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Assessment of Cathepsin S (CTSS) function in several diseases

Abstract

Cathepsin S, abbreviated as CTSS, is a potential constituent of the peptidase C1 family, characterized by cysteine residues. Lysosomal cysteine protease CTSS accepts a noteworthy portion in antigen appearance and network debasement. Major histocompatibility complex (MHC) class II molecules appear antigenic peptides on cell surfaces for affirmation by CD4(+) Resistant framework microorganisms also MHC class II molecules occurred on competent antigen-presenting cells (APCs) found in the bone marrow (BM), dendritic cells, lymphocyte B, Macrophages, as well as within the thymic epithelium. CTSS is included within the corruption of invariant chains in human and mouse APCs. The raised expression of CTSS has been related to different dangerous development sorts, therefore CTSS expression has appeared in several circumstances and ailment states, checking it out as both a biomarker and a conceivable therapeutic objective. CTSS can also be obtained from further cells inside the tumor microenvironment, counting macrophages, endothelial cells, and lymphocytes.This study delves into the CTSS role in diverse diseases, particularly emphasizing its involvement in cancer.

Keywords: *Cathepsin,cancer, tumor-associated macrophages (TAMs), Psoriasis*

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Introduction

There are six distinct classes that Proteases are categorized into, namely aspartic, glutamic, metallo, cysteine, threonine, and serine proteases, based on their catalytic forms. These protein enzymes perform hydrolysis of peptide bonds (1). The aforementioned entities can be categorized into two distinct classifications: exopeptidases and endopeptidases, Exopeptidases function in proximity to the terminus of the polypeptide chain, whilst endopeptidases selectively cleave peptide bonds located interiorly within the chain (1). In 1929, chemists R. Willstätter and E. had a research breakthrough that coined the term "CTSS" for these proteases, derived from the Greek words "kata" and "Hepsien", which signify the action of reducing or boiling down(2). The chemical compound CTSS is created as inactive pre-enzymes and undergoes post-translational glycosylation, By utilizing cellular Mannose-6-phosphate receptors, they are coordinated toward the lysosomal compartment, additionally, a few cells can emit critical sums of developing and pro-CTSS(3). The primary physiological role of CTSS is to induce protein degradation within the lysosomes through bulk proteolysis, subsequently, this process highlights the compensatory relationship evident between different Cathepsin isoforms, which exhibit unique substrate specificities, Specifically, the human Cathepsins consist of 15 individual proteases, consisting of 11 cysteine proteases (Cathepsin B, C, X, L, K, H, V, S, O, F, and W), two aspartic proteases (E and D), and two serine proteases (A and G) (4-6). CTSS belongs to the group of cysteine cathepsins and possesses intriguing features, particularly its limited expression in tissues so this specific expression pattern is predominantly observed in cells that present antigens, found in lymph nodes, spleen, and also in other immune cells like macrophages that are deemed biologically benign(7). In addition to its more commonly observed protease activity, CTSS contains distinctive and unique features within the cysteine cathepsin subfamily that are not performed by other members (8,9). From a biochemical standpoint, CTSS exhibits a unique characteristic compared to several other family members owing to its capability to maintain enzymatic activity at a neutral pH(9). The aforementioned characteristics draw attention to CTSS as a promising candidate for therapeutic intervention, due to its restricted expression in addition to its regulatory role over other members of its family, thus implying its greater potential for participation in extracellular proteolysis(7). Furthermore, cathepsin S is a highly characterized cysteine protease with particular attention given to its involvement in presenting antigens to CD4+ T-cells, and Its connection to allergic and autoimmune disorders development, where CD4+ T-cells are believed to be imperative players, in well-established, especially in the cases of rheumatoid arthritis and bronchial asthma(10). The role of CTSS within the cellular environment predominantly centers around the processing of antigens, Explicitly, the MHC class II invariant chain (Ii) cleavage is vital to generating a class II-associated invariant chain peptide also known as CLIP, which subsequently facilitates the binding of exogenous antigens consequently this process is widely recognized as a crucial step in the presentation of antigens by MHC class II molecules (11). The process of breaking down Ii through proteolysis is facilitated by CTSS, along with other proteases, Following this, the CLIP segment is cleaved and transported to the antigen-presenting cell plasma membrane, which then triggers the CD4+ T cells(7, 11). As with numerous other types of proteases, the linkage between CTSS and a wide variety of

substrates and disease states is progressively becoming recognized(9). With the development of tools such as genetic elimination models, chemical assays, and substances, the role of CTSS in these infectious diseases is being thoroughly scrutinized, thus emphasizing its potential as an advantageous therapeutic target (9). Accordingly in this article, we are progressing to talk about the impact of CTSS on cancer, lung diseases, Cardiovascular illness, and immune system deficiency diseases. As specified CTSS has extracellular and intracellular parts which may affect various sicknesses. Within recent times, CTSS and its part in sicknesses such as cancer have been broadly realized. Hence, these novel affiliations between CTSS and maladies made significant consideration in considering CTSS as a restorative target and its compelling characteristics in observing a few maladies. Even though there are many articles and pieces of data approximately Proteases (CTSS), it isn't cruel that there's no requirement for more inquiries about new data.

