Correlation of cathepsin S with coronary stenosis degree, carotid thickness, blood pressure, glucose and lipid metabolism and vascular endothelial function in atherosclerosis

SHENGYANG HUANG and YU CAO

Cardiovascular Department, The Third Xiangya Hospital of Central South University,
Changsha, Hunan 410000, P.R. China

Abstract. Correlation of cathepsin S with coronary stenosis degree, carotid thickness, blood pressure, glucose and lipid metabolism, and vascular endothelial function in patients with atherosclerosis was investigated. Data from 120 patients with increased cathepsin S levels (increased group) and 120 subjects with normal cathepsin S levels (normal group) were retrospectively analyzed. The serum cathepsin S level and Gensini score were compared between the healthy subjects and patients with coronary atherosclerotic heart disease, and the correlation between serum cathepsin S level and Gensini score was analyzed. The carotid thickness, mean arterial pressure, and indexes related to glucose and lipid metabolism, as well as vascular endothelial function were compared between the two groups. The correlation of the serum cathepsin S level with carotid intima-media thickness (IMT), mean arterial pressure, fasting blood glucose, total cholesterol (TC) and nitric oxide (NO) was also investigated. Patients with multi-vessel coronary artery disease (CAD) had higher serum cathepsin S level than those with double-vessel and single-vessel disease, and higher level than that of healthy subjects. The Gensini score of patients with multi-vessel CAD was higher than that of patients with double-vessel and single-vessel disease, as well as that of healthy subjects. The serum cathepsin S level was positively correlated with the Gensini score. Patients with increased cathepsin S level had greater IMT, higher mean arterial pressure, fasting blood glucose, fasting insulin (FINS), triglyceride (TG), TC, and endothelin-1 (ET-1), however, lower NO level than those of healthy subjects. The serum cathepsin S level was positively correlated with IMT, mean arterial pressure, fasting blood glucose, and TC, however, it was negatively correlated with the NO level. In conclusion, as the serum cathepsin S level is elevated, the coronary stenosis is aggravated, the carotid thickness and blood pressure are increased, and the glucose and lipid metabolism, as well as vascular endothelial function are significantly abnormal.

Introduction

As a papain cysteine protease and one of lysosomal proteases, cathepsin S mainly participates in the degradation of various tissue proteins and acts as a catalytic enzyme in the process of proteolysis, and therefore it is the most common endonuclease in the body (1). Cathepsin S can not only degrade and transform intracellular proteins under acid conditions, but can also exert physiological effects (2), vascular activity-regulating effects and modulatory effects on the proliferation and differentiation of endothelial cells (3) under extracellular neutral conditions. Moreover, it has important clinical value in the proliferation and migration of a variety of cytokines (4).

Cathepsin S can also promote the degradation of type I and IV collagens, as well as their laminins among the components of extracellular matrix (5). In the physiological process, it degrades the collagens in the above mentioned intercellular substances mainly through the chemotaxis and aggregation of smooth muscle cells toward the macrophages, fibrous cap cells, tunica media and other sites, thus leading to rupture of atherosclerotic plaques (6). Moreover, cathepsin S is able to accelerate the production of inflammatory cytokines in the body, further degrading elastic fibrous protein and collagen in the atherosclerotic plaques causing attenuation and even rupture of the atherosclerotic plaques. Finally, it can migrate to the vicinity of the vascular intima media, and positive feedback can increase the secretion and release of cathepsin S, thereby triggering the formation of massive foam cells in the body and prominently speeding up the instability of the atherosclerotic plaques (7). Although related clinical studies have verified that (8) the level of cathepsin S is associated with the formation of atherosclerosis, there are few reports on the correlation of cathepsin S with the coronary stenosis degree and carotid thickness in atherosclerosis patients. This study investigated these issues and analyzed the relation of cathepsin S with blood pressure, glucose and lipid metabolism, and vascular endothelial function.

