Type 2 Cystatins in Human Immune and Cancer

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Type 2 cystatins are a group of small secreted protease inhibitors that regulate cysteine protease cathepsins and legumain. These enzymes regulate important cellular processes that are linked to the immune response and tumor progression, playing important roles in both autoimmune diseases and various types of cancers. Cysteine cathepsins are associated with the development of autoimmune diseases, tumor progression, and metastasis. Cystatins are categorized into three subfamilies: type 1, type 2, and type 3. The type 2 cystatin subfamily is the largest, containing 10 members, and consists entirely of small secreted proteins. Although type 2 cystatins have many shared biological roles, each member differs in structure, post-translational modifications (e.g., glycosylation), and expression in different cell types. These distinctions allow the type 2 cystatins to have unique biological functions and properties.

cystatin cathepsin protease inhibitor immunity inflammation tumor progression

1. Cathepsin, Legumain, and Cystatins as Immune Modulators

To introduce the immune-modulatory role of cystatins, it is important to also briefly cover the immunomodulatory role of their target proteins, which are cathepsins and legumain. Cathepsin C, S, L, K, and legumain are involved in autoimmune regulation and exhibit pro-inflammatory functions.

Cathepsin C regulates the maturation of neutrophil serine proteases (NSPs). The secretion of NSPs helps to degrade invading microorganisms and represents one of the major anti-bacterial mechanisms of neutrophils. NSPs also participate in inflammatory response regulation by proteolytically modifying or degrading extracellular inflammatory cytokines and chemokines and catalyzing the activation of inflammatory response-related receptors [1]. NSPs are initially generated as zymogens, which have a dipeptide structure at their N-terminus, keeping the protein in an inactive state. Cathepsin C cleaves this dipeptide to activate the NSPs [2]. In addition, cathepsin C regulates the activity of granzyme B, which is related to the immune response of CD8+ T cells and natural killer (NK) cells [3].

Cathepsin S is required for MHC class II antigen presentation since maturation of the MHC class II molecules depends on cathepsin S activity [4][5]. In antigen-presenting cells, the MHC-Ii chaperone complex is first generated. The Ii peptide in the MHC-Ii complex is a 10 kDa invariant peptide chain that masks the antigen binding site of MHC class II molecules, thereby inactivating the whole MHC class II molecule. The MHC-Ii complex is then

delivered to the lysosome and the Ii peptide is cleaved by cathepsin S to activate the MHC class II molecule [6][7]. As a result, cathepsin S is mainly an immune modulator that enhances immune surveillance.

Cathepsin L is also involved in the maturation of MHC class II molecules in macrophages [8]. Additionally, cathepsin L is an activator of perforin, a key enzyme involved in pore formation by cytotoxic lymphocytes [3][9].

Cathepsin K, a collagenase that is selectively expressed in osteoclasts, is associated with autoimmune disease. It plays an important role in bone matrix remodeling and mediates the inflammatory stress on the bone surface by degrading collagen I, II, and elastin [4][10].

Legumain, as the target of CYSC, CYS6, and CYSF, also participates in immune regulation. Like cathepsin S and L, legumain promotes the maturation of MHC class II molecules and participates in the direct cleavage of antigens, thereby facilitating overall antigen presentation. Legumain can also activate Toll-like receptors, an upstream receptor of the Toll-like receptor signaling pathway, which are key players in the innate immune response [11].

Overall, cathepsins and legumain can trigger immune responses, and their dysregulation often correlates with the pathogenesis of autoimmune diseases, including rheumatic arthritis, systemic lupus, Sjogren's syndrome, asthma, and psoriasis [4].

Since type 2 cystatins inhibit cathepsins and legumain, which in turn suppress inflammatory responses and immune cell activation, type 2 cystatins can be considered immune modulators. Indeed, most of the type 2 cystatins are immunosuppressive due, at least in part, to their ability to inhibit protease function. Type 2 cystatins play key roles in DC maturation and neutralizing cytotoxic lymphocyte cytotoxicity. Additionally, some of them can also act as ligands to activate anti-inflammatory pathways. The following subsections will talk about this in detail for each member of type 2 cystatins.