Besides its role in breaking down damaged and unnecessary proteins in the lysosome, CTSS is prominently accompanied by performing a vital function in immune cells (9). Nonetheless, the extensive scope of the CTSS movement is being elucidated and supported by identifying potential components within various natural phenomena, while acknowledging its detrimental effects on certain conditions (9). Some diseases that can affect people are breathing problems, cancer, heart disease, and diabetes. Scientists have noticed that the cathepsin protein is often higher in cancer cells than in normal tissues, so they are studying it to understand more about cancer(12). The extension of cathepsin for a prolonged duration is intrinsically linked to inadequate prognoses in several forms of cancer, such as breast, lung, and colorectal cancer (CRC), and numerous other malignancies(12). CTSS is especially pertinent within the setting of pneumonic infection due to its capacity to apply elastase movement, inactivate aviation routes have defense proteins, initiate ECM remodeling, and alteration bodily fluid generation over a broad pH spectrum (13). as well as CTSS, maybe a protein that's delivered in reaction to incendiary boosts and its hereditary removal can constrict MHCII introduction, a few intrigued has verifiably been centered on the protease as a target in immunological disorders(10, 13). Researchers have looked to get it part of CTSS in Cardiovascular diseases and frameworks by assessing the molecule's possible components of action(14). One of the systemic components as of late considered is CTSS's part in cardiovascular aggravation and calcification(14). The findings illustrate a mechanism by which CTSS participates in the degradation of the elastin matrix in instances of atherosclerotic lesions and calcified valves, Additionally, this process is accompanied by the dysfunction of the tissue layer, which results in the proliferation and mineralization of mesenchymal cells, namely Smooth muscle cells (SMCs) (13,14). Also, CTSS might be involved in problems with the regulation of blood sugar and the affront digestion system, once CTSS levels are higher it may make it harder for the body to diminish affront affectability and an expanded hazard of creating diabetes(11, 15). Several factors have highlighted a connection between CTSS, diabetes, and obesity(15). The inadequacy of CTSS manifests in a significant decline in blood glucose(BG), particularly evident in diet-induced obesity in animal models and adult mice(11, 15). Interests, concealment of Cathepsin S signaling diminished hepatic glucose generation without moving forward affront sensitivity(7). Chronic torment, whether nociceptive, neuropathic, or nociplastic, influences roughly 3 in 10 individuals universally (9, 16). The potential usefulness of CTSS is not limited to being a mere target rather, owing to its distinctive expression patterns in various diseases, this molecule possesses inherent diagnostic value as a biomarker that can predict disease prognosis and outcome, Furthermore, CTSS expression can assist in classifying patients for treatment interventions, thereby augmenting the efficacy of existing and novel precision medicine treatment strategies(7).

1. Respiratory diseases

1.1. Chronic obstructive pulmonary disease (COPD)

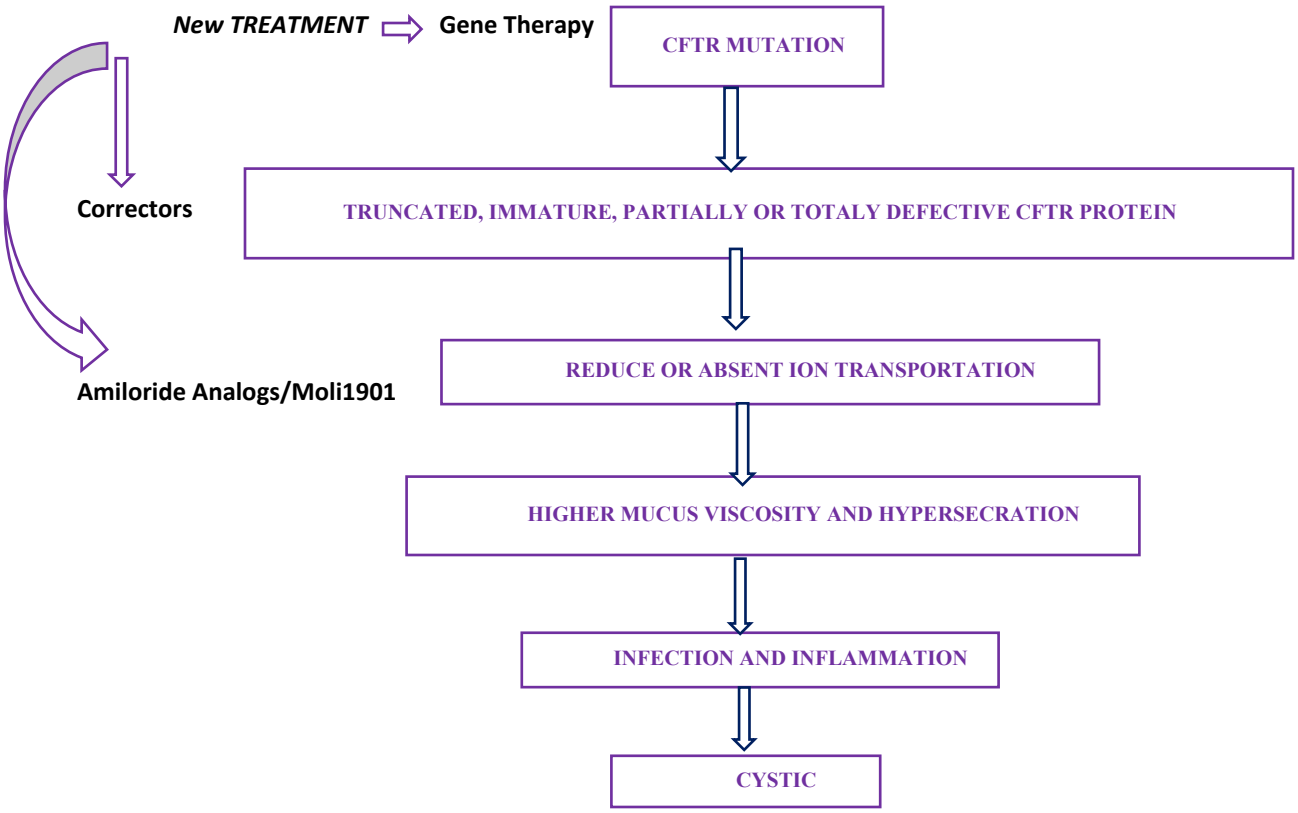
Chronic obstructive pulmonary disease (COPD) has become a major well-being issue, which is expanding worldwide, particularly in developing countries(17). It's presently one of the driving causes of passing and inability, with a predominance of over 10% of people over the age of 40 a long time in most countries(17). COPD is distinguished by the constriction of bronchioles and deterioration of lung tissue, primarily resulting from persistent pulmonary inflammation that involves elevated numbers of macrophages, neutrophils, oxidative stress, CD8-positive T lymphocytes, and the apoptosis of alveolar cells (18). Risk variables for this infection improvement incorporate physical inertia, presentation to poisons, repetitive diseases, and most strikingly, cigarette smoke exposure(9, 19). Moreover, COPD is frequently related to a constellation of disorders, like cardiovascular disease, muscular weakness, and lung cancer (9, 19). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has established a hierarchical categorization system consisting of five stages for the goal of assessing the severity of COPD, so the assessment is based on the degree of airflow obstruction observed during forced expiration, as referenced by various sources (18, 19). The determination of an organization is ascertained through the measurement of the forced expiratory volume in one second (FEV1) after complete inhalation, as well as the calculation of the FEV1 to Forced Vital Capacity