Correspondence to: Dr Yu Cao, Cardiovascular Department, The Third Xiangya Hospital of Central South University, 138 Tongzipo Road, Hexi Yuelu, Changsha, Hunan 410000, P.R. China
E-mail: kyzrz245@163.com

Patients and methods

General data. Relevant data of 120 patients with increased cathepsin S levels, admitted and treated in The Third Xiangya Hospital of Central South University (Changsha, China) from February 2016 to August 2018 (increased group), and data from 120 subjects with normal cathepsin S levels, enrolled in the same time period (normal group), were retrospectively analyzed. In the increased group, there were 40 patients definitely diagnosed with coronary atherosclerotic heart disease, including 23 males and 17 females, 50-70 years of age, with an average age of 63.3±2.1 years. The course of disease was 3-21 years, with an average of 8.4±0.4 years. Forty patients were definitely diagnosed with carotid intima-media thickening, including 21 males and 19 females, 50-70 years of age, with an average age of 63.4±2.0 years. The course of disease was 3-20 years, with an average of 8.5±0.4 years. There were 40 patients with hypertension, including 23 males and 17 females, 50-70 years of age, with an average age of 63.5±2.1 years, a disease course of 5-25 years and an average course of 9.4±0.4 years. Normal group consisted of 63 males and 57 females, 50-70 years of age, with an average age of 63.4±2.0 years. The general data of the groups are presented in Table I. The study was approved by the Ethics Committee of The Third Xiangya Hospital of Central South University. Signed informed consents were obtained from all participants before the study.

Methods. The level of cathepsin S was detected in all patients using enzyme-linked immunosorbent assay (R&D Systems, Inc.). The serum cathepsin S level and Gensini score were compared between the healthy subjects and patients with coronary atherosclerotic heart disease, and the correlation between serum cathepsin S level and Gensini score was analyzed. The carotid thickness, mean arterial pressure and indexes related to glucose and lipid metabolism, as well as vascular endothelial function were compared. Also, the correlation of the serum cathepsin S level with carotid intima-media thickness (IMT), mean arterial pressure, fasting blood glucose, total cholesterol (TC) and nitric oxide (NO) was investigated. Fasting blood glucose and TC were measured by an Automatic Biochemistry Analyzer (Abbott 8200; Abbott Pharmaceutical Co. Ltd.). NO was measured by a Nitric Oxide Colorimetric Assay kit (K262-200; AmyJet Scientific, Inc.).

Evaluation criteria. Coronary artery stenosis was evaluated on the basis of coronary angiography. All coronary angiography results were entered into a software (CAAS II System; Pie Medical Imaging BV) and then analyzed by physicians with >5 years of experience in interventional therapy or interventional therapy in the Department of Cardiology. Patients with a degree of coronary artery stenosis >50% were assessed as positive and diagnosed with coronary artery disease (CAD), and those with a degree of coronary artery stenosis <50% were assessed as negative. The degree of vascular stenosis was evaluated with reference to the Gensini scoring system of the American Heart Association, including 1 point (stenosis degree of each coronary artery, <25%), 2 points (stenosis degree of each coronary artery, 26-50%), 4 points (stenosis degree of each coronary artery, 51-75%), 8 points (stenosis degree of each coronary artery, 76-90%), 16 points (stenosis degree of

Table I. General data.

Factors	Increased group	Normal group
Sex		
Male	66	63
Female	54	57
Age (years)	63.4±2.1	63.2±2.2
CAD		
Yes	40	5
No	80	115
IMT		
Yes	40	9
No	80	111
Hypertension		
Yes	40	11
No	80	109

CAD, coronary artery disease; IMT, intima-media thickness.

each coronary artery, 91-99%) and 32 points (stenosis degree of each coronary artery, 100%). In terms of IMT, the thickness at 2 cm of the proximal part of bilateral internal carotid arteries of all the patients was measured using GE Vivid 7 color ultrasound diagnostic instrument (GE Healthcare), which was regarded as the carotid IMT, with a normal value of <1.0 mm. The indexes of glucose metabolism included fasting blood glucose (normal reference value for adults, 3.9-6.1 mmol/l) and fasting insulin (FINS) (normal reference value for adults, 3.0-24.9 U/ml). The indexes of lipid metabolism consisted of triglyceride (TG) (normal reference value for adults, 0.56-1.71 mmol/l) and TC (normal reference value for adults, 2.83-5.17 mmol/l). The indexes of vascular endothelial function were endothelin-1 (ET-1) (normal reference value for adults, 43.50-58.38 ng/l) and NO (normal reference value for adults, 13.8-34.6 μmol/l).