1.1. Cystatin SN (CYS1, *CST1*)

CYS1 contributes to allergic responses and the pathogenesis of allergic respiratory diseases. CYS1 and cystatin SA are highly expressed in the nasal epithelial surface of patients who have chronic rhinosinusitis (CRS) with nasal polyps. Using proteomics, researchers have discovered that the mucus of CRS patients contains high concentrations of CYS1 [12][13]. CYS1 is related to the Th2 immune response—an inflammation-related response that is highly associated with allergic responses and induced by IL-4. Currently, CYS1 serves as a biomarker for the activated Th2 immune response, which is mainly triggered by CD4+ T cells [14]. *CST1* expression can be induced by IL-4 stimulation and is positively correlated with the upregulation of the Th2 immune response markers IL-33 and TSLP in eosinophilic CRS cases [15]. In addition, recombinant human CYS1 induces secretion of several Th2-related cytokines, including IL-5, IL-13, and IL-4, with an increase in Th2 cell infiltration [12]. For this reason, *CST1* is a well-accepted biomarker for CRS diagnosis. Since CYS1 regulates the Th2 immune response, it is a good biomarker for asthma and allergic rhinitis. *CST1* is upregulated in epithelial cells of the upper and lower airways in patients with asthma and allergic rhinitis [16][17]. The upregulation of *CST1* is correlated with severe allergic respiratory disease [18][19]. Interestingly, allergic respiratory diseases are treated with corticosteroids which

downregulate *CST1* expression in the airway epithelial cells [16]. One study showed that CYS1 promotes the proliferation and migration of airway smooth muscle cells by activating the PI3K/AKT signaling pathway in an in vitro asthma model. This indicates that CYS1 participates in airway remodeling events and maybe a main contributor to asthma development [20].

Because CYS1 promotes the secretion of IL-4 in the immune cells, CYS1 may introduce an anti-inflammatory response in the microenvironment. Indeed, patients with CRS who have high *CST1* expression in their nasal epithelial cells also have high levels of CCL18. CCL18 is an M2 macrophage polarizing cytokine that induces immunosuppression and anti-inflammatory responses [21][22]. In addition, *CST1* plays an important role in introducing an anti-inflammatory response in acute liver failure (ALF) models [23]. CYS1 can directly bind to IFNGR1/2, acting as a competitive inhibitor of the pro-inflammatory cytokine IFN-γ. As a consequence, CYS1 inhibits the activation of the JAK/STAT1 pathway induced by IFN-γ and promotes the M2 polarization of macrophages in the liver [23]. In summary, CYS1 plays a role in the allergic Th2 immune response and anti-inflammatory processes.

1.2. Other SD-Type Cystatins (*CST2, CST4, CST5*, encoding CYS2, CYSS, CYSD)

In addition to *CST1*, clinical studies have shown that the other SD-type cystatins (*CST2*, *CST4*, and *CST5*) also participate in immune response regulation. To date, the mechanism behind their immune regulatory function is unknown. As a result, conclusions about their function in immune regulation cannot be drawn.

Although *CST1* is the preferred clinical biomarker for allergic respiratory diseases, like asthma and CRS, *CST2* can also be used as a clinical biomarker for allergic respiratory diseases [24][25][26]. *CST4* is used as an anti-inflammatory marker since it is downregulated in rheumatic arthritis and Sjogren's syndrome [27][28].

Unlike the other SD-type cystatins which are used as anti-inflammatory biomarkers, *CST5* is used as an inflammatory biomarker [29][30][31]. An in vitro experiment on the human MRC-5 diploid lung cell transfection model showed that CYSD inhibits the replication of OC43 and 229e coronavirus strains at its physiological concentration, showing that CYSD has an anti-viral function [32].

