Upregulation of ADAMTS-7 and downregulation of COMP are associated with spontaneous abortion

YANG MU, DAN-NI ZHOU, NA-NA YAN, JIN-LI DING and JING YANG

Reproductive Medicine Center, Renmin Hospital of Wuhan University, Hubei Clinic Research Center for Assisted Reproductive Technology and Embryonic Development, Wuhan University, Wuhan, Hubei 430060, P.R. China

Received February 13, 2018; Accepted August 7, 2018

DOI: 10.3892/mmr.2019.9898

Abstract. A disintegrin and metalloproteinase with thrombospondin motifs 7 (ADAMTS-7) has been revealed to serve an important role in inflammation-associated diseases. However, the role of ADAMTS-7 in spontaneous abortion (SA) remains unclear. In the present study, human and mouse decidual tissues were used to detect the expression of ADAMTS-7 and cartilage oligomeric matrix protein (COMP) in mice with lipopolysaccharide (LPS)-induced abortion (10 mice/group), and in SA humans and the corresponding control group (21 participants in the SA group and 15 participants in the control group). The results revealed that ADAMTS-7 expression was upregulated and that COMP expression was downregulated in the mouse decidual tissue of the LPS-induced abortion group, when compared with that of the normal control group. The results were further confirmed by western blot analysis and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis, which revealed increased ADAMTS-7 and decreased COMP expression at the protein and mRNA levels in mice treated with LPS. Additionally, the expression of ADAMTS-7 was negatively correlated with the expression of COMP in mice, with a correlation coefficient of -0.936 (P<0.001). In addition, the expression of ADAMTS-7 and COMP exhibited was similar in the decidual tissue of SA patients when compared with the levels observed in the tissues of the normal control participants, as demonstrated by increased ADAMTS-7 expression and decreased COMP expression. Western blotting and RT-qPCR analysis revealed that ADAMTS-7 was increased and COMP was decreased in the decidual tissue of SA subjects. The correlation analysis of ADAMTS-7 and COMP in human decidual tissue also revealed a similar result, with a correlation coefficient of -0.836 (P<0.001). The results of the present study demonstrated that ADAMTS-7 was upregulated and COMP was downregulated in the decidual tissues of humans and mice with SA, and a negative correlation was identified between the expression levels of ADAMTS-7 and COMP, thereby providing novel evidence for a better understanding of the pathogenesis of SA, which may lead to improvements in the clinical pregnancy outcomes of these individuals.

Introduction

Recurrent miscarriage is a highly heterogeneous disease, which is defined as at least three pregnancy losses before 22 weeks of gestation, and affects approximately 0.5-3% of fertile couples (1,2). The pathogenesis of recurrent spontaneous miscarriage is complicated and remains mostly unknown. Immunological factors and inflammation have been reported to participate in the pathological process of recurrent miscarriage (3-9).

A disintegrin and metalloproteinase with thrombospondin motifs 7 (ADAMTS-7) is a proteolytic member of the ADAMTS family (a disintegrin and metalloproteinase with thrombospondin-like motifs) and has been identified to exert important effects on inflammatory diseases, such as arthritis and atherosclerosis (10-12). Previous studies have demonstrated that systematic inflammation is correlated with recurrent implantation failure and recurrent spontaneous abortion (SA) in humans (13). Over the past few decades, Th17 cells have been reported to be involved in the pathological process of recurrent miscarriage (3-9).

A disintegrin and metalloproteinase with thrombospondin motifs 7 (ADAMTS-7) is a proteolytic member of the ADAMTS family (a disintegrin and metalloproteinase with thrombospondin-like motifs) and has been identified to exert important effects on inflammatory diseases, such as arthritis and atherosclerosis (10-12). Previous studies have demonstrated that systematic inflammation is correlated with recurrent implantation failure and recurrent spontaneous abortion (SA) in humans (13). Over the past few decades, Th17 cells have been reported to be involved in the pathological process of recurrent miscarriage (3-9).