Statistical analysis. Statistical Product and Service Solutions (SPSS) 20.0 software (IBM Corp.) was used. The measurement data, such as the data of serum cathepsin S level, Gensini score, carotid thickness, mean arterial pressure and related indexes to glucose and lipid metabolism, as well as vascular endothelial function, were expressed as mean ± standard deviation (mean ± SD). t-test was performed for the comparison of the mean between two groups. Comparison among multiple groups was carried out using one-way ANOVA followed by a post hoc test (Tukey's honestly significant difference). Also, Pearson's correlation analysis was applied to analyze the correlation of serum cathepsin S level with Gensini score, IMT, mean arterial pressure, fasting blood glucose, TC and NO. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Serum cathepsin S level in healthy subjects and patients with coronary atherosclerotic heart disease. The serum cathepsin S
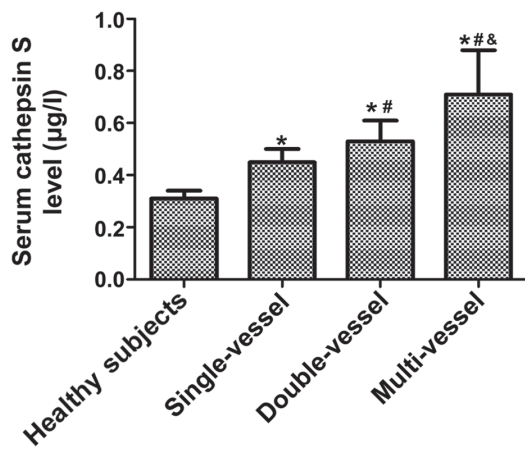
Figure 1. Comparison of serum cathepsin S levels between healthy subjects and patients with coronary atherosclerotic heart disease. The serum cathepsin S level in the patients with multi-vessel coronary artery disease was higher than that in patients with double-vessel and single-vessel disease, as well as in healthy subjects. *P<0.05, compared with healthy subjects; #P<0.05, compared with single-vessel disease patients; &P<0.05, compared with double-vessel disease patients.
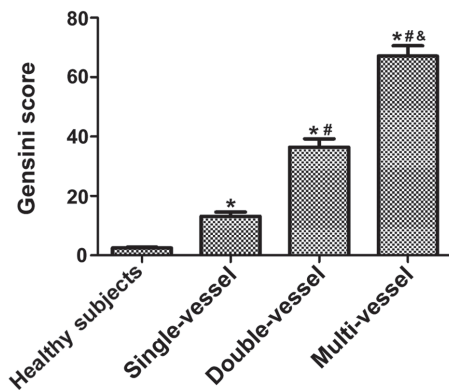

Figure 2. Comparison of Gensini scores between healthy subjects and patients with coronary atherosclerotic heart disease. The Gensini score in the patients with multi-vessel coronary artery disease was higher than that in patients with double-vessel and single-vessel disease, as well as in healthy subjects. *P<0.05, compared with healthy subjects; #P<0.05, compared with single-vessel disease patients; &P<0.05, compared with double-vessel disease patients.

level was 0.31±0.03 μg/l in healthy subjects, 0.45±0.05 μg/l in patients with single-vessel CAD, 0.53±0.08 μg/l in patients with double-vessel disease, and 0.71±0.17 μg/l in patients with multi-vessel disease. The patients with multi-vessel CAD had a higher serum cathepsin S level than those with double-vessel and single-vessel disease, and a higher level than the healthy subjects (F=7.493, P<0.05) (Fig. 1).

Gensini score in healthy subjects and patients with coronary atherosclerotic heart disease. The Gensini scores were 2.5±0.3, 13.2±1.4, 36.4±2.8 and 67.1±3.5 points in healthy subjects, patients with single-vessel CAD, patients with double-vessel disease and patients with multi-vessel disease, respectively. The patients with multi-vessel CAD had a higher Gensini score than those with double-vessel and single-vessel disease, and a higher score than the healthy subjects (F=9.201, P<0.05) (Fig. 2).
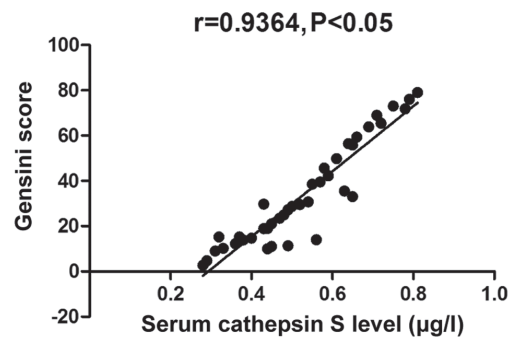

Figure 3. Correlation analysis of the serum cathepsin S level and Gensini score. The serum cathepsin S level is positively correlated with Gensini score (P<0.05).