1.3. Cystatin C (CYSC, *CST3*)

CYSC has been shown to have anti-inflammatory properties. Immature DCs express high levels of *CST3*, and this upregulation gradually disappears during DC maturation [33]. The expression of CYSC protein in immature DCs prevents the protease activity of cathepsin S from activating the MHC class II molecules. Therefore, immature DCs are less able to complete antigen presentation and a following immune response [34]. A high level of CYSC positively correlates with the severity of several autoimmune diseases, including sepsis and rheumatoid arthritis [35][36]. A high level of CYSC also correlates with more severe HIV infections, which can be suppressed by antiviral treatment [37].

On the other hand, CYSC also shows pro-inflammatory activities. In hematopoietic cells, CYSC is expressed at higher levels in macrophages and DCs than in T cells [38][39]. In macrophages, CYSC modulates the immune response by enhancing macrophage responses to IFN-γ. This consequently upregulates the activation of the NF-κB pathway and promotes immune-related cytokine NO and TNF-α secretion [40]. CYSC expression can inhibit the secretion of the anti-inflammatory cytokine IL-10 and it is an antagonist of TGF-β [41][42]. At the same time, IL-10 and TGF-β can also modulate the expression of CYSC via the upregulation of its transcription factor IRF-8, forming a negative feedback loop [40][41].

1.4. Cystatin E/M (CYS6, *CST6*)

The immunomodulatory role of CYS6 has not been reported in the current literature. However, some predictions can be made based on the current mechanistic studies of CYS6. CYS6 can inhibit the activation of NF-κB signaling by both canonical and non-canonical pathways [43][44]. CYS6 can also be internalized by macrophages where it highly suppresses osteoclast cathepsin K [44]. Given this evidence, CYS6 has the potential for development as a therapeutic agent to alleviate rheumatic arthritis [4].

1.5. Cystatin F (CYSF, *CST7*)

CYSF is an important immune modulator that acts as a natural immunosuppressant in the human body. High levels of CYSF in NK cells, T cells, and DC cells have been used to counteract the activated immune response mediated by cathepsins. A high level of CYSF reduces the cytotoxicity of CD8+ T cells and NK cells. The inhibition of cathepsin C, L, and H in NK cells and CD8+ T cells suppresses the expression of the downstream cytotoxic-related protein perforin and granzymes [45][46]. In contrast, CYSF co-localizes with cathepsin S in immature DCs and weakens as the DCs mature [47]. The inhibition of cathepsin S by CYSF in immature DCs likely suppresses antigen presentation induced by the MHC class II molecules in DCs. Studies suggest that CYSF is associated with inflammatory responses in the central nervous system induced by microglia, a type of cell that is closely related to macrophages in the neural system [48][49].

In conclusion, besides CYSD and CYSC's non-protease inhibitory function, the type 2 cystatins are all anti-inflammatory factors and are potential immunosuppressants.

2. The Role of Cathepsins, Legumain, and Type 2 Cystatins in Cancer Development

Type 2 cystatins are cysteine cathepsin inhibitors and this is also the reason why they have immunosuppressive effects. Theoretically, type 2 cystatins should have pro-tumor effects on cancer models as they are immunosuppressants. However, the situation is complex because several cathepsins also play roles in tumorigenesis-enhancing cellular events. The activity of cathepsin B, a ubiquitous cathepsin, is highly related to tumor progression and various devastating immunosuppressive events. These events include reduction in CD8+ T cell persistence, infiltration of immunosuppressive tumor-associated macrophages (TAMs), myeloid-derived

suppressor cells (MDSCs), and regulatory T cells (Tregs) [4][50]. In addition, cathepsin B, L, S, and K participate in the cleavage and degradation of the extracellular matrix (ECM). As a result, the activation of these cathepsins facilitates the migration, invasion, and metastasis of tumor cells [51]. Cathepsins also have a protective effect on tumor cells and are involved in the chemoresistance of cancer.