A disintegrin and metalloproteinase with thrombospondin motifs 7 (ADAMTS-7) is a proteolytic member of the ADAMTS family (a disintegrin and metalloproteinase with thrombospondin-like motifs) and has been identified to exert important effects on inflammatory diseases, such as arthritis and atherosclerosis (10-12). Previous studies have demonstrated that systematic inflammation is correlated with recurrent implantation failure and recurrent spontaneous abortion (SA) in humans (13). Over the past few decades, Th17 cells have been reported to be involved in the pathological process of recurrent miscarriage (3-9).
Accumulative evidence has indicated that women with adverse pregnancy outcomes are associated with a higher risk of suffering from cardiovascular disease, with preeclampsia as the most documented (17,18). It is also reported that women with a history of recurrent miscarriage are more likely to experience cardiovascular disease (19-21). Therefore, an underlying association was proposed between the molecular mechanism of recurrent miscarriage and cardiovascular disease. A recent study found that circulating ADAMTS-7 levels could reflect the degree of ventricle remodeling after acute myocardial infarction in a rat model (22). Moreover, it was also reported that ADAMTS-7 participates in the pathological process of atherosclerosis through degradation of cartilage oligomeric matrix protein (COMP) (23-25), which has been confirmed to be involved in some pathophysiological pathways, including vascular calcification, atherosclerosis and neo-intima formation post-injury (26,27).

Our study aimed to detect the expression of ADAMTS-7 and its substrate COMP in the decidua of both LPS-treated mice and humans with a history of SA as well as the corresponding control group. We aimed to find a potential association between the expression of ADAMTS-7 and COMP in the decidua of LPS-treated mice and SA humans, which would be helpful to further understand the pathogenesis of recurrent SA in order to find effective measures for treating this disease.

**Materials and methods**

**Animals.** Eight- to ten-week-old C57/BL mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). The mice were housed in an environment controlled for temperature (22–24°C) and conditions of light (12 h light and 12 h darkness), with free access to standard mouse food and water. 2 female mice were caged with one male mouse every other day, and vaginal plugs were checked the next morning as a sign of mating behavior. The day of plug detection was defined as embryonic day 0.5 (E 0.5). The pregnant mice were randomly divided into lipopolysaccharide (LPS) group and control group, with 10 mice in each group. LPS (Sigma, Saint Louis, MO, USA) was intraperitoneally injected in pregnant C57BL/6 female mice at E 7.5 to induce abortion. Mice in control group in saline was intraperitoneally injected in pregnant C57BL/6 mice at E 7.5 and the embryo resorption rate were calculated by dividing the number of resorbed embryos by the number of implantations, and the decidua were collected for further experiments. All of the experiments involving animals in this study were carried out in accordance with the protocols of the Guidelines for the Care and Use of Laboratory Animals published by the United States National Institutes of Health (NIH Publication, revised 2011) and the Guidelines for the Care and Use of Laboratory Animals of the Chinese Animal Welfare Committee. The procedures were approved by the Animal Use Committees of Renmin Hospital of Wuhan University (Wuhan, China).

**Human study.** The procedures involving human experiments were performed in accordance with the Declaration of Helsinki and were approved by the Human Research Ethics Committees of Renmin Hospital of Wuhan University (Wuhan, China). All participants were patients who went to the department of obstetrics and gynecology for treatment, and informed consent was signed by each participant. People with a history of SA before 22 weeks of gestation were divided into the SA group. People who went to the hospital for artificial abortion were placed into the control group. Subjects who had a history of autoimmune- or thyroid-related disease, uterine malformation, ultrasonographic evidence of hydrosalpinx, and hormone therapy within three months were excluded from this study. All participants shared similar baseline demographics. Finally, a total of 36 people were involved in this study, with 15 people in the control group and 21 people in the SA group.