Correlation analysis between the serum cathepsin S level and Gensini score. The serum cathepsin S level was positively correlated with Gensini score (r=0.9364, P<0.05) (Fig. 3).

Comparison of carotid thickness, mean arterial pressure and indexes related to glucose and lipid metabolism, as well as vascular endothelial function. Patients with increased serum cathepsin S level had greater IMT (P<0.05), higher mean arterial pressure (P<0.05), fasting blood glucose, FINS (P<0.05), TG, TC (P<0.05) and endothelin-1 (P<0.05), however, lower NO level (P<0.05) than those of healthy subjects (Table II).

Correlation analysis of the serum cathepsin S level with IMT, mean arterial pressure, fasting blood glucose, TC and NO. The serum cathepsin S level was positively correlated with IMT, mean arterial pressure, fasting blood glucose and TC levels (P<0.05), however, was negatively correlated with NO level (P<0.05) (Figs. 4-8).

Discussion

As a papain with the richest functions in the mammalian elastase system, cathepsin S is of great value in numerous pathophysiological processes, such as gene transcription and regulation through controlling the promoter of protein genes (9). Therefore, it is considered as the most common candidate gene for the occurrence and development of atherosclerosis (10). Immunohistochemical assay results have indicated that remarkable expression of cathepsin S exists in macrophages, smooth muscle cells of fibrous cap and intimal elastic lumina during atherosclerotic process (11). However, western blotting combined with elastase analysis have suggested that the expression levels of cathepsin S and cathepsin K in the extracts of atherosclerotic tissues are markedly elevated, thus strengthening the dissociation activity of elastic tissues (12). As a result, cathepsin S plays a vital role in the occurrence and development of atherosclerosis. Another study has identified cathepsin S as a marker of adiposity and it has been proposed that cathepsin S represents a molecular link between obesity and atherosclerosis (13). In addition, large quantities of studies have indicated that (14) the activity of lysosomal cysteine proteases has great impact on the occurrence and development of atherosclerosis, and cathepsin S is also the most important lysosomal cysteine protease. Chen *et al* (15)

Table II. Comparison of carotid thickness, mean arterial pressure, and indexes related to glucose and lipid metabolism, as well as vascular endothelial function (mean ± SD) between the two groups.

Groups	IMT (mm)	Mean arterial pressure (mmHg)	Fasting blood glucose (mmol/l)	FINS (mU/l)	TG (mmol/l)	TC (mmol/l)	ET-1 (ng/l)	NO (µmol/l)
Normal group	0.82±0.03	108.3±1.6	5.0±0.3	4.2±0.1	1.7±0.1	3.0±0.1	51.6±3.0	30.7±3.2
Increased group	1.78±0.11	143.2±2.8	9.7±0.7	9.1±0.3	3.4±0.2	5.5±0.3	129.5±4.5	8.8±1.3
t value	92.234	118.549	67.604	169.741	83.283	86.603	157.785	69.457
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

$P < 0.05$ indicates statistical significance; IMT, intima-media thickness; FINS, fasting insulin; TG, triglyceride; TC, total cholesterol; ET-1, endothelin-1; NO, nitric oxide.
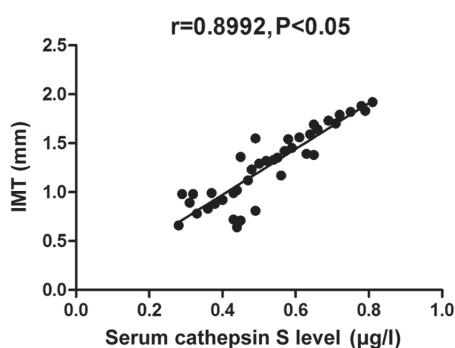

Figure 4. Correlation analysis of the serum cathepsin S level and IMT. The serum cathepsin S level is positively correlated with IMT ($P < 0.05$). IMT, intima-media thickness.
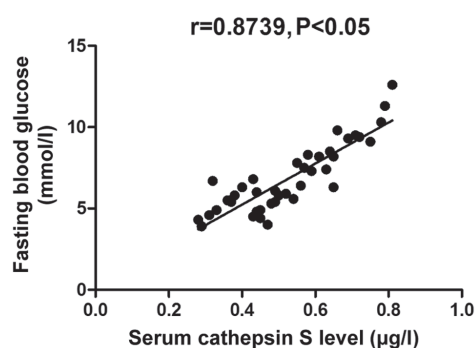