(FVC) ratio, Reduced levels of these indices are indicative of a less severe illness (20). Investigation of subjects included within the National Health Services Directory (NHSD) showed that smoking within puberty alters how early-life exposures such as childhood respiratory sicknesses, packing, and contamination levels affect midlife FEV1(20). Comes about of the Lung Wellbeing Ponder illustrated that in men with FEV1/FVC less than 0.7 and FEV1 55–90% anticipated, each year of self-reported word-related smolder introduction was related with a 0.25% diminishment in FEV1 as a rate of the anticipated value(21). Proteases are important in causing COPD(11, 20 , 21).

A high level of CTSS is detected in the bronchoalveolar lavage fluid, lung tissue, and plasma of individuals suffering from COPD, as well as in individuals who are currently smoking, whether or not they have developed COPD(11, 18, 21, 22). CTSS is communicated in proficient antigen-presenting cells related to COPD such as B cells, macrophages, and dendritic cells(22, 23). This protein plays a pivotal activity in collecting MHC class II -Ag complexes and advances antigen handling, and introduction, and along these lines actuates the actuation of CD4+ T cells(23). Too IFN- γ causes conspicuous alterations in protease-antiprotease to adjust within the lung(22). IFN- γ was a strong stimulator of CTSS mRNA and protein, this incitement was seen within the lungs of transgenic mice after 24 hours of doxycycline (dox) organization illustrating that CTSS protein may as it was be acknowledged as uncommon so these studies prove that IFN-γ could be a strong stimulator of macrophage and epithelial cell CTSS (23). Doherty et al., report novel and interrelated discoveries utilizing a mouse show (Ctss-/-) of constant presentation to cigarettes(24). This study has indicated a positive correlation between cigarette smoke and the upregulation of CTSS quality and protein expression in the lung, this increase in enzymatic activity has been detected in both lung tissue and Bronchoalveolar lavage fluid (BALF), consequently, these results recommend a direct involvement of the aforementioned molecular changes in the detected loss of lung role as a consequence of cigarette smoking (22). A plausible technique for mitigating the resistance to chemotherapy-induced apoptotic cell death and enhancing cytotoxicity in the context of cancer therapy is the inhibition of protein phosphatase 2A, this enzyme plays a crucial role in regulating inflammatory and proteolytic pathways (24, 25). Hindrance of PP2A in mice sometime recently smoke introduction upgraded CTSS expression and lung inflammation(24).

1.2. Cystic Fibrosis

Cystic fibrosis is a hereditary condition that results from changes in the gene accountable for manufacturing the cystic fibrosis transmembrane conductance regulator (CFTR) protein, Although other organs may be affected, The leading etiology of morbidity and mortality is lung involvement (26) and flawed particle channels lead to the generation of adhesive emissions from exocrine glands(26, 27). In CF, natural insusceptibility is ineffectual because of disabled mucociliary clearance and resistant cellular causes(26, 27). The protease has been observed to slice the secretory leukocyte protease inhibitor (SLPI), a natural suppressor of neutrophil elastase that is heavily involved in breaking down the elastin in the lungs of individuals with Cystic Fibrosis(7, 27). The contamination or smoking habit has been discovered to increase the SPLI levels in the lungs as well It is hypothesized that SLPI affects the microbial cell layer through its positive charge, and in its role as an anti-inflammatory protein, SLPI reduces the expression of lattice metalloproteinase (MMP)1 in monocytes (28). The research appears that CTSS plays numerous parts within the pathophysiology of Cystic Fibrosis counting actuation of the epithelial sodium channel (ENaC) and cleavage of defense proteins counting surfactants and LL-37(8, 10, 11, 23). CTSS is the foremost strong elastase known to conjointly have the capacity to debase fibrillar collagens, fibronectin, and laminin(29). Besides, Cathepsin discharge has been portrayed for distinctive cell sorts counting macrophages and aviation route epithelium but not neutrophils, which are the transcendent provocative moving cell in Cystic Fibrosis aspiratory irritation, A few things, in any case, recommend that CTSS is included in neutrophil enrollment to the lung(29). Furthermore, CTSS possesses the capability to cleave and subsequently cripple crucial antimicrobial entities situated within the cystic fibrosis (CF) airways, including but not limited to surfactant protein A, lactoferrin, and those belonging to the β-defensin lineage (8, 30).



Cystic fibrosis pathophysiology arrangement.

