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ORIGINAL ARTICLE

The role of increased synovial fluid A disintegrin and metalloproteinase with thrombospondin motifs4 and serglycin levels in osteoarthritis

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Abstract

Background The first research to determine synovial fluid ADAMTS4 and serglycin levels in osteoarthritis and OA progression.
Aim We aimed to determine ADAMTS4 and serglycin levels, interactions, and changes in the synovial fluid of knee OA, and also to determine effective in OA progression.
Methods A case-control study was carried out including a total of 88 participants (29 patients late OA [LOA], 28 early OA [EOA], and 30 controls). Synovial fluid serglycin and ADAMTS4 levels were measured by commercially available ELISA kits, and knee functions of the patients were evaluated with The Western Ontario and McMaster Universities Osteoarthritis score (WOMAC). Logistic regression analysis was applied for the associated with progression of OA.
Results Synovial fluid ADAMTS4 and serglycin levels were significantly higher in LOA than EOA and control groups ($p < .001$ and $p < .001$; $p = .038$ and $p = .007$, respectively). All parameters were evaluated after adjustment for age. LOA patients had significantly higher levels of WOMAC score than EOA and controls ($p < .001$ and $p < .001$). According to the logistic regression analysis, synovial fluid ADAMTS4, serglycin levels, and WOMAC score were found to be significantly associated with progression of OA.

Keywords ADAMTS4 · Knee osteoarthritis · Serglycin · Synovial fluid · WOMAC score

Introduction

Osteoarthritis (OA) is the most common form of degenerative joint disease in the world and a major cause of severe pain and disability. Etiopathogenesis of the knee OA is a heterogeneous. Obesity, age, and joint damage are important risk factors [1]. Despite these risk factors, the etiopathogenesis that initiates degeneration of cartilage is not clear. However, extracellular matrix (ECM) structural and functional changes are the most important mechanisms in the development of OA. Cartilage has no vascular and nerve tissue. ECM is the main component of the cartilage structure. ECM is predominantly composed of collagen, especially type 2 collagen, and proteoglycans [2].

A disintegrin and metalloproteinase with thrombospondin motifs4 (ADAMTS4) and ADAMTS5, called aggregganase, have been shown to play a role in the progression of OA by degrading the proteoglycans in the extracellular matrix that constitutes the primary structure of the cartilage [3]. ADAMTS4 plays a role in the degradation of aggrecan which is major proteoglycan of the extracellular matrix and other proteoglycans in the structure of cartilage [4]. Yaykasli et al. showed that ADAMTS4, 5, and 9 expressions were increased in patients with OA and rheumatoid arthritis (RA) [5]. Malfait and et al., that showed ADAMTS4 and ADAMTS5, represent a potential target for the treatment of osteoarthritis [6].

Serglycin is a proteoglycan that is stored in the cell, and is secreted in conditions such as inflammation and tissue damage [7]. Serglycin is also involved in endothelial cells [8]. Rheumatoid arthritis had high levels of serglycin in the joint fluid and blood [9]. Zhang et al. examined the interaction of matrix metalloproteinase-13 with proteoglycans such as decorin, syndecan 4, and serglycin in chondrocytes and demonstrated the interaction of serglycin and MMP-13 for the first time [10]. In spite of these studies, there is no research yet to

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reveal the relationship of ADAMTS4 and serglycin proteoglycans with OA and progression of OA.

In our study, we aimed to determine ADAMTS4 and serglycin levels, interactions, and changes in the synovial fluid of patients with knee OA, and also to determine whether synovial fluid ADAMTS4 and serglycin were effective in OA progression.

Material and methods

A prospective case-control study was performed between March 2018 and June 2018 in the Orthopedics Department. A total of 88 participants were included in the study. The diagnosis of knee OA was determined according to the radiographic features and magnetic resonance imaging (MRI). Twenty-nine patients were diagnosed as late-stage knee OA (LOA) and 28 patients were diagnosed as early-stage knee OA (EOA) by the Kellgren-Lawrence (K&L) scale, which is the accepted as a reference standard of the World Health Organization [11]. Body mass index (BMI) matched patients with knee OA diagnosed by radiographic features. Thirty, uncomplicated participant with normal radiographic features were selected as the control group and were matched with the other groups for BMI. All participants included in the study were evaluated at the initial admission. All participants provided written informed consent. The study protocol was performed according to the principles of the Declaration of Helsinki and was approved by the local Ethical Committee. (approval date/number: 03.05.2018/006).