Figure 6. Correlation analysis of the serum cathepsin S level and fasting blood glucose. The serum cathepsin S level is positively correlated with fasting blood glucose ($P < 0.05$).
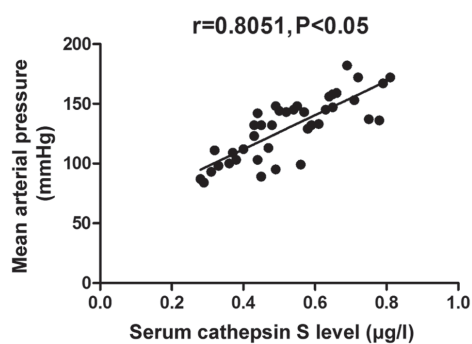

Figure 5. Correlation analysis of the serum cathepsin S level and mean arterial pressure. The serum cathepsin S level is positively correlated with mean arterial pressure ($P < 0.05$).
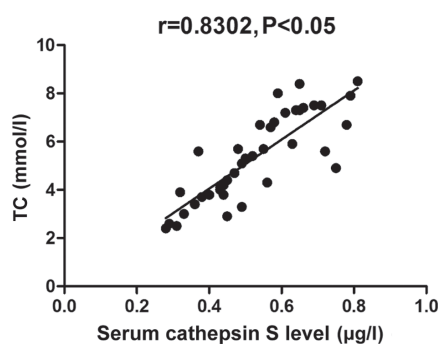

Figure 7. Correlation analysis of the serum cathepsin S level and total cholesterol. The serum cathepsin S level is positively correlated with total cholesterol ($P < 0.05$).

found that cathepsin S and insulin resistance are independent of each other. At the same time, increased blood pressure, abnormal glucose and lipid metabolism, as well as vascular endothelial function are relevant or independent risk factors for atherosclerosis. However, there is no previous research report on the correlation of cathepsin S with blood pressure change, glucose and lipid metabolism and vascular endothelial function.

This investigation focused on the comparisons of serum cathepsin S level and Gensini score between healthy subjects and patients with coronary atherosclerotic heart disease, and it was discovered that the patients with multi-vessel CAD
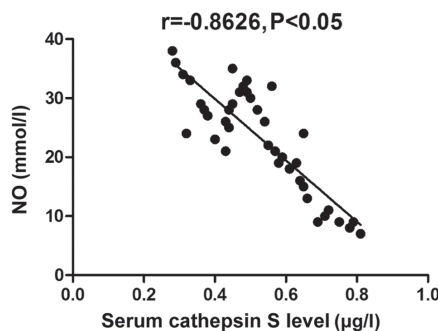

Figure 8. Correlation analysis of the serum cathepsin S level and NO. The serum cathepsin S level is negatively correlated with NO ($P < 0.05$). NO, nitric oxide.

have higher serum cathepsin S level and Gensini score than those with double-vessel and single-vessel disease, as well as healthy subjects. Furthermore, correlation analysis between the serum cathepsin S level and Gensini score revealed that the serum cathepsin S level is positively correlated with Gensini score. These results suggest that for the patients with coronary atherosclerotic heart disease, the wider the extent of the lesion is, the higher the serum cathepsin S level will be, and the elevated serum cathepsin S level will lead to a higher Gensini score. Also, the serum cathepsin S level, carotid thickness, mean arterial pressure and indexes related to glucose and lipid metabolism, as well as vascular endothelial function were compared. The results showed that the patients with increased serum cathepsin S level have greater IMT, higher mean arterial pressure, fasting blood glucose, FINS, TG, TC and ET-1, however, lower NO level than healthy subjects. Patients with elevated serum cathepsin S level had also increased carotid IMT, raised levels of blood pressure, blood glucose and blood lipid and impaired vascular endothelial function. Finally, correlation analysis of the serum cathepsin S level with IMT, mean arterial pressure, fasting blood glucose, TC and NO demonstrated that the serum cathepsin S level is positively correlated with IMT, mean arterial pressure, fasting blood glucose and TC levels, and negatively correlated with NO level, further suggesting that the serum cathepsin S level is not only related to the degree of coronary artery stenosis in the patients with coronary atherosclerotic heart disease, but also positively correlated with IMT, mean arterial pressure, fasting blood glucose and TC levels, and negatively associated with NO level, a cytokine related to the vascular endothelial function.