**Immunohistochemistry.** Decidua tissue was collected and washed by PBS three times. The decidua tissues were then put into 10% formaldehyde at room temperature for 24 h, followed by deparaffinization and dehydration. Then, the samples were cut into 5-µm sections for further immunohistochemistry detection. Endogenous peroxidase was blocked with 3% H2O2. Non-specific staining was blocked using 5% bovine serum albumin for 20 min. Subsequently, the sections were incubated with primary antibody targeted to ADAMTS-7 (1:200) and COMP (1:200) at 4°C overnight. Thereafter, the decidua sections were exposed to biotinylated anti-rabbit immunoglobulin G solution (Proteintech Group, Inc.) at 37°C for 30 min followed by incubation with horseradish peroxidase-labeled streptavidin (Proteintech Group, Inc.) at 37°C for 30 min. After washing with PBS three times, the sections were counterstained with hematoxylin and dehydrated. Then, the sections were observed under a microscope (Nikon E100; Nikon Corporation, Tokyo, Japan), and the photomicrographs were obtained by Image-Pro Plus 6.0, and the mean of the integrated optical density was obtained to represent the expression of ADAMTS-7 and COMP.

**Western blot and reverse transcription-quantitative polymerase chain reaction (RT-qPCR).** Briefly, the decidua were weighed, cut and homogenized in a 1:10 (w/v) RIPA buffer using a homogenizer. After chilling on ice for 30 min, the suspension was centrifuged at 1,409 x g at 4°C for 15 min and the supernatants were collected. Then, the protein concentration was determined using a BCA Protein Assay kit (Pierce; Thermo Fisher Scientific, Inc., Waltham, MA, USA). A total of 20 µg protein were separated on SDS-PAGE gels and then transferred to a PVDF membrane. Subsequently, the membrane was blocked with 5% non-fat milk dissolved in TBST at room temperature for 2 h. Then, the membrane was incubated with the following primary antibodies at 4°C overnight: Rabbit anti-GAPDH antibody (1:5,000), rabbit anti-ADAMTS-7 antibody (1:1,000, ab28557; Abcam, Cambridge, UK) and rabbit anti-COMP antibody (1:1,000, ab42225; Abcam). After washing the membrane with TBST three times, the membranes were incubated with secondary antibody for 2 h at room temperature. Finally, the bands were scanned using a two-color infrared imaging system (Odyssey; LI-COR, Lincoln, NE, USA). Band intensity was quantified.
using Odyssey, as described previously, and the densities of the bands were normalized to GAPDH.

Total RNA was extracted using the TRIzol (Invitrogen; Thermo Fisher Scientific, Inc.) method according to the manufacturer's instructions. RNA concentration was detected using an absorbance at 260 and 280 nm (A260/280). Total RNA was reverse-transcribed into cDNAs using a PrimeScript™ RT-PCR Kit (04896866001; Roche Diagnostics, Indianapolis, IN, USA). Quantitative RT-PCR analysis was conducted using LightCycler 480 SYBR Green 1 Master Mix (04707516001; Roche Diagnostics). The primer sequences for Adamts-7 were as follows: Forward: 5’TCAACACGGTTCCTTGACCGTG-3’ and reverse: 5’CCACGTPTGGACGGTGTTG-3’. The primer sequences for Comp were as follows: Forward: 5’GGCGGCA GTGTGCAAGGACAA-3’ and reverse: 5’TGGTTTTCG AACAGCGGCG-3’. The primer sequences for Gapdh were as follows: Forward: 5’TGCACAACGGGAACCCCATC-3’ and reverse: 5’CTGCAGTTCCACACCACCA-3’. Expression of Adamts-7 and Comp was determined using the 2^ΔΔCq method and normalized to Gapdh (28).

Statistical analysis. All data were expressed as the mean ± standard deviation. The group sizes of the experiments were estimated based on power analysis of ADAMTS-7 mRNA expression, with an α error of 5% and a power of 80%, which is consistent with a published article (29). To detect a 10% change in ADAMTS-7 mRNA expression with an expected SD of 5%, we needed 5 animals per group. We had 10 mice in each group, and for humans, the sample size in the SA and control groups was 21 and 15, respectively, which fulfilled the requirement. Statistical analysis was performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA). All the data in the present study were normally distributed (P<0.05), as determined by the Kolmogorov-Smirnov’s test. The difference between two groups was then evaluated using independent samples t-tests (two-sided). The correlation between ADAMTS-7 and COMP was assessed by Spearman’s analysis. P<0.05 was considered to indicate a statistically significant difference.