Legumain is largely expressed on TAMs and cancer cells from the breast, prostate, and liver. The overexpression of legumain is highly correlated with tumor migration, invasion, poor prognosis, and inferior survival. Legumain can activate MMP-2&9, PI3K/AKT, and integrin signaling pathways to promote epithelial-mesenchymal transition (EMT) and the TGF-β signaling pathway. Additionally, it also cleaves and inactivates the tumor suppressor protein p53 [52].

Since type 2 cystatins inhibit both protease-induced inflammatory responses and pro-tumor activity, they exhibit a complex dual effect on tumorigenesis. In the following subsections, the role of each type 2 cystatin in cancer development is discussed.

2.1. Cystatin SN (CYS1)

CST1 is a pro-tumor gene in multiple cancer models, including esophageal, breast, colon, gastric, liver, and lung cancer [53][54][55][56][57][58]. In lung cancer, *CST1* is hypomethylated [59], resulting in upregulation of *CST1*. This upregulation is often correlated with poor prognosis, metastasis, and recurrence [54][55][57][58]. Compared to CYSC, CYS1 is a weaker inhibitor but it displays a higher affinity for cathepsin B, which is known to be involved in tumor progression. Therefore, overexpression of CYS1 can partially neutralize the inhibitory effect of CYSC on cathepsin B, inducing stronger tumor invasiveness mediated by enhanced cathepsin B activity [60]. In addition to its ability to neutralize CYSC, CYS1 also upregulates AKT phosphorylation and activates the PI3K/AKT pathway. This subsequently downregulates E-cadherin and facilitates EMT, promoting tumor metastasis [58]. CYS1 directly interacts with the ferroptosis mediator GPX4 by interfering with the ubiquitination of GPX4 and stabilizing it, thus inhibiting tumor cell ferroptosis. This consequently promotes tumor progression and metastasis in gastric cancer models [53].

2.2. Other SD-Type Cystatins (*CST2, CST4, CST5*)

Since SD-type cystatins share a highly similar amino acid sequence and protein structure, it is not surprising that CYS2 and CYSS exhibit pro-tumor functions. However, studies on these cystatins are limited, which makes it difficult to conclude whether they have the same pro-tumor mechanism as CYS1. Upregulation of *CST2* correlates with tumor metastasis of prostate and gastric cancer [61][62]. CYS2 may help regulate the TGF-β signaling pathway and promote EMT like CYS1, but the mechanism needs further exploration to be certain [61]. *CST4* is upregulated in esophageal, colon, and gastric cancer and is associated with poor prognosis [63][64][65]. The overexpression of CYSS in gastric tumor cells upregulates a protein called ELFN2, which directly inhibits the expression of E-cadherin and promotes EMT, like CYS1 and CYS2 [64]. However, there are very few studies on ELFN2 and its connection with tumor invasiveness. Thus, future studies are needed to determine how CYSS promotes tumor growth.

In contrast, based on biomarker studies of colon, gastric, and prostate cancer, *CST5* is considered an antitumor gene [66][67][68]. *CST5* expression is induced by vitamin D, which is known to have antitumor activity and is downregulated in human colon cancer cells [69][70][71]. CYSD inhibits the Wnt/β-catenin signaling pathway and oncogenic c-MYC expression, which consequently extends the cell cycle and reduces the proliferation, migration, and invasiveness of colorectal tumor cells [69]. Importantly, some studies have suggested that *CST5* is a downstream target of p53 [72]. The p53 protein enhances *CST5* expression by interacting with the *CST5* promoter region and simultaneously downregulating EMT-promoting transcription factor SNAIL, which in turn downregulates *CST5* expression [72].

2.3. Cystatin C (CYSC)

CYSC has a dual effect on cancer development. It was observed to have an antitumor function on several cancer types, including pancreatic cancer, breast cancer, and leukemia [73][74][75][76]. Currently, there are at least two mechanisms that can explain the antitumor function of CYSC. First, the antitumor effect of CYSC is highly related to its strong inhibitory effect on cathepsin B. Compared with other type 2 cystatins, CYSC is the strongest inhibitor of cathepsin B [77]. Because CYSC inhibits cathepsin B, CYSC acts as a suppressor of cell migration, thereby inhibiting tumor invasion and metastasis [78]. CYSC is also an inhibitor of the TGF-β pathway. CYSC directly interacts with TGF-β receptor 2 and competes with the binding of the TGF-β ligand. By inhibiting the TGF- β signaling pathway, CYSC inhibits multiple metastatic events in tumor cells, such as loss of cell contacts, downregulation of cell polarization, and increased cell migration [79].