Figure1. The process of how cigarette smoke exposure induces the expression of cathepsin S is demonstrated in this illustration.

2. Psoriasis

Psoriasis is a prevalent skin condition that causes significant physical and psychological distress (31). Psoriasis may manifest itself at any stage of life, including from birth onwards, and among elderly individuals in their advanced years (31). Accurately determining the age at which this disease first appears can pose a challenge, as it often relies on the patient's recollection of the onset of symptoms which may not be entirely reliable, However, it is generally believed that psoriasis first manifests between the ages of 15 to 20 and experiences a second peak at 55 to 60 years of age(32). The controlled degradation of proteins, commonly known as proteolysis, is of utmost importance to the maintenance of healthy skin through enhancement, isolation, restoration, and regulation. Recent investigations conducted over ten years have highlighted the significant involvement of cathepsins in these proteolytic mechanisms at both intra- and extracellular levels(31). The cytokines belonging to the IL-1 family Significantly contribute to regulating the innate immune system and orchestrate several inflammatory responses, After an infection, IL-1 cytokines are rapidly produced and can promote inflammation through various mechanisms such as increased cytokine release, movement of cells responsible for presenting antigens, and activation and infiltration of white blood cells (33). Of late discovered from the IL-1 family, IL-36α, IL-36β, and IL-36γ belong to the group of cytokines with agonistic properties (32). In the typical integumentary system of humans, cathepsin S immunostaining is localized within the dermis, predominantly in T cells, macrophages, Langerhans cells, and endothelial cells albeit absent in keratinocytes (33,34). Cathepsin S exhibits a degree of cognizance towards the activation of IL-36γ, which is conveyed throughout the inflammatory processes occurring within psoriatic skin, The protease enzyme known as Cathepsin S has demonstrated the ability to trigger the induction of IL-36γ, an inflammatory agent found within psoriatic skin (34). IL-36γ receptor-deficient mice are safe to Imiquimod-induced psoriasiform dermatitis. Cathepsin S is altogether overexpressed in cell societies of psoriatic patients and psoriasis models(34).

3. Cancer

The pathological condition referred to as cancer might be characterized by the unfettered proliferation of undifferentiated cells which contributes to the formation of a localized mass, commonly known as a tumor (7). The multifaceted nature of this disease, however, involves the dysregulation of various hallmark traits beyond uncontrolled

cellular growth (35), Moreover, cells partition and develop wildly, shaping threatening tumors, and attacking encompassing tissues(102). The metastasis of cancerous cells to distant sites via either the lymphatic or circulatory systems is a well-documented phenomenon(7). In the realm of oncology, neoplastic cells of varying origins and characteristics constitute the heterogeneous components of carcinomatous growths, which are in turn interconnected with stromal cells and tissue, collectively referred to as tumor-associated stroma (35, 36).CTSS make significant commitments to tumor movement in various cancer sorts through an assortment of diverse components additionally CTSS are significant corrosive hydrolases inside the lysosome and speak to the foremost effecters of protein catabolism and autophagy(5, 35, 36).

3.1. Colorectal cancer(CRC)

Colorectal cancer is the 3rd most joint and the 4th most common cancer cause of passing globally(37). The rate is nether at ages more youthful than 50 a long time but unequivocally increments with age(37). CRC could be an exceptionally heterogeneous malady that's caused by the interaction of hereditary and natural factors(36). Although anybody can create CRC, a few variables are related to an expanded hazard for the disease(38).

Some chance components are modifiable, such as slimming down, weight, need for physical action, tobacco utilization, and moderate-to-heavy alcohol use(37, 38). Protective components have been related to a diminished frequency of Colorectal cancer incorporating customary physical movement, eating less wealthy in natural products and vegetables, tall fiber down, Calcium, Dairy items, Vitamin D, Vitamin B6, magnesium admissions, angle utilization, standard utilization of Ibuprofen, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)(38). As mentioned CRC creates through a progressive aggregation of hereditary and epigenetic changes, changing typical colonic mucosa into obtrusive cancer(37). There are four diverse agreement atomic subtypes (CMSs) of CRCs named CMS1, CMS2, CMS3, and CMS4(39).CMS1 is characterized by hypermutated, microsatellite solid, and unsteady safe actuation, while CMS2 is known for MYC signaling enactment, besides, CMS3 is characterized by apparent metabolic dysregulation, and CMS4 is related with noticeable changing development factor-β actuation, angiogenesis, and stromal invasion(39). Cathepsins have moreover been found to have main parts in different infectious substances such as cancers(2). The expression and action of these Cathepsins are for the most part upregulated in aggravation and cancers, Subsequently, they are overexpressed in tumors, conspicuously for CTS S and CTS B, counting in many sorts of cancer such as brain, gastric, breast, colon, follicular lymphoma, and pancreatic cancer(40). The study conducted by Burden and colleagues has revealed that there was a significant elevation in CTSS expression among CRC patients as compared to that observed in the usual colon tissue in clinical trials (39, 40). The use of the Fsn0503 monoclonal counteracting agent for CTSS in vitro attack measures resulted in inhibited attack, attributed to extracellular proteolysis by released CTSS and also the present study involved in vivo assessments wherein the administration of Fsn0503 to HCT116 xenograft tumors was observed to significantly impede the progression of angiogenesis and tumor growth, thus signifying its potential as a critical therapeutic strategy(40). A few past things have recommended that CTSS advances attack and neoangiogenesis through ECM(extracellular network) corruption and discharge of matrix-derived development variables that drive the angiogenic switch(36). The current attention on CTSS involves the implementation of a humane counteracting agent that possesses a safe effector function so this approach has been directed towards the specific targeting of tumor-killing common executioner cells, resulting in a reduced cytotoxic impact(14). The utilization of a counteractive agent inhibitor, namely Fsn0503, towards CTSS presents an innovative therapeutic approach in cancer treatment that not only addresses tumor invasion but also targets neovascularization moreover It’s preferential binding to CTSS, which exclusively targets extracellular pathologic CTSS, may prevent off-target effects(40).