Figure 1. Expression of ADAMTS-7 and COMP in mouse decidua by immunohistological analysis. (A) Immunostaining of ADAMTS-7 and COMP in the mouse decidua of the control and LPS-induced abortion group (n=6). Scale bar, 50 µm; magnification, x400. (B) Mean optical density of COMP in the mouse decidua of the control and LPS-induced abortion group (n=6). *P<0.05 vs. Con. ADAMTS-7, A disintegrin and metalloproteinase with thrombospondin motifs 7; COMP, cartilage oligomeric matrix protein; Con, control; LPS, lipopolysaccharide.

The expression of ADAMTS-7 and COMP in the human decidua of the SA group and the control group. As shown in Fig. 4, the expression of ADAMTS-7 was clearly increased in the human decidual tissue of the SA group. The expression of COMP was decreased in the human decidua of the SA group compared with that of the control group. Spearman’s analysis showed that the expression of ADAMTS-7 was negatively correlated with the expression of COMP in human decidual tissue, which had a correlation coefficient of -0.836 (P<0.001; Fig. 5).

The protein levels of ADAMTS-7 and COMP showed similar results the mice model, manifested as increased ADAMTS-7 and decreased COMP levels (Fig. 6A). The mRNA level of Admats-7 was increased, and the mRNA level of COMP was decreased in the SA group compared with the control group (Fig. 6B).

Discussion

In the present study, we first detected the expression of ADAMTS-7 and COMP in the decidual tissues of both LPS-treated mice and human subjects with SA. As demonstrated, ADAMTS-7 was increased, and COMP was decreased in the decidual tissue of the LPS-treated mouse model compared with that of the control group, as depicted by immunohistochemistry, western blot and RT-qPCR. Moreover, we also revealed
that ADAMTS-7 was negatively correlated with COMP in the decidual tissue of mice. The results in humans were similar to the results in mice. ADAMTS-7 was upregulated, and COMP was downregulated in the decidual tissue of the human subjects with SA compared with the corresponding control group, as demonstrated by immunohistochemistry, western blot and
was closely associated with inflammation. Elevated TNF-α osteoarthritis (24,26,37-41). COMP, an extracellular matrix protein mainly expressed in cartilage and bone tissue (42,43), was also reported as a substrate of ADAMTS-7 and plays a pivotal role in multiple epiphyseal dysplasia and cancer (44-46). To assess whether COMP is associated with ADAMTS-7, the expression of COMP was also determined in the decidual tissues of mice and humans. As demonstrated by immunohistochemistry, COMP was decreased in the LPS-treated group and SA group compared with the corresponding control group. Thus, it was hypothesized that the downregulation of COMP was associated with the upregulation of ADAMTS-7. Spearman’s analysis further confirmed our hypothesis and revealed that COMP was negatively correlated with ADAMTS-7. Thus, upregulation of ADAMTS-7 and downregulation of COMP were associated with SA.

However, there are also limitations in this study. First, we only described the expression of ADAMTS-7 and COMP in the decidua of both the LPS-treated mice and human subjects with SA. A functional study of ADAMTS-7 and COMP in SA as well as a determination of the potential regulatory molecular mechanism of ADAMTS-7 and COMP in the pathological process of SA still remain to be performed.

In conclusion, the present study, for the first time, presents the expression levels of ADAMTS-7 and COMP in the decidual tissues of mice and humans suffering from SA. The findings suggest that upregulation of ADAMTS-7 and downregulation of COMP are associated with SA. In addition, a negative correlation was found between ADAMTS-7 and COMP in both mice and humans. Further studies are required to elucidate the potential mechanisms underlying the role of ADAMTS-7 and COMP in SA.

Acknowledgements
Not applicable.

Funding
The present study was supported by the Key Project Grant of Natural Science Foundation of Hubei Province (grant no. 2015CFA074).

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Authors' contributions

YM and JY were involved in the study design and preparation of the manuscript. YM, DZ and NY carried out the experiments. JD and YM analyzed the data, drafted the manuscript and critically discussed the results with JY.