In contrast, there are also several studies stating that a high CYSC level correlates with a worse prognosis. High levels of CYSC were found in tumor tissue of ovary, colon, and esophageal cancer [80][81][82]. Cathepsin B has been found to promote apoptosis and this could be linked to the observed phenomenon that CYSC suppresses apoptosis of tumor cells [83][84]. However, the mechanism by which CYSC promotes tumor progression is unknown. CYSC can be used as a biomarker for cancer prognosis. However, recent studies suggest that renal function, which is frequently altered in cancer, heavily influences the levels of serum CYSC and intercellular CYSC [85][86]. This could negatively impact the use of CYSC as an effective biomarker for cancer prognosis.

2.4. Cystatin E/M (CYS6)

CYS6 has been found to have dual effects, exhibiting pro-tumor properties in some cancers and anti-tumor properties in others. *CST6* is an antitumor gene that is hypermethylated in breast, prostate, brain, and cervical cancer [43][87][88][89]. The antitumor effect of *CST6* has been mostly studied in breast cancer models and its downregulation correlates with higher levels of migration and invasiveness in both in vivo and in vitro models of breast cancer [87]. The epigenetic silencing of *CST6* is strongly correlated to breast cancer bone metastasis [87]. CYS6 also inhibits the pro-oncogenic function of legumain [90][91]. In addition, CYS6 inhibits cathepsin B, which is frequently upregulated in breast cancer [92]. Cathepsin B cleaves SPHK1, an enzyme that inhibits osteoclast differentiation by inhibiting p38 activation induced by RANKL [92]. Uncontrolled osteoclast differentiation disrupts bone homeostasis, causes bone disease, and promotes cancer bone metastasis [93]. Furthermore, CYS6 inhibits

cathepsin K, an enzyme that is predominantly expressed in osteoclasts and participates in bone matrix remodeling [44]. Therefore, CYS6 suppresses bone metastasis of tumor cells by inhibiting osteoclastogenesis. CYS6 also inhibits NF-κB signaling in both canonical and non-canonical pathways [43][44].

In contrast, *CST6* has also been found to have pro-tumor functions in pancreatic, liver, gastric, and triple-negative breast cancer [94][95][96][97]. Additionally, a small fraction of patients with multiple myeloma express high levels of *CST6* [44]. A recent paper has identified *CST6* as a factor involved in the dysregulation of necroptosis in gastric tumor cells, resulting in a poor prognosis for patients with gastric cancer [97].

2.5. Cystatin F (CYSF)

Although there are extensive reports on the immunoregulatory function of CYSF, the role of CYSF in cancer is unclear. Given the immunosuppressive function of CYSF, uncontrolled upregulation of *CST7* likely enhances tumor progression. Indeed, high levels of *CST7* are associated with poor prognosis and lower survival rates in patients with liver, oral, and brain cancer [46][98][99]. The current literature has shown that the pro-tumor effects of CYSF are highly correlated to its immunosuppressive function. Upregulation of *CST7* causes a decrease in the cytotoxicity of NK cells to tumor cells [98]. In contrast, multiple studies suggest that *CST7* downregulation is associated with higher invasiveness of tumors, more metastatic events, and tumor progression in prostate cancer, lung cancer, pancreatic cancer, and lymphoma [100][101][102][103]. Since *CST7* downregulation is correlated with metastasis and tumor progression, this indicates that *CST7*, like other type 2 cystatin family members, regulates the cathepsin B-L metastatic axis. However, further studies are needed to draw definitive conclusions on the role of *CST7* in cancer progression.

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