Clinical examination was performed and anthropometric measurements as well as the previous radiographic features and medical history were recorded. Knee function was assessed using the Western Ontario and McMaster Universities Osteoarthritis score (WOMAC). The WOMAC score is composed of 24 parameters that include pain (score range, 0–20), stiffness (score range, 0–8), and functional impairment (score range, 0–68) [12]. Patients with a WOMAC score of 70% and above were evaluated with having a distorted knee function [13].

Patients were excluded if any of the following disorders were present: infectious diseases, history of total knee arthroplasty or other types of knee surgery, septic arthritis, obesity, use of systemic/local steroids or intra-articular hyaluronic acid injections, bone tumors, osteoporosis- or trauma-related fractures, diabetes mellitus, immune system disorder.

All participants synovial fluid samples were stored at − 80 until the day of analysis. In this study, 2-cc joint fluid was injected intraarticularly with a 5-cc sterile needle and − 80 was done without centrifugation. In the control group, joint fluid was obtained from patients who had no signs of infection and had swelling in the knee without any previous joint surgery. The synovial fluid serglycin levels were analyzed using a human serglycin enzyme-linked immunosorbent assay (ELISA) kit (Wuhan USCN Business Co., Ltd., China) with an immunoassay (ALISEI) fully automatic ELISA device, and the results are presented as nanograms per milliliter and ADAMTS4 levels were analyzed using a Eastbiopharm branded human ADAMTS4 ELISA kit with immunoassay device and presented in picograms per milliliter.

Statistical analysis

For data analysis, we used the IBM-Statistical Package for the Social Sciences (IBM-SPSS) version 22.0 and PASTE programmes. We used parametric methods for the analysis of the variables with a normal distribution. The descriptive analyses for normally distributed variables are expressed as the mean ± standard deviation. We used one-way ANOVA and Kruskal-Wallis H tests for the comparison of LOA, EOA, and control groups. The non-parametric post hoc test [14] and LSD test were used for the post hoc analysis. Degrees of association between continuous variables were evaluated by partial correlation analyses after adjustment for age. ADAMTS4, serglycin, and WOMAC score receiver operator characteristic (ROC) curve were performed in OA patients. Best cut-off value, sensitivity, specificity, and area under the curve (AUC) for synovial fluid serglycin, joint fluid ADAMTS4, and WOMAC scores in OA. Single and multi categorical logistic regression analysis was used to determine the associated with OA among synovial fluid serglycin, ADAMTS9, and WOMAC score. The Pearson correlation and Spearman Rho tests were used to examine the correlations of variables. The data were examined at the 95% confidence level, and a p value of < 0.05 was considered significant.

Results

A total of 88 patients were enrolled in the study (29 LOA, 28 EOA, and 30 uncomplicated controls). The baseline demographic, clinical, and laboratory characteristics of all groups are given in Table 1. Synovial fluid ADAMTS4 levels were 202.45 ± 85.79 pg/ml in LOA, 132.69 ± 33.10 pg/ml in EOA, and 126.34 ± 31.65 pg/ml in control group. Synovial fluid ADAMTS4 levels significantly higher in LOA than EOA and control groups ($p < .001$ and $p < .001$). Synovial fluid serglycin levels were 1.88 ± 0.74 ng/ml in LOA, 1.55 ± 0.49 in EOA, and 1.46 ± 0.53 ng/ml in control group ($p = .038$ and $p = .007$). Total WOMAC score, pain, stiffness and physical function were significantly higher in the LOA group compared to the EOA and control groups ($p < .001$ and $p < .001$) (Table 1).