Ethics approval and consent to participate

Animal procedures were approved by the Animal Use Committees of Remnin Hospital of Wuhan University (Wuhan, China). The studies involving patients were approved by the Human Research Ethics Committees of Remnin Hospital of Wuhan University (Wuhan, China). Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Stirrat GM: Recurrent miscarriage. Lancet 336: 673-675, 1990.
2. Jivraj S, Anstie B, Cheong YC, Fairlie FM, Laird SM and Li TC: Obstetric and neonatal outcome in women with a history of recurrent miscarriage: A cohort study. Hum Reprod 16: 102-106, 2001.
3. Hughes GR: Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br Med J (Clin Res Ed) 287: 1088-1089, 1983.
4. Geva E, Lerner-Geva L, Burke M, Vardimon N, Lessing JB and Amit A: Undiagnosed systemic lupus erythematosus in a cohort of infertile women. Am J Reprod Immunol 51: 336-340, 2004.
5. Heller-Frischkorn K, Wach K, Heller L, Tempfer C and Grimm C: Serologic markers of autoimmunity in women with recurrent pregnancy loss. Am J Reprod Immunol 77: e12635, 2017.
6. Vitagliano A, Noventa M and Gizzo S: Autoimmunity, systemic inflammation, and their correlation with repeated implantation failure and recurrent miscarriage: Is chronic endometritis the missing piece of the jigsaw? Am J Reprod Immunol 77: e12597, 2017.
7. Mekinian A, Cohen J, Alijotas-Reig J, Carbillon L, Nicolas-Roland P, Kayem G, Darai E, Pain O and Bornes M: Unexplained recurrent miscarriage and recurrent implantation failure: Is there a place for immunomodulation? Am J Reprod Immunol 76: 8-28, 2016.
8. Comba C, Bastu E, Dural O, Yasa C, Keskin G, Ozsuremeli M, Buyru F and Serdaroglu H: Role of inflammatory mediators in patients with recurrent pregnancy loss. Fertil Steril 104: 1467-1474.e1, 2015.
9. Ahmad SK, Mahmood N, Malalla ZH, Alsobyani FM, Ahmed SK, Mahmood N, Malalla ZH, Alsobyani FM, Appelton CT, Beier F, Gloe F, Lai Y, Bai X, Zhao Y, Tian Q, Lin EA, Chen Y, Lee B, Guo F, Lai Y, Tian Q, Lin EA, Kong L and Liu C: ADAMTS-7 is associated with a high-risk phenotype of helper T cell (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. J Reprod Immunol 84: 164-170, 2010.
10. Wang SS, Zhang W, Zhang YQ, Zhao Y, Liu Y, Li JK, Zhang HX, Cheng L and Nie L: IL-17A enhances ADAMTS-7 expression through regulation of TNF-alpha in human nuclear pulposus cells. J Mol Histol 46: 475-483, 2015.
11. Mosca L, Benjamin EJ, Berra K, Bezzanona JL, Dolor RJ, Lloy-Jones DM, Newby LK, Piña IL, Rogers VL, Shaw LJ, et al: Effectiveness-based guidelines for the prevention of cardiovascular disease in women: 2011 update to a guideline from the American Heart Association. J Am Coll Cardiol 57: 1404-1423, 2011.
12. Wu P, Hathaithouwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA and Mamas MA: Preeclampsia and future cardiovascular health: A systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 10: pii: e003497, 2017.
13. Ranthe MF, Andersen EA, Wohlfahrt J, Bgaarda H, Melbye M and Boyd HA: Pregnancy loss and later risk of atherosclerotic disease. Circulation 127: 1775-1782, 2013.
14. Ollivier-Williams CT, Heydon EE, Smith GC and Wood AM: Miscarriage and future maternal cardiovascular disease: A systematic review and meta-analysis. Heart 99: 1636-1644, 2013.
15. Wagner MM, Bhattacharya S, Visser J, Hannaford PC and Bloemenkamp KW: Association between miscarriage and cardiovascular disease in a Scottish cohort. Heart 101: 1954-1960, 2015.