Serum cathepsin S can reduce the adhesiveness of extracellular matrix, promote the migration of atherosclerotic factors in the coronary tunica intima toward the site below the tunica intima (16), and trigger atherosclerosis-induced thickening of tunica intima of coronary artery and carotid artery, ultimately aggravating the vascular stenosis induced by atherosclerotic plaque, and promoting the disease progression (17). Additionally, serum cathepsin S is able to reduce the stability of collagen fiber and fibrous cap in the atherosclerotic plaque, thereby enhancing the instability of atherosclerotic plaque (18). As the most important protease for degrading the extracellular matrix during atherosclerosis formation, serum cathepsin S is also capable of accelerating the migration of monocytes to subintimal sites through the arterial intima (19), further causing the thickening of arterial intima, promoting the formation of fibrous plaque, and aggravating the atherosclerotic lesions (20). At the same time, it was also indicated in this research that the patients with elevated serum cathepsin S level also have increased blood pressure, and they are prone to abnormalities in glucose and lipid metabolism and vascular endothelial function. Differently, some studies have indicated that high levels of cathepsin K and L are closely linked with the presence of CAD, and are both independent biomarkers for CHD (21,22). The present study also has some limitations. The main limitation is the lack of *in vitro* or *in vivo* experiments. Cathepsin S-deficient animals or cells should be employed to verify our results.

In conclusion, the serum cathepsin S level is significantly correlated with the coronary stenosis degree, carotid thickness, blood pressure, glucose and lipid metabolism and vascular endothelial function. With the elevation of serum cathepsin S level, the coronary stenosis becomes more severe, the carotid artery is thicker, the blood pressure is higher, and the glucose and lipid metabolism and vascular endothelial function are significantly abnormal.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SH and YC designed the study and performed the experiments. SH and YC collected the patients' data, analyzed the data and prepared the manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Third Xiangya Hospital of Central South University (Changsha, China). Signed informed consents were obtained from all participants before the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhou PP, Zhang WY, Li ZF, Chen YR, Kang XC and Jiang YX: Association between SNPs in the promoter region in cathepsin S and risk of asthma in Chinese Han population. Eur Rev Med Pharmacol Sci 20: 2070-2076, 2016.
2. Ignatov M, Liu C, Alekseenko A, Sun Z, Padhorny D, Kotelnikov S, Kazennov A, Grebenkin I, Kholodov Y, Kolosvari I, *et al*: Monte Carlo on the manifold and MD refinement for binding pose prediction of protein-ligand complexes: 2017 D3R Grand Challenge. J Comput Aided Mol Des 33: 119-127, 2019.
3. Xiao L, Han X, Wang XE, Li Q, Chen Y, Cui Y and Chen Y: Cathepsin S in the spinal microglia facilitates morphine-induced antinociceptive tolerance in rats. Neurosci Lett 690: 225-231, 2019.
4. Luo L, Zhu M and Zhou J: Association between CTSS gene polymorphism and the risk of acute atherosclerotic cerebral infarction in Chinese population: A case-control study. Biosci Rep 38: BSR20180586, 2018.
5. Lee BC, Kang I, Lee SE, Lee JY, Shin N, Kim JJ, Choi SW and Kang KS: Human umbilical cord blood plasma alleviates age-related olfactory dysfunction by attenuating peripheral TNF-α expression. BMB Rep 52: 259-264, 2019.

6. Chen CY, Chen CY, Liu CC and Chen CP: Omega-3 polyunsaturated fatty acids reduce preterm labor by inhibiting trophoblast cathepsin S and inflammasome activation. Clin Sci (Lond) 132: 2221-2239, 2018.

7. Wuopio J, Hilden J, Bring C, Kastrup J, Sajadieh A, Jensen GB, Kjøller E, Kolmos HJ, Larsson A, Jakobsen JC, et al: Cathepsin B and S as markers for cardiovascular risk and all-cause mortality in patients with stable coronary heart disease during 10 years: A CLARICOR trial sub-study. Atherosclerosis 278: 97-102, 2018.