Table 1 Baseline demographic, clinical, and laboratory features in LOA, EOA, and control groups

		Control (a)	EOA (b)	LOA (c)	*p* value*	*p* value**
BMI (kg/m^2)		28.48 ± 4.24	31.03 ± 4.49	29.72 ± 6.05	P(ab) = .053 P(ac) = .337 P(bc) = .326	.152
WOMAC score	Pain	5.81 ± 2.94	6.21 ± 4.16	11.41 ± 3.32	P(ab) = .656 *P(ac) < .001* P(bc) < .001	*<.001*
	Stiffness	3.00 ± 1.57	3.46 ± 2.06	6.00 ± 1.46	P(ab) = .301 *P(ac) < .001* *P(bc) < .001*	*<.001*
	Physical function	11.61 ± 2.08	32.93 ± 9.59	46.59 ± 13.19	P(ab) = .264 *P(ac) = .001* *P(bc) < .001*	*<.001*
	Total score	45.06 ± 14.13	42.29 ± 12.92	63.52 ± 14.30	P(ab) = .443 *P(ac) < .001* *P(bc) < .001*	*<.001*
ADAMTS4 (pg/ml)		126.34 ± 31.65	132.69 ± 33.10	202.45 ± 85.79	P(ab) = .664 *P(ac) < .001* *P(bc) < .001*	*<.001*
Serglycin (ng/ml)		1.46 ± 0.53	1.55 ± 0.49	1.88 ± 0.74	P(ab) = .567 *P(ac) = .007* *P(bc) = .038*	*.019*

Results were analyzed by one-way ANOVA (Brown-Forsythe), post hoc test (LSD-Games Howell). *p* value* statistical significance within groups, *p* value** statistical significance between groups. < .05 statistically significant. Statistically significant *p* values are marked in italics. *BMI* body mass index, *WOMAC score* The Western Ontario and McMaster Universities Osteoarthritis score, *ADAMTS4* A disintegrin and metalloproteinase with thrombospondin motif 4

Synovial fluid ADAMTS4 and serglycin levels and total WOMAC score were again evaluated with ROC analysis (Fig. 1); cut-off levels were determined and AUC values were calculated. The AUC, best cut-off values, sensitivity, and specificity for distinguishing the groups for each parameter are given in Table 2. Synovial fluid ADAMTS4 levels and WOMAC score were found to be statistically significant ($p = .004$ and $p = .029$) (Table 2).

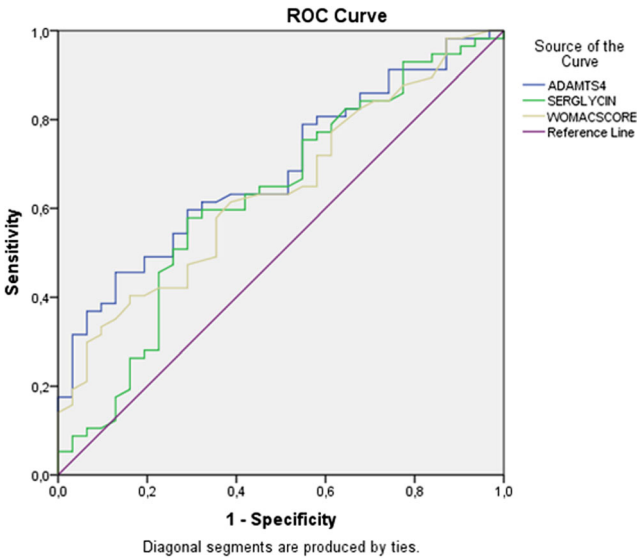

Fig. 1 Synovial fluid ADAMTS4, serglycin, and WOMAC score ROC curve in OA patients

All statistically significant parameters according to the univariate analysis were further evaluated by multivariate logistic regression analysis (Table 3). Increased synovial fluid ADAMTS4 levels and knee stiffness which are the parameters of the WOMAC score were significantly associated with OA (OR 1.014, 95% CI = 1.000–1.028, $p = .044$ and OR 1.412, 95% CI = 1.023–1.950, $p = .036$) (Table 3). The synovial fluid serglycin level was not significant according to the multivariate analysis (Table 3). But increased synovial fluid ADAMTS4, serglycin levels, and WOMAC score were significantly associated with LOA (OR 1.025, 95% CI = 1.007–1.043, $p = .005$; OR 3.143, 95% CI = 1.104–8.946, $p = .032$; and OR 1.078, 95% CI = 1.031–1.127, $p = .001$, respectively) (Table 3). The synovial fluid serglycin, ADAMTS4 levels, WOMAC score, and other variables were not significant according to the multivariate analysis in EOA (Table 4).

