*, 2019). The clinical relevance of CTSS expression in the stroma and epithelium of breast cancer patients was elucidated, and it was shown that stromal CTSS expression was associated with a poor prognosis, and epithelial CTSS played a similar impact in patients with triple-negative breast cancer as it did in those with HER2 positive breast cancer (El-Ashmawy *et al.*, 2022).

Fluorescence-Guided Breast Cancer Surgery Using Cathepsin-Targeted Probes:

Using fluorescence-guided surgery, the tumor bed may be seen in real-time, allowing for more thorough removal (Wang *et al.*, 2021). Furthermore, tumor cells and tumor-stromal cells, such as TAMs (tumor-associated macrophages), produce cysteine cathepsins, which suggests that cathepsin-targeted probes may produce a more uniform tumor signal than probes that target tumor cell-specific proteins, like EGFR, which frequently exhibit significant intratumor and interpatient variability (Linders *et al.*, 2023). Substrate-based probes (SBP) and activity-

based probes (ABP) are two categories that may be used to classify the activatable cathepsin-targeted fluorescent agents (Linders *et al.*, 2023). SBPs are enzyme-cleavable probes used to identify the enzyme of interest. The substrate is cut in half, and the tagged fragment remains inside the cell. The electrophilic warhead of ABPs facilitates covalent attachment to the target (Beroske *et al.*, 2021). HyCoSuL is the current gold standard for rapidly identifying sequences with high activity and selectivity for individual proteases; it uses a mixture of natural and unnatural amino acids in conjunction with positional scanning library technology to investigate a larger chemical

space surrounding protease active site (Poreba *et al.*, 2018).

Conclusions

In conclusion, cysteine cathepsins are a family of proteases that play important roles in breast cancer (Fig 1). The overexpression of cysteine cathepsins in breast cancer is associated with poor prognosis. This suggests that cysteine cathepsins could be used as biomarkers for early detection and diagnosis of breast cancer. Further research is needed to investigate the role of cysteine cathepsins in breast cancer. This research could lead to the development of new treatments for breast cancer.

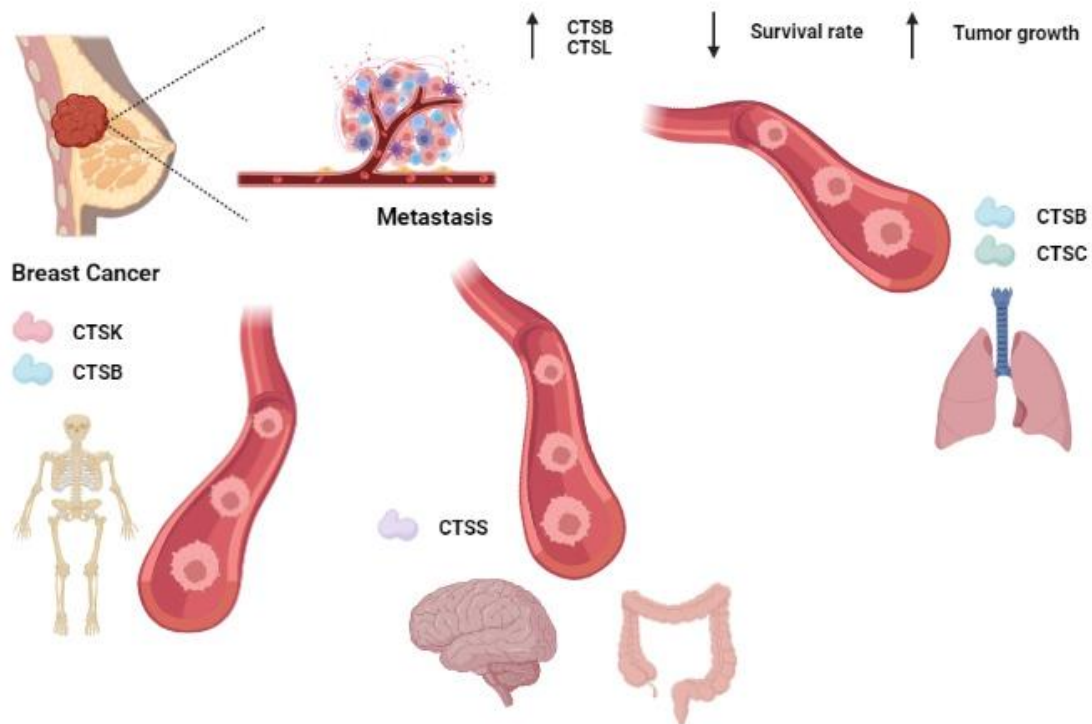


Fig 1: Role of cysteine cathepsins in breast cancer progression.

List of Abbreviations:

CTs: Cysteine cathepsins; **CTSB:** Cathepsin B; **CTSC:** Cathepsin C; **CTSK:** Cathepsin K; **CTSL:** Cathepsin L; **CTSO:** Cathepsin O; **ER:** Estrogen Receptor; **EGFR:** Epidermal Growth Factor Receptor; **TGF- β :** Transforming Growth Factor- β ; **CTSS:** Cathepsin S; **MHC II:** Major Histocompatibility Complex class II; **Cys F:**

cystatin F; **CTSV:** Cathepsin V; **CTSF:** Cathepsin F; **CTSH:** Cathepsin H; **PR:** Progesterone Receptor; **HER2:** Human Epidermal Growth Factor Receptor 2; **TNBC:** Triple Negative Breast Cancer; **THCA:** Thyroid Carcinoma; **CTSX:** Cathepsin X; **CTSW:** Cathepsin W; **RNAi:** RNA interference; **IAV:** Influenza A virus; **NETs:** Neutrophil Extracellular Traps; **MSL:**

Mesenchymal Stem-like; **TAMs**: Tumor Associated Macrophages; **SBP**: Substrate - based probes; **ABP**: Activity-based probes.

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