TLAR 1947

Arch Rheumatol 2018;33(4):498-504
doi: 10.5606/ArchRheumatol.2018.6595

REVIEW

Cathepsin G and Its Role in Inflammation and Autoimmune Diseases

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ABSTRACT

Cathepsin G belongs to the neutrophil serine proteases family, known for its function in killing pathogens. Studies over the past several years indicate that cathepsin G has important effects on inflammation and immune reaction, and may be a key factor in the pathogenesis of some autoimmune diseases. In this article, we discuss the roles of cathepsin G in inflammation, immune reaction, and autoimmune diseases. To our knowledge, this is the first study providing important information about cathepsin G in the pathogenesis of autoimmune diseases and suggesting that cathepsin G may be a new biomarker or treatment target.

Keywords: Autoimmune disease; cathepsin G; immune reaction; inflammation.

Cathepsin G (CTSG) is a member of the serine proteases family, which was first found in the azurophilic granules of neutrophil leukocytes and named in 1976.[1,2] Then, CTSG was detected in other myeloid cells, such as B cells, primary human monocytes, myeloid dendritic cells, plasmacytoid dendritic cells, and murine microglia.[3] Recently, studies proved that CTSG also existed in neutrophil traps and human urine exosomes.[4,5] The gene for CTSG was located on chromosome 14q11.2, spans 2.7kb, and consists five exons and four introns,[6] prepro-CTSG was a 255-amino-acid residue protein. After cleavage of the signal peptide, two amino acids and 11 amino acids remain at the N-terminal and C-terminal side of pro-CTSG, respectively. Both of these may be released by proteases.[7] CTSG was stored in primary granules in the aforementioned cells, and when the cells were stimulated by immune complexes, some pharmacological agents or phagocytosis, CTSG was released to the extracellular space or bound on the surface of those cells[1,8] which were the two active forms of CTSG.[9] Released CTSG can evade its inhibitors, which exist in the extracellular space, by binding to cell membranes, forming sequestered microenvironments, binding to its substrates tightly, and inactivating its inhibitors.[10]

Cathepsin G has many functions. It can clear pathogens, regulate inflammation by modifying the chemokines, cytokines, cell surface receptors,[11-14] and C components,[1] control the blood pressure, and induce thrombogenesis.[15,16] Purified CTSG also has important effects on increasing the permeability of endothelial cells[17] and epithelial cells.[18] Furthermore, studies have shown that mice with loss-of-function mutations in CTSG were resistant to experimental arthritis,[19] and had marked decrease in tubular cells apoptosis and collagen deposition after renal ischemia/reperfusion injury.[20] Inhibition of CTSG with its inhibitor reduced tumor growth factor-beta signaling, which subsequently reduced tumor vascularity by decreasing in both monocyte chemotactic protein-1 and vascular endothelial

Received: July 24, 2017 ***Accepted:*** December 23, 2017 ***Published online:*** January 22, 2018

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Citation:
Gao S, Zhu H, Zuo X, Luo H. Cathepsin G and its role in inflammation and autoimmune diseases. Arch Rheumatol 2018;33(4):498-504.

growth factor.[21] The CTSG family members may become new biomarkers or treatment targets for autoimmune diseases and other diseases in the following years. In this article, we reviewed the effects of CTSG in inflammation and immune reaction, and discussed the important roles of CTSG in autoimmune diseases.