Further analysis was also performed to determine whether there was a correlation between synovial fluid ADAMTS4 and serglycin levels and WOMAC score or not in OA. WOMAC score was positively correlated with synovial fluid ADAMTS4 levels in OA. (Spearman's $r = 0.413$; $p = .001$). No correlation was observed synovial fluid serglycin levels with WOMAC score in OA (Table 5).

Discussion

Previous studies have shown that ADAMTS4 is associated with cartilage degeneration and progression in osteoarthritis

Table 2 Best cut-off value, sensitivity, specificity, and AUC (95%Cl) of synovial fluid ADAMTS4, serglycin, and WOMAC score in OA

	Cut off	Spe %	Sen %	AUC (95%Cl)	*p* value*
ADAMTS4 (pg/ml)	198.70	63	61	0.686 (0.575–0.797)	*.004*
Serglycin (ng/ml)	1.73	63	58	0.626 (0.501–0.751)	.052
WOMAC score	36	61	61	0.642(0,525–0.759)	*.029*

p value; statistical significance between groups. <.05 statistically significant

AUC area under curve, *WOMAC score* The Western Ontario and McMaster Universities Osteoarthritis score, *ADAMTS4* A disintegrin and metalloproteinase with thrombospondin motif 4

[3]. Proteases and inflammatory processes have proven effects in the etiopathogenesis of OA [15]. He et al. showed that ADAMTS4 and 5 and matrix metolloproteinase-9 and -13 were activated in bovine cartilages stimulated with tumor necrosis factor alpha (TNF-α) and oncostatin M (OSM) [16]. Moulharat et al. reported that TGF beta stimulated aggrecan deregulation by increasing ADAMTS4 expression in human cartilage [17]. The increase in ADAMTS4 level in synovial fluid has been shown to be associated with progression in OA joint degeneration [18]. Also, Pens et al. reported that ADAMTS4 had tripled in synovial fluids of early-stage OA patients compared to late-stage OA [19]. Zhang et al. showed that ADAMTS4 expression in the synovial fluid was increased in early-stage OA compared to middle- and late-stage OA [20]. In addition, Kamm et al. showed that the expression of ADAMTS4 and inflammatory cytokines in synovial fluids increased along with the severity of OA in horses [21]. In our study, we found that the ADAMTS4 level in the synovial fluid was increased in the advanced OA group compared to the early-stage OA and the control group. Bau et al. showed that expression of ADAMTS4 and ADAMTS5 patients was increased in knee cartilage of late-stage OA compared to early-stage OA patients [22].

It is known that ADAMTS4 is synthesized as zymogen and it is activated intracellularly by furin-like proprotein convertase (PC) [23], and it interacts with the CD44 and syndecan family on the cell surface [24]. Ariyoshi et al. showed increased ADAMTS4 and ADAMTS5 gene expression in chondrocytes accompanied by activity of CD44 cell surface receptors [25]. Kataoka et al. reported that the expression of ADAMTS4 decreased with CD44 receptor blockade in OA synovial tissue [26]. ADAMTS4 and CD44, which are involved in ECM remodeling, were induced by IL-1β in the nucleus pulposus (NP) cells [27].

Serglycin is also secreted by proteases, chemokines, and cytokines, especially [28] via the CD44 receptor [29] in the hemopoietic system, especially platelets [30]. Serglycin level was found to be high in platelet extracts [31]. Today, platelet-rich plasma is used in the treatment of OA and it has been shown to provide cartilage degeneration [32]. In the light of the above studies, ADAMTS4 and serglycin interact with similar mechanisms such as proinflammatory cytokines and CD44 receptors. We have no data on synovial fluid or blood serglycin and ADAMTS4 levels in patients with osteoarthritis. Omtvedt et al. reported that increased synovial fluid and blood levels of serglycin played a role in the inflammatory process in