8. Poulsen CB, Al-Mashhadi AL, von Wachenfeldt K, Bentzon JF, Nielsen LB, Al-Mashhadi RH, Thygesen J, Tolbod L, Larsen JR, Frøkiær J, et al: Treatment with a human recombinant monoclonal IgG antibody against oxidized LDL in atherosclerosis-prone pigs reduces cathepsin S in coronary lesions. Int J Cardiol 215: 506-515, 2016.

9. Bonfante R, Napimoga MH, Macedo CG, Abdalla HB, Pieroni V and Clemente-Napimoga JT: The P2X7 receptor, cathepsin S and fractalkine in the trigeminal subnucleus caudalis signal persistent hypernociception in temporomandibular rat joints. Neuroscience 391: 120-130, 2018.

10. Ji C, Tang M, Harrison J, Paciorkowski A and Johnson GVW: Nuclear transglutaminase 2 directly regulates expression of cathepsin S in rat cortical neurons. Eur J Neurosci 48: 3043-3051, 2018.

11. He X, Man VH, Ji B, Xie XQ and Wang J: Calculate protein-ligand binding affinities with the extended linear interaction energy method: Application on the Cathepsin S set in the D3R Grand Challenge 3. J Comput Aided Mol Des 33: 105-117, 2019.

12. Chaput L, Selwa E, Elisée E and Iorga BI: Blinded evaluation of cathepsin S inhibitors from the D3RGC3 dataset using molecular docking and free energy calculations. J Comput Aided Mol Des 33: 93-103, 2019.

13. Taleb S, Lacasa D, Bastard JP, Poitou C, Cancello R, Pelloux V, Viguerie N, Benis A, Zucker JD, Bouillot JL, et al: Cathepsin S, a novel biomarker of adiposity: Relevance to atherogenesis. FASEB J 19: 1540-1542, 2005.

14. Kubo K, Kawato Y, Nakamura K, Nakajima Y, Nakagawa TY, Hanaoka K, Oshima S, Fukahori H, Inami M, Morokata T, et al: Effective suppression of donor specific antibody production by cathepsin S inhibitors in a mouse transplantation model. Eur J Pharmacol 838: 145-152, 2018.

15. Chen RP, Ren A and Ye SD: Correlation between serum cathepsin S and insulin resistance in type 2 diabetes. Exp Ther Med 6: 1237-1242, 2013.

16. Gautam J, Banskota S, Lee H, Lee YJ, Jeon YH, Kim JA and Jeong BS: Down-regulation of cathepsin S and matrix metalloproteinase-9 via Src, a non-receptor tyrosine kinase, suppresses triple-negative breast cancer growth and metastasis. Exp Mol Med 50: 118, 2018.

17. Janga SR Sr, Shah M, Ju Y, Meng Z, Edman MC and Hamm-Alvarez SF: Longitudinal analysis of tear cathepsin S activity levels in male non-obese diabetic mice suggests its potential as an early stage biomarker of Sjögren's Syndrome. Biomarkers 24: 91-102, 2019.

18. Seo SU, Min KJ, Woo SM and Kwon TK: Z-FL-COCHO, a cathepsin S inhibitor, enhances oxaliplatin-mediated apoptosis through the induction of endoplasmic reticulum stress. Exp Mol Med 50: 107, 2018.

19. Nguyen DD, Cang Z, Wu K, Wang M, Cao Y and Wei GW: Mathematical deep learning for pose and binding affinity prediction and ranking in D3R Grand Challenges. J Comput Aided Mol Des 33: 71-82, 2019.

20. Altieri A, Piyadasa H, Recksiedler B, Spicer V and Mookherjee N: Cytokines IL-17, TNF and IFN-γ alter the expression of antimicrobial peptides and proteins disparately: A targeted proteomics analysis using SOMAscan technology. Vaccines (Basel) 6: 51, 2018.

21. Cheng XW, Kikuchi R, Ishii H, Yoshikawa D, Hu L, Takahashi R, Shibata R, Ikeda N, Kuzuya M, Okumura K, et al: Circulating cathepsin K as a potential novel biomarker of coronary artery disease. Atherosclerosis 228: 211-216, 2013.

22. Liu Y, Li X, Peng D, Tan Z, Liu H, Qing Y, Xue Y and Shi GP: Usefulness of serum cathepsin L as an independent biomarker in patients with coronary heart disease. Am J Cardiol 103: 476-481, 2009.