ROLES OF CATHEPSIN G IN INFLAMMATION AND IMMUNE REACTION

Cathepsin G has important roles in the development of inflammation. It promotes the migration of neutrophils, monocytes and antigen presenting cells (APCs) by changing chemokine (C-X-C motif) ligand 5 and chemokine (C-C motif) ligand 15 into more potent chemotactic factors by proteolytic processing of CTSG,[22,23] and converting prochemerin into chemerin, which is a novel chemoattractant factor that specifically attracts APCs through its receptor ChemR.[23,24] CTSG is able to cleave chemokine (C-C motif) ligand 23 at its N-terminal or C-terminal, resulting in potent CC-type chemokine receptor 1 and formyl peptide receptor-like 1 activity, which is an attractant of monocytes and neutrophils *in vitro*, and recruit leukocytes *in vivo*.[25] CTSG can also promote inflammation by activating the cell surface receptors. For example, CTSG directly activates protease-activated receptors 4 (PAR4) at the surface of platelets, which may lead to platelet secretion and aggregation, and the interaction between neutrophils and platelets at the sites of inflammation or vascular injury.[26] CTSG is able to activate protease-activated receptors 2 (PAR2) on the surface of human gingival fibroblasts by cleaving the peptide corresponding to the N terminus of PAR2, which leads to the production and secretion of interleukin-8 and monocyte chemoattractant protein 1 and may play roles in a number of inflammatory processes such as periodontitis.[27] CTSG stimulates monocytes to produce oxidative burst and pro-inflammatory cytokines by releasing soluble CD23 fragments, which is independent of any co-stimulatory signals.[28]

The roles of CTSG in immune reaction are mediated by regulating the autoantigen processing, and activating lymphocytes, and so on. It has been proven that CTSG degraded the immunodominant myelin basic protein (MBP) epitope (MBP85-99), generated another T cell epitope (MBP115-123), and eliminated its binding to major histocompatibility complex (MHC) class II and a MBP-specific T cell response, thus participating in the immunopathogenesis of multiple sclerosis.[29] CTSG also plays a critical role in processing proinsulin into several intermediates, which can polarize T cell activation in type 1 diabetes.[30] Selective inhibition of CTSG result in reduced tetanus toxin C-fragment and hemagglutinin processing and presentation to $CD4^+$ T cells,[31] and CTSG augments antigen specific antibody via activation of T cells by involving both T helper 1 (Th1) and Th2 pathways in BALB/c mice.[32] Some scientists show that CTSG on the U937 cell surface is able to cleave complement 3 (C3) into C3a-, C3b-, C3c- and C3d-like fragments, and these active fragments are likely to be involved in cell-protein interactions, and cell-cell interactions, and in mediating immune reaction and inflammatory response.[33]

Cathepsin G augments the production of antigen-specific antibody by activating T cells in BALB/C mice.[32] CTSG binds to lymphocytes, including $CD4^+$, $CD8^+$, natural killer, and B cells with a thrombin-like receptor,[34] increases the cytotoxicity of natural killer cells, activates reactive T cells, and increases cytokines and antigen-specific antibody production. All the above functions are CTSG dose dependent.[35]

ROLES OF CATHEPSIN G IN VASCULAR PERMEABILITY

Cathepsin G affects the cell shapes and causes the formation of intercellular gap in the endothelial cells and epithelial cells, which can increase their permeability. The exact mechanism may relate to breaking the balance of calcium homeostasis, which may lead to increased inositol phosphate and the activation of protein kinase C, and increase albumin flux across the endothelial monolayer;[36] or relate to cleaving the extracellular part of vascular endothelial cadherin, an essential protein to maintain vascular integrity.[37] Scientists have found that neutrophil surface-bound proteases could cleave vascular endothelial

cadherin of human umbilical vein endothelial cells inducing the formation of gaps and increasing the transmigration of neutrophils, and these could be reduced by specific inhibition of CTSG.[37,38] CTSG can also increase the permeability of human microvascular endothelial cell monolayers by degrading the tight junction protein occludin and vascular endothelial-cadherin, which may mediate the vasogenic edema during diabetic ketoacidosis.[39] The mechanisms of CTSG increasing the vascular permeability may also have some relationship with its role in cleaving extracellular matrix components.