Table 3 Univariate and multivariate regression analyses of different variables**

		OA				LOA			
		Univariate		Multivariate		Univariate		Multivariate	
		OR (95%Cl)	*p* value	OR (95%Cl)	*p* value	OR (95%Cl)	*p* value	OR (95%Cl)	*p* value
BMI (kg/m^2)		1.084 (0.986–1.191)	.097			1.001 (0.916–1.094)	.976		
WOMAC score	Pain	1.220 (1.073–1.388)	*.022*	1.212 (0.938–1.565)	.141	1.747 (1.377–2.216)	< *.001*		
	Stiffness	1.555 (1.208–2.002)	*.001*	1.412 (1.023–1.950)	*.036*	2.769 (1.776–4.316)	< *.001*		
	Physical function	1.023 (0.987–1.060)	.215			1.081 (1.039–1.124)	< *.001*		
	Total score	1.032 (1.003–1.063)	*.033*	0.961 (0.909–1.016)	.163	1.091 (1.051–1.132)	< *.001*	1.078 (1.031–1.127)	*.001*
ADAMTS4 (pg/ml)		1.017 (1.005–1.029)	*.007*	1.014 (1.000–1.028)	*.044*	1.028 (1.014–1.042)	< *.001*	1.025 (1.007–1.043)	*.005*
Serglycin (ng/ml)		2.218 (0.950–5.179)	.066			2.906 (1.254–6.736)	*.013*	3.143 (1.104–8.946)	*.032*

BMI body mass index, *WOMAC score* The Western Ontario and McMaster Universities Osteoarthritis score, *ADAMTS4* A disintegrin and metalloproteinase with thrombospondin motif 4

< .05 statistically significant. Statistically significant *p* values are marked in italics

**Logistic regression model (binary logistic regression with a single and multi categorical predictor) was used to determine the possible risk factors for Osteoarthritis (OA) and LOA

Table 4 Univariate and multivariate regression analyses of different variables**

		EOA			
		Univariate		Multivariate	
		OR (95%Cl)	*p* value	OR (95%Cl)	*p* value
BMI (kg/m^2)		1.146 (1.010–1.300)	*.035*	1.142 (1.005–1.298)	.052
WOMAC score	Pain	1.033 (0.894–1.195)	.658		
	Stiffness	1.111 (0.794–1.554)	.540		
	Physical function	0.970 (0.922–1.019)	.228		
	Total score	0.984 (0.946–1.024)	.427		
ADAMTS4 (pg/ml)		1.006 (0.990–1.023)	.443	1.005 (0.988–1.023)	.552
Serglycin (ng/ml)		1.419 (0.515–3.909)	.498	1.641 (0.556–4.845)	.370

BMI body mass index, *WOMAC score* The Western Ontario and McMaster Universities Osteoarthritis score, *ADAMTS4* A disintegrin and metalloproteinase with thrombospondin motif 4

< .05 statistically significant. Statistically significant *p* values are marked in italics

**Logistic regression model (binary logistic regression with a single and multi categorical predictor) was used to determine the possible risk factors for early-stage osteoarthritis (EOA)

rheumatologic diseases [9]. We found that the levels of synovial fluid serglycin increased simultaneously with ADAMTS4 in OA patients according to the control group. In addition, we saw that the levels of synovial fluid serglycin were significantly higher in the LOA patients than the EOA. In addition, we found that increased synovial fluid ADAMTS4, serglycin levels, and WOMAC score were risk factors for late-stage OA, and that there was only synovial fluid ADAMTS4 risk factor in all OA without phase difference.

Conclusion

The increased synovial fluid ADAMTS4 and serglycin levels are indicative of cartilage degeneration at each stage of OA. In addition, the increased synovial fluid level of serglycin with ADAMTS4 appears to be a risk factor in the advanced stage OA compared to early-stage OA, which may be due to the increased release of intracellular stores by the recent breakdown of cells and cell proliferation by OA progression. We think that the increase of synovial fluid syglycin and ADAMTS4 may be indicative in the end stage of osteoarthritis.