3.2. Breast cancer

Breast cancer (BC) poses a substantial public health concern on a global scale (41). Although breast cancer prevalence tends to increase with advancing age, the rate of increase slows down after menopause. It follows, therefore, that BC may be a hormonally-driven disease, given the decrease in the concentrations of estrogens and, particularly, progesterone in post-menopausal women (41). Breast cancer is a condition characterized by marked heterogeneity, and may be subdivided into discrete subtypes (42). The categorization of breast cancer has been determined by the existence or absence of some receptors such as the estrogen receptor or human epidermal growth factor receptor 2 amplification, therefore allowing targeted therapies including tamoxifen and trastuzumab to be employed (42). Over the final two decades, atomic information emerging from an assortment of procedures counting comparative genomic hybridization (CGH), quality expression profiling, Sanger sequencing, and enormously parallel sequencing have been utilized to hone breast cancer classification and create predictive as well as prescient subgroups(43). Metastasis is established as a multifaceted and dynamic process that encompasses a series of events, such as

the intravasation, invasion, and extravasation of cancer cells, according to existing literature (34, 43). The phenomenon of invasion in cancer is marked by the acquisition of migratory competence by neoplastic cells, affording their transit through the basement membrane and extracellular matrix, so the discerning correlation between the progression of the disease and inimical clinical outcomes experienced by cancer patients may be traced to the expression levels and functional actions of proteolytic enzymes, particularly CTSS (42, 43). Cancerous breast cells demonstrated the capability to alter the extracellular microenvironment to promote the growth of cathepsin enzymes (9). The rise in the level of manifestation and functionality of select members belonging to the cathepsin family, as compared to their conventional counterparts, has emerged as an area of considerable interest in the realm of cancer investigation (44). As of late, the quantity of CTSS in triple-negative breast tumor tissues has been illustrated to perform a basic part in MDA-MB-231 the triple-negative breast cancer (TNBC) invasion(43, 44). The one-of-a-kind properties of CTSS in influencing the extracellular framework microenvironment along with aggravation and the resistant reaction demonstrate that CTSS may play a dynamic part in tumorigenesis, angio, beginning, intrusion, and metastasis(36). Through a research experiment involving the MDA-MB-231 breast cancer cell line, an association has been identified between the activity of Voltage-gated sodium channels and the functioning of CTSS, Although NaV channels do not have a direct impact on the upregulation of CTSS expression levels or its release into the extracellular milieu, they have been concerned in promoting a conducive pH environment that facilitates the initiation of CTSS function(11). CTSS has been recommended as a valuable therapeutic target that doesn't have damaging effects on the role of MHC class II molecules, as evidenced by previous research (42). It has been reported that CTSS exhibits limited tissue diffusion, thereby making it a desirable mark for the management of cancer metastasis within the biological system(10).

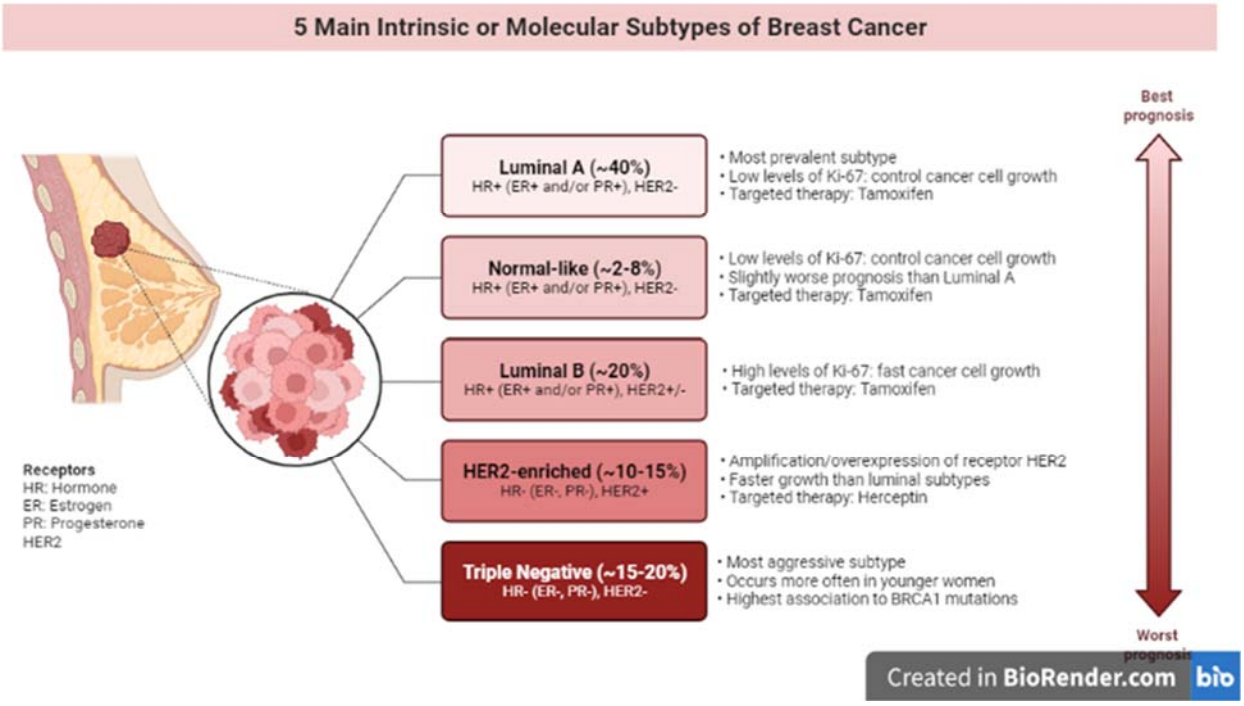


Figure 2. The 5 main varieties of breast cancer and their prevalence.