Cathepsin G increases the permeability of type II epithelial monolayers in some types of acute and chronic lung disease, which is accompanied by structural changes in the monolayers with enlarged intercellular gaps visible by scanning electron microscopy.[40] CTSG increases the paracellular permeability of intestinal epithelial barriers through PAR4, and increases the phosphorylation of myosin light chain, leading to the disruption of epithelial tight junction in ulcerative colitis.[41,42]

Cathepsin G affects tissue remodeling directly by degrading components of the matrix and indirectly by cleaving and activating matrix-degrading metalloproteinases. It has been proven that CTSG induces the activation of promatrix metalloproteinase-2 in a dose- and time-dependent way, and injuries the microvasculature, thus playing roles in tumor invasion and angiogenesis.[43] CTSG has been found in the physiologic and pathologic vascular regression, and to be capable of activating matrix metalloproteinase-1 and matrix metalloproteinase-10, participating in capillary tube regression and collagen gel contraction.[44]

Increased vascular permeability is found in numerous diseases, such as sepsis, acute lung injury, encephaledema, and so on. Thus, CTSG may involve in the development and progression of these diseases, but the specific molecular mechanism needs further studies.

CATHEPSIN G AND AUTOIMMUNE DISEASES

As mentioned above, the role of CTSG in immune reaction and inflammation is complicated and various, and CTSG participate in the pathogenesis of some autoimmune diseases. The concentration and activity of CTSG are increased in the synovial fluids of rheumatoid arthritis (RA) patients when compared with healthy controls or patients with osteoarthritis. However, the CTSG messenger ribonucleic acid (mRNA) levels are not higher in $CD14^+$ cells of RA, because CTSG mainly play roles in peripheral joints.[45] As a monocyte chemoattractant, CTSG affected the involvement of monocytes in synovial lesions of RA patients, and CTSG concentration in the synovial fluid of RA patients was significantly correlated with the count of lymphocytes.[46] Studies have shown that CTSG in the adjacent cartilage-pannus junction can degrade articular cartilage in RA.[47] CTSG is one of the antigens of anti-neutrophil cytoplasmic antibodies in Japanese patients with RA, but the difference between the positive and negative groups in terms of clinical manifestations and laboratory parameters is not significant.[48] Further studies are necessary to elucidate how CTSG increases monocyte chemotaxis and its exact role in the pathogenesis of RA.

Cathepsin G was the major antigen for anti-neutrophil cytoplasmic antibodies in systemic lupus erythematosus (SLE), and the CTSG antibodies in the sera of active SLE patients were significantly increased than inactive patients and healthy controls, and rapidly decreased after the corticosteroid therapy.[49] Other studies also proved that CTSG in the sera of SLE patients may correlate with disease activity and vasculitis, but has no relationship with organic involvement.[50,51] Anti-CTSG anti-neutrophil cytoplasmic antibodies were the major antigenic targets of antineutrophil cytoplasmic autoantibodies in systemic sclerosis, but were not significantly associated with any clinical or serological features. However, the exact role in scleroderma needs to be clarified.[52,53]

The mRNA levels of CTSG increase in peripheral blood mononuclear cells and muscles of dermatomyositis patients. The activity of serum CTSG also increase in dermatomyositis and correlate with creatine kinase and lactate dehydrogenase levels; moreover, patients with Jo-1 auto-antibody have higher activity of CTSG. Besides, CTSG increases the lymphocytes infiltration through inducing the expression of protease activated receptor 2 and altering the

cytoskeleton of human dermal microvascular endothelial cells.[54]

As for multiple sclerosis, CTSG participated in the disease development as a rate-limiting protease for the degradation of intact myelin basic protein. CTSG can directly destroy the major immunodominant myelin basic protein epitope, which may enable myelin basic protein-specific autoreactive T cells to escape negative selection, therefore involving in the pathogenesis of multiple sclerosis.[29,55]