The limitations of our study are mainly the lack of the evaluation of other proteases and proteoglycans which is risk factors of OA, small number of patients, and the lack of randomization. Further prospective studies in larger cohorts are needed to validate the results of the present study.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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Table 5 Correlation analysis between WOMAC score, synovial fluid ADAMTS4, and serglycin levels in OA **

	WOMAC score	
	r	*p* value
BMI (kg/m^2)	0.021	.877
ADAMTS4 (pg/ml)	0.413	*.001*
Serglycin (ng/ml)	0.142	.293

r correlation coefficient, *WOMAC score* The Western Ontario and McMaster Universities Osteoarthritis score, *ADAMTS4* A disintegrin and metalloproteinase with thrombospondin motif 4

< .05 statistically significant. Statistically significant *p* values are marked in italics

**Pearson's correlation test-Spearman's Rho test were used

References

1. Dillon CF, Rasch EK, Gu Q et al (2006) Prevalence of knee osteoarthritis in the United States: arthritis data from thethird national health and nutrition examination survey 1991–94. J Rheumatol 33(11):2271–2279
2. Maroudas A (1976) Balance between swelling pressure and collagen tension in normal and degenerate cartilage. Nature (London) 260:808–809
3. Song RH, Tortorella MD, Malfait AM et al (2007) Aggrecan degradation in human articular cartilage explants is mediated by both ADAMTS-4 and ADAMTS-5. Arthritis Rheum 56:575–585
4. Arner EC (2002) Aggrecanase-mediated cartilage degradation. Curr Opin Pharmacol 2:322–329
5. Yaykasli KO, Hatipoglu OF, Yaykasli E et al (2015) Leptin induces ADAMTS-4, ADAMTS-5, and ADAMTS-9 genes expression by mitogen-activated protein kinases and NF-κB signaling pathways in human chondrocytes. Cell Biol Int 39(1):104–112. https://doi.org/10.1002/cbin.10336
6. Malfait AM, Liu RQ, Ijiri K, Komiya S, Tortorella MD (2002) Inhibition of ADAM-TS4 and ADAM-TS5 prevents aggrecan degradation in osteoarthritic cartilage. J Biol Chem 277:22201–22208
7. Scully OJ, Chua PJ, Harve KS, Bay BH, Yip GW (2012) Serglycin in health and diseases. Anat Rec (Hoboken) 295(9):1415–1420. https://doi.org/10.1002/ar.22536
8. Schick BP, Gradowski JF, San Antonio JD (2001) Synthesis, secretion, and subcellular localization of serglycin proteoglycan in human endothelial cells. Blood 97(2):449–458
9. Omtvedt LA, Kolset SO, Thoen J, Førre Y, Gill MR (2001) Serglycin expression in CD2+ and CD14+ cells from patients with various rheumatic diseases. Scand J Rheumatol 30(3):164–166
10. Zhang L, Yang M, Yang D, Cavey G, Davidson P, Gibson G (2010) Molecular interactions of MMP-13 C-terminal domain with chondrocyte proteins. Connect Tissue Res 51(3):230–239. https://doi.org/10.3109/03008200903288902
11. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494e502
12. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW (1988) Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15:1833–1840
13. Tüzün EH, Eker L, Aytar A, Daşkapan A, Bayramoğlu M (2005) Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthr Cartil 13(1):28–33
14. Miller RG. (1966) Simultaneous statistical inference. McGraw-Hill: New York
15. Xue J, Wang J, Liu Q et al (2013) Tumor necrosis factor-α induces ADAMTS-4 expression in human osteoarthritis chondrocytes. Mol Med Rep 8(6):1755–1760. https://doi.org/10.3892/mmr.2013.1729
16. He Y, Zheng Q, Jiang M, Sun S, Christiansen TG, Kassem M, Karsdal MA, Bay-Jensen AC (2015) The effect of protease inhibitors on the induction of osteoarthritis-related biomarkers in bovine full-depth cartilage explants. PLoS One 10(4):e0122700. https://doi.org/10.1371/journal.pone.0122700
17. Moulharat N, Lesur C, Thomas M, Rolland-Valognes G, Pastoureau P, Anract P, de Ceuninck F, Sabatini M (2004) Effects of transforming growth factor-beta on aggrecanase production and proteoglycan degradation by human chondrocytes in vitro. Osteoarthr Cartil 12(4):296–305