In a previous investigation concerning the elevated CTSS expression observed in Triple-negative breast cancer, it was discovered that there existed a correlation between CTSS expression and the 5-hydroxytryptamine receptor 7 (5-HT7) signaling pathway. Specifically, TNBC cells were found to exhibit elevated levels of tryptophan hydroxylase 1, the rate-limiting enzyme accountable for 5-hydroxytryptamine (5-HT) synthesis, as well as heightened expression of 5-HT7 receptors in contrast to hormone-sensitive cell lines (45). The signaling through 5-HT7 receptors is related to Akt and extracellular signal-regulated kinase (ERK) to upgrade network metalloproteinase (MMP)-9 (43). The PI3K/Akt and Ras/Raf/MAPK paths are recognized for their ability to regulate the action of the translational factor NF-κB. Thus, it is hypothesized the activation of NF-κB plays a facilitating role in the upregulation of CTSS expression observed in triple-negative breast cancer (2, 45). The analysis of CTSS in TNBC revealed the invasiveness and metastatic behavior of TNBC

cells were significantly reduced through the implementation of either CTSS downregulation or MMP-9 inhibition.

3.3. Prostate cancer

Prostate cancer is a prevalent illness that can have a noteworthy effect on the health and well-being of men worldwide also Prostate cancer is acknowledged as the most rampant malignant neoplasm among males. It represents a complex and heterogeneous neoplasm that can be further categorized into distinct subtypes including aggressive and non-aggressive, high-grade and low-grade, in addition to early-onset PC, manifesting prior to the age of 55 years, and indolent PC (46), The anomalous growth of the prostate organ is accompanied by the atypical division of cells which are distinctive features of this condition, therefore, The mortality rate of individuals diagnosed with prostate cancer predominantly arises from metastasis, whereby the malignant cells extend to various regions of the anatomy, including the retroperitoneal spinal cord, bladder, lymph nodes, rectum, brain, and bones. (47). The conclusion and treatment of PC are based on an arrangement of clinical states (46). These states start with localized illness, taken after by a rising specific antigen named PSA state and the non-castrate metastatic state(47). Radical prostatectomy is the foremost joint treatment for patients with restricted PC(48). Even though Radical Prostatectomy is regularly healing for localized PC, the rates of Biochemical recurrence (BCR) may reach 30–40% (48). Cancer cells' ability to invade the extracellular matrix. and in the long run, metastasizing includes the utilization of diverse sorts of protease and an escalating amount of such proteins and their inhibitors(9, 15). Among diverse Cathepsins, cysteine protease Cathepsins are found in B, K, L, and S forms(49). Cathepsins have powerful elastolytic movement and are able of corrupting a few ECM atoms at impartial pH(22). Cathepsin S-deficient mice appear flawed microvessel arrangement amid wound recuperation and Cat S lack has moreover appeared to disable tumor angiogenesis within the RIP1-Tag2 tumor model(40, 49). The removal of angiogenesis inhibitors, for instance, canstatin and type IV collagen inhibitors, and the increase in construction of pro-angiogenic γ2 subunits (γ2’ and γ2χ) from laminin could be the possible reasons for the angiogenic impact of Cat S(49). Raised levels of CTTS have been extensively stated in numerous types of human malignancies, including glioma, astrocytoma, and lung and prostate cancer, Despite extensive research, there is limited understanding of how CTTS expression relates to the development of prostate cancer (15). Finally, this protease is included within the support of ordinary retinal work, conceivably through the control of other lysosomal proteins Cathepsin D(15).

3.4. Lung Cancer

Lung cancer is one of the most prominent sorts of cancer on a global scale, in charge of the uppermost amount of cancer-related deaths among males and the 2nd highest among females. It ranks third in terms of occurrence, following breast and colorectal cancers, among both genders (50). Smoking is the overwhelming hazard calculated for lung cancer(50). Secondhand smoke presentation is additionally a hazard factor(51). The most prevalent method of determining the likelihood of lung cancer related to one's occupation involves asbestos exposure, Other typical occupational factors that contribute to lung cancer development of contact with nickel, radon, vinyl chloride, arsenic, and ionizing radiation (51). Hereditary components are too critical contributors(52). Hereditary variations from the norm, such as epidermal development calculate receptor (EGFR), have been embroiled in the improvement of lung cancer(53). EGFR could be a transmembrane receptor tyrosine kinase protein that's communicated in a few ordinary epithelial, mesenchymal tissue(50). Lung cancer could be a heterogeneous bunch of cancers, Tumor heterogeneity has been portrayed in a few tumors and it has been tended to in a few ways: histological, cellular, and molecular/genetic(52). Tumor heterogeneity has a critical effect not as it were on tumor classification but too on characterizing forecast and treatment decisions(52, 53). The intricate interplay between tumor-infiltrating macrophages and tumor cells plays an imperative part in the advancement of cancers (54). Tumor-associated macrophages (TAMs) represent a highly prevalent group of cancer-associated stromal cells that are integral to the immune system(55). Transcendent penetration of neoplastic tissue by tumor-associated macrophages (TAMs) has been connected with a destitute guess for patients with a few threatening tumors(55). Tumor-associated macrophages (TAMs) are inferred from blood monocytes, that are pulled into a tumor by cytokines and chemokines, such as CCL2, CCL3, CCL4, CCL5, CCL8, and VEGF(56).CTSS has appeared to take part in the disintegration and remodeling of connective tissue and cellar layers within the forms of tumor development, intrusion, and metastasis(49). Cathepsin S proteolytic corruption of nidogen-1, a fundamental component of the storm cellar layer and a substrate of Cathepsin S, is unequivocally related to non-small cell lung cancer(11). It has been suggested that Nidogen-1 may serve as a potential substrate for cathepsin-S at positions (57). The corruption of nidogen-1 through CTSS results in hindered regulatory interaction between nidogen-1 and laminin, type IV collagen, and perlecan, thereby exerting an impact on the properties of the basement membrane(57). A subsequent concomitant investigation revealed an augmented and selective expression of CTSS in circulating cancer cells of lung cancer,