Both the transcript level and activity of CTSG were increased in type 1 diabetes mellitus patients compared with healthy control donors. CTSG degraded proinsulin after internalization into endocytic compartments, and activated proinsulin reactive T cells. This process can be significantly reduced by a CTSG inhibitor.[30] In non-obese diabetic mice, the expression of CTSG was increased. Treating the mice with CTSG-specific inhibitor reduced the blood glucose level, improved the function of islet beta cells, and reduced the activation of $CD4^+$ T cells. Using CTSG small interfering RNA in the pre-diabetic mellitus stage improved the function of islet beta cells, reduced islet inflammation and beta cell apoptosis, and lowered the activation level of $CD4^+$ T cells, thus slowing down the progression of diabetes.[56]

In conclusion, CTSG has important roles in the development and progression of some autoimmune diseases. Although the specific role needs further clarification, it may involve the activation of immune cells and the mobilization of immune reaction by inducing the production of lymphokines, which in turn promote T cell-dependent cellular immunity and antigen-specific antibody production.

OTHER CATHEPSINS AND AUTOIMMUNE DISEASES

Except for CTSG, other cathepsins also play important roles in autoimmune diseases and serve as useful biomarkers. The concentration and activity of cathepsin B,[57-59] cathepsin D,[60] cathepsin K,[61,62] cathepsin L,[63,64] and cathepsin S[65] were increased in synovial cells, synovial fluid and even in the sera of RA patients. When inhibited by specific inhibitor, they could suppress autoimmune inflammation of the joints, and osteoclastic bone resorption, leading to less cartilage damage. The upregulation of cathepsin K in the sera of RA patients correlated with the degree of radiological damage, and erythrocyte sedimentation rate.[62] The level of cathepsin L and cathepsin S in the synovial fluid was higher in patients with anti-cyslic citrullinated peptides, immunoglobulin M-rheumatoid factor and immunoglobulin A-rheumatoid factor.[64]

In SLE patients, the activity of serum cathepsin D correlated with renal involvement.[65] In MRL-Fas(lpr) mice, cathepsin S could promote SLE by driving MHC II mediated T and B cell priming, germinal center formation and B cell maturation towards the plasma cells, which could be reversed by its antagonists.[66]

In Sjögren's syndrome; cathepsin B, cathepsin D, and cathepsin S were present and had greater immunoreactivity in the acini and tears of patients.[67,68] and cathepsin S inhibitor was effective in preventing the autoimmune lesions of the salivary and lacrimal glands in the Sjögren's syndrome model.[69] Cathepsin K was also strongly expressed in ankylosing spondylitis patients at the sites of bone destruction.[70] The expression and activity of cathepsin B,[71,72] cathepsin D, and cathepsin S[73] were elevated in multiple sclerosis patients, and were associated with the physiologic degradation of myelin basic protein. It has been proven that single nucleotide polymorphisms within cathepsin S gene were closely associated with the immunotherapies for multiple sclerosis.[74] Cathepsin B[75] and cathepsin S[76] also had a potential role in the pathology of Graves' disease and myasthenia gravis.

In conclusion, cathepsin G is an important regulator of immune reaction and inflammation. Studies over the past years demonstrate that, besides clearing pathogens, CTSG can regulate immune reaction and inflammatory response by modifying chemokines, cytokines, and cell surface receptors, and activate some lymphocytes. It can also increase the permeability of endothelial cells and epithelial cells. Recently, more and more reports show that CTSG family members play pivotal roles in the development and progression of autoimmune diseases, and their concentrations or activities correlate with the clinical or serological features of diseases. Nonetheless, the exact

mechanism needs further studies. Studies indicate that inhibition of CTSG may be an effective approach for the treatment of atopic dermatitis, psoriasis, psoriatic arthritis, RA, and other clinical conditions.[77] Along with other studies on the pathogenesis of CTSG in inflammation and autoimmune disease, CTSG may become a new biomarker or therapeutic targets in some diseases.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

This work was supported by grants from National Natural Science Foundation of China (81373206, 81401357), National High Technology Research and Development Program of China (2012AA02A513), Hunan Natural Science Foundation (13JJ5010), Hunan Special Fund for Science and Technology Development Program (2013WK3022), and Independent Innovation Projects of Central South University (2016zzts131).

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