18. Roberts S, Evans H, Wright K, van Niekerk L, Caterson B, Richardson JB, Kumar KHS, Kuiper JH (2015) ADAMTS-4 activity in synovial fluid as a biomarker of inflammation and effusion. Osteoarthr Cartil 23(9):1622–1626. https://doi.org/10.1016/j.joca.2015.05.006
19. Peng S, Zheng Q, Zhang X, Dai L, Zhu J, Pi Y, Hu X, Cheng W, Zhou C, Sha Y, Ao Y (2013) Detection of ADAMTS-4 activity using a fluorogenic peptide-conjugated Au nanoparticle probe in human knee synovial fluid. ACS Appl Mater Interfaces 5(13):6089–6096. https://doi.org/10.1021/am400854z.
20. Zhang E, Yan X, Zhang M, Chang X, Bai Z, He Y, Yuan Z (2013) Aggrecanases in the human synovial fluid at different stages of osteoarthritis. Clin Rheumatol 32(6):797–803. https://doi.org/10.1007/s10067-013-2171-0
21. Kamm JL, Nixon AJ, Witte TH (2010) Cytokine and catabolic enzyme expression in synovium, synovial fluid and articular cartilage of naurally osteoarthritic equine carpi. Equine Vet J 42(8):693–699. https://doi.org/10.1111/j.2042-3306.2010.00140.x
22. Bau B, Gebhard PM, Haag J, Knorr T, Bartnik E, Aigner T (2002) Relative messenger RNA expression profiling of collagenases and aggrecanases in human articular chondrocytes in vivo and in vitro. Arthritis Rheum 46:2648e57
23. Wang P, Tortorella M, England K, Malfait AM, Thomas G, Arner EC, Pei D (2004) Proprotein convertase furin interacts with and cleaves pro-ADAMTS4 (Aggrecanase-1) in the trans-Golgi network. J Biol Chem 279(15):15434–15440
24. Mayer G, Hamelin J, Asselin MC, Pasquato A, Marcinkiewicz E, Tang M, Tabibzadeh S, Seidah NG (2008) The regulated cell surface zymogen activation of the proprotein convertase PC5A directs the processing of its secretory substrates. J Biol Chem 283(4):2373–2384
25. Ariyoshi W, Takahashi N, Hida D, Knudson CB, Knudson W (2012) Mechanisms involved in enhancement of the expression and function of aggrecanases by hyaluronan oligosaccharides. Arthritis Rheum 64(1):187–197. https://doi.org/10.1002/art.33329
26. Kataoka Y, Ariyoshi W, Okinaga T, Kaneuji T, Mitsugi S, Takahashi T, Nishihara T (2013) Mechanisms involved in suppression of ADAMTS4 expression in synoviocytes by high molecular weight hyaluronic acid. Biochem Biophys Res Commun 432(4):580–585. https://doi.org/10.1016/j.bbrc.2013.02.043
27. Erwin WM, Islam D, Inman RD, Fehlings MG, Tsui FWL (2011) Notochordal cells protect nucleus pulposus cells from degradation and apoptosis: implications for the mechanisms of intervertebral disc degeneration. Arthritis Res Ther 13(6):R215. https://doi.org/10.1186/ar3548
28. Korpetinou A, Skandalis SS, Labropoulou VT, Smirlaki G, Noulas A, Karamanos NK, Theocharis AD (2014) Serglycin: at the crossroad of inflammation and malignancy. Front Oncol 3:327. https://doi.org/10.3389/fonc.2013.00327
29. D'Ascola A, Scuruchi M, Avenoso A, Bruschetta G, Campo S, Mandraffino G, Campo GM (2018) Serglycin is involved in inflammatory response in articular mouse chondrocytes. Biochem Biophys Res Commun 499(3):506–512. https://doi.org/10.1016/j.bbrc.2018.03.178
30. Toyama-Sorimachi N, Kitamura F, Habuchi H, Tobita Y, Kimata K, Miyasaka M (1997) Widespread expression of chondroitin sulfate type serglycins with CD44 binding ability in hematopoietic cells. J Biol Chem 272(42):26714–26719
31. Lord MS, Cheng B, Farrugia BL, McCarthy S, Whitelock JM (2017) Platelet factor 4 binds to vascular proteoglycans and controls both growth factor activities and platelet activation. J Biol Chem 292(10):4054–4063
32. de Girolamo L, Kon E, Filardo G, Marmotti AG, Soler F, Peretti GM, Vannini F, Madry H, Chubinskaya S (2016) Regenerative approaches for the treatment of early OA. Knee Surg Sports Traumatol Arthrosc 24(6):1826–1835. https://doi.org/10.1007/s00167-016-4125-y