which holds the potential for predicting distant metastasis, Further, the targeting of Cathepsin S may effectively hinder tumor dissemination to distant sites (26). Additionally, CTSS occupies a decisive role in mediating Ca2+ homeostasis over the regulation of stromal interaction molecule (STIM) 1 trafficking, and the inhibition of CTSS leads to reduced cell motility and invasion (11, 56, 57). Notably, CTSS also assists in the pericellular hydrolysis of the extracellular matrix in the tumor microenvironment, thereby facilitating endothelial invasion (11, 40).

4. Diabetes

Diabetes mellitus is a condition with persistently high levels of blood sugar and impaired breakdown of carbohydrates, lipids, and proteins that occur due to a comprehensive or partial deficiency of insulin secretion, and activity. There are two primary types of diabetes, namely Type 1 diabetes mellitus and Type 2 diabetes mellitus that differ in their dependence on insulin (58). The abundance of type 2 diabetes has reached widespread proportions in several parts of the globe (58). Diabetes type 2 is widely acknowledged to be a complex condition resulting from a combination of a multitude of factors, including but not limited to, reduced sensitivity to insulin in target tissues, commonly known as insulin resistance, as well as inadequate secretion of insulin by the body (59). Type 2 diabetes occurs later in life and advances as a consequence of a compound assortment of components displayed at both hereditary and natural levels(7). Recognizable proof of hazard components for Type 2 diabetes has been challenging since the hereditary and way of life variables are interrelated and related to affront resistance and metabolic conditions(59). CTSS is a notable lysosomal enzyme that is excreted from prime sophisticated microglia and activated by the P2X7 receptor, which is associated with matrix metalloproteinases and serine protease and involved in the external proteolytic breakdown. CTSS performs significant physiological tasks in the extracellular environment, such as degrading the extracellular matrix, regulating growth factors, controlling the vascular expansion of various cytokines, and managing cell migration and apoptosis (60).CTSS might be involved within the primary dysregulation of glucose and affront digestion system as advanced quantity serum CTSS was related to diminished affront affectability and an expanded chance of creating diabetes(11, 15). In a later consideration, Watt et al. explored the impacts of recombinant CTSS on glycaemic regulation, and findings revealed that the intraperitoneal administration of recombinant CTSS in obese mice significantly improved glucose tolerance(20). Whereas expanded plasma affront levels were detailed, no coordinate CTSS-mediated work on pancreatic β-cells was identified(61). Likewise, a lack of cathepsins brings about a vigorous lessening in blood glucose, Interest, and concealment of CTSS signaling diminished hepatic glucose generation without making strides affront sensitivity(26, 15).CTSS was recognized as a vital controller of PAR2-mediated endothelial brokenness that advances microvascular diabetes complications(61).

5. Cardiovascular disease (CVD)

Cardiovascular disease (CVD) is the chief reason for impermanence universally, and considerable efforts have been undertaken in a wide array of disciplines, including but not limited to medical imaging, computational modeling, biomechanics, bioengineering, medical devices, animal and clinical studies, population-based analyses, as well as genomic, molecular, cellular, and organ-level investigations. These endeavors aim to develop enhanced strategies for the early detection, diagnosis, prevention, and treatment of CVD (62). Most cardiovascular illnesses are related to powerless plaques(62). Cardiovascular illnesses include a few conditions related to obsessive forms including the heart and vascular framework, and the by and large support of this framework is driven by a protease: anti-protease balance(7). Out of all the cathepsin varieties, CTTS was known as the predominant cathepsin expressed in atherosclerotic plaques in humans. (7, 49). Previous studies have suggested that damage caused by vascular atherosclerotic injuries is associated with a rise in the expression of elastolytic and collagenolytic CTTS, though there is no variation in the expression of their natural inhibitor, cystatin C, This indicates an imbalance in the regulation of cathepsins and their inhibitor, which promotes the remodeling of the cardiovascular wall(63). CTSS plays a substantial part in the development of various cardiovascular diseases, as well as atherosclerosis, remodeling after myocardial infarction, and abdominal aortic aneurysms (AAA)(11). Studies have shown that ordinary human supply routes inadequately express CTSS, though CTSS expression increments from the early greasy streaks to progressed human atherosclerotic plaques, with expression in macrophages and smooth muscle cells(64). CTSS has also been detailed as a valuable biomarker in a choice of other cardiovascular circumstances, Regularly related to hereditary inclination, hypertrophic cardiomyopathy may be a driving reason for abrupt cardiac passing in youthful people(9, 64). Similarly, CTSS has appeared to be a potential prognostic marker in heart-disappointment patients(9).CTSS has moreover been indicated as a marker inside Von Willebrand disease (VWD), an acquired condition that's the result of inconsistencies within the von Willebrand clotting factor(9, 62, 64). Histone deacetylases (HDACs) refer to a class of proteins that facilitate the acetyl group elimination from lysine residues present in histone as well as non-histone

proteins. Through this mechanism, HDACs contribute to the maintenance of epigenetic equilibrium, which is central to the regulation of gene expression(65).HDAC6 plays an essential part in tweaking the relocation and expansion of cancer cells(65), and ordinary cells(62). On the other hand, the family of cathepsin is thoroughly linked to numerous basic signaling pathways, including the peroxisome proliferator-activated receptor γ pathway (CTTS), moreover detailed that the theory that CTTS action seems to balance HDAC6 enactment to fortify VSMC relocation and expansion in vascular remodeling and neointimal hyperplasia in reaction to injury(62-65).

6. Sjögren syndrome

Sjögren syndrome (SS) may be a systemic immune system illness related to irritation of the lacrimal organ (LG), and salivary organ (SG), coming about in serious dryness of the mouth and eyes(66). The LG is responsible for producing a significant fluid called lacrimal liquid, which plays an indispensable role in sustaining the overall health of the ocular surface, this liquid comprises a sophisticated assortment of compounds, including water, hydrolases, electrolytes, various proteins such as antibodies, cytokines, proteases, and protease inhibitors(66). The pathogenesis of SS involves the entrapment of Th1 and Th17 cytokines. Although results vary, Th1 cytokines (e.g., IL-2, IFN-γ) have been consistently implicated in the pathogenic process. The aforementioned cytokines, interferon-γ (IFN-γ), interleukin (IL)-2, and Th17 cytokines (for instance, IL-17 and IL-21), hold paramount importance in the immune response and are commonly used as markers to assess immune function. Their roles in modulating various aspects of immune defense have been well-established, and investigations are underway to further elucidate their functions in diverse settings. Tumor necrosis factor (TNF)-α and interleukin-17 (IL-17) are extremely expressed in individuals diagnosed with Sjögren's syndrome(67). similar to expanded MHC class II atoms in SG acinar cells(68). Sjögren syndrome (SS) may be a systemic safe framework ailment related to aggravation of the LG and SG, coming approximately in genuine dryness of the eyes and mouth(66). The LG, being an exocrine gland, is responsible for generating lacrimal fluid that substantially contributes to safeguarding the overall welfare of the ocular surface. The fluid is a complicated mixture comprising water, electrolytes, enzymes, and various proteins like the immune system's antibodies, compounds that promote cell growth, chemicals that regulate the body's immune response, enzymes that break down proteins, and compounds that stop these enzymes from working (66). Th1 and Th17 cytokines are caught inside the pathogenesis of SS; in show disdain toward the reality that comes approximately are variable, Th1 cytokines (e.g. interferon-γ (IFN-γ), interleukin (IL)-2 and Th17 cytokines (e.g. tumor decay figure (TNF)-α and IL-17) are exceedingly communicated in SS patients(67, 68). in parallel with extended MHC class II molecules in SG acinar cells(67, 69). CTTS has a place in the bunch of cysteine cathepsins and is nearly solely communicated by antigen-presenting cells (APCs) so CTTS cleaves the invariant chain (li)-derived pro-peptide Lip10 (p10) in the long run clearing out the CLIP (lesson II related invariant chain peptide) on the MHC, As it were CLIP-loaded MHCII particles can be stacked with exogenous peptide arrangements inside the phagolysosome, the cleavage action of CTTS is vital for antigen introduction to CD4 T cells, In this way, it is conceivable that hoisted CTTS action may lead to hoisted MHCII expression and autoimmunity, though hindrance of CTTS may speak to a novel approach to smother MHCII-mediated T cell reactions in autoimmunity(69). Xiaodong Li and his team conducted a study where they observed that CTSS movement in male Gesture show was significantly increased in SS quiet tears compared to tears of individuals with non-SS dry eye or other diseases related to the immune system. (59, 70). The findings from in vitro analyses suggest that heightened levels of tear cathepsin S (CTSS) have the potential to perturb the homeostasis of the ocular surface by inducing the upregulation and secretion of pro-inflammatory cytokines and matrix metallopeptidase 9, a protein implicated in extracellular matrix remodeling, in a corneal cell line. Moreover, these analyses reveal that in male Gesture mice, CTSS expression and activity were not only elevated in tears but also in the lacrimal gland acinar cells that secrete proteins, indicating additional effects of CTSS activity(67, 70). Protease-activated receptor-2 (PAR-2) could be a G-protein-coupled receptor enacted by particular proteases such as trypsin, pole cell tryptase, and other serine proteases. PAR-2 is actuated through cleavage of its extracellular space, creating a fastened ligand that actuates downstream intracellular signaling pathways(66-70).

Conclusion

The mechanism by which CTSS advances resistance is likely clarified by its basic impact on the rate of peptide stacking of MHC lesson II particles. When there's no cathepsin S, the timing of these occasions alters but when its expression increments, it causes different maladies. The protein that has been included within the COPD is CTSS, it is strongly communicated by the cells, counting macrophages as well as dendritic cells. In a study found that cystatin C and CTSS plasma quantity were impressively higher in COPD(18). CTSS is competent in part and inactivating major antimicrobials within the respiratory tract of CF. Totally different considering, expected the pathogenicity of CTSS in CF, isn't however clear(29). The study conducted by RUO et al. demonstrates a remarkable correlation between the serum level

of Cathepsin S (CTSS) and patients diagnosed with type 2 diabetes. However, this correlation does not appear to be associated with insulin resistance, and further investigation is warranted. Significant evidence currently exists, highlighting the critical role of CTSS as an intermediary in the progression of various types of tumors. The suppression of tumor-associated cathepsin, particularly CTSS, is an emerging and effective approach within the realm of cancer immunotherapy.

Ethical approval: None

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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