16. Wu W, Wang H, Yu C, Li J, Gao Y, Ke Y, Wang Y, Zhou Y and Zheng J: Association of ADAMTS-7 levels with cardiac function in a rat model of acute myocardial infarction. Cell Biochem Biophys 88: 950-958, 2016.
17. Kessler T, Zhang L, Liu Z, Yin X, Huang Y, Wang Y, Fu Y, Mayr M, Ge Q, Xu Q, et al: ADAMTS-7 inhibits re-endothelialization of injured arteries and promotes vascular remodeling through cleavage of thrombospondin-1. Circulation 131: 1191-1201, 2015.
18. Wang L, Zheng J, Bai X, Liu B, Liu CJ, Xu Q, Zhu Y, Wang N, Kong W and Wang X: ADAMTS-7 mediates vascular smooth muscle cell migration and neointima formation in balloon-injured rat arteries. Cir Res 104: 688-698, 2009.
19. Riessen R, Fenchel M, Chen H, Axel DI, Karsch KR and Lawler J: Cartilage oligomeric matrix protein (thrombospondin-5) is expressed by human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 21: 47-54, 2001.
20. Dub Y, Wang Y, Wang L, Liu B, Tian Q, Liu CJ, Zhang T, Xu Q, Zhu Y, Ake O, et al: Cartilage oligomeric matrix protein inhibits vascular smooth muscle cell calcification by interacting with bone morphogenetic protein-2. Circ Res 108: 917-928, 2011.
21. Bond AR, Hultgården-Nilsson A, Knutsson A, Jackson CL and Rauch U: Cartilage oligomeric matrix protein (COMP) in murine brachiocephalic and carotid atherosclerotic lesions. Atherosclerosis 236: 366-372, 2014.
22. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods 25: 402-408, 2001.
23. Puhl SL, Karakov A, Müller A, Fries P, Wagner DR, Böhm M, Maack C and Devaux Y: Adenosine A1 receptor activation attenuates cardiac hypertrophy and fibrosis in response to dl-adrenoreceptor stimulation in vivo. Br J Pharmacol 173: 88-102, 2016.
24. Wagstaff L, Kelwick R, Decock J and Edwards DR: The roles of ADAMTS metalloproteinases in tumorigenesis and metastasis. Front Biosci (Landmark) 17: 1861-1872, 2012.
25. Liu CJ, Kong W, Ihalov K, Yu S, Xu K, Prazak L, Fajardo M, Sehgal B and Di Cesare PE: ADAMTS-7: A metalloproteinase that directly binds to and degrades cartilage oligomeric matrix protein. FASEB J 20: 988-998, 2006.
26. González LF, Lai Y, Tian Q, Liu EA, Li L, Liu C and García-Fernández: ADAMTS-7 is involved in atherosclerotic plaque phenotype in human atherosclerosis. Sci Rep 7: 3753, 2017.
27. Liu CJ: The role of ADAMTS-7 and ADAMTS-12 in the pathogenesis of arthritis. Nat Clin Pract Rheumatol 5: 38-45, 2009.
28. Galgani M, Insabato L, Cali G, Della Gatta AN, Papaccio F, Santopaolo M, Alviggi C, Mollo A, Strina E, et al: Regulatory T cells, inflammation, and endoplasmic reticulum stress in women with defective endometrial receptivity. Fertil Steril 103: 1579-1586.e1, 2015.
29. Nakashima A, Ito M, Shima T, Bac ND, Hidaka T and Saito S: Accumulation of IL-17-positive cells in decidua of inevitable abortion cases. Am J Reprod Immunol 64: 4-11, 2010.
30. Wang WJ, Hao CF, Yi-Lin, Yin QJ, Bao SH, Qiu LH and Lin QD: Increased prevalence of helper T cell (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. J Reprod Immunol 84: 164-170, 2010.
31. Wang SS, Zhang W, Zhang YQ, Zhao Y, Liu Y, Li JK, Zhang HX, Cheng L and Nie L: IL-17A enhances ADAMTS-7 expression through regulation of TNF-alpha in human nuclear pulposus cells. J Mol Histol 46: 475-483, 2015.
34. Jones GC and Riley GP: ADAMTS proteinases: A multi-domain, multi-functional family with roles in extracellular matrix turnover and arthritis. Arthritis Res Ther 7: 160-169, 2005.
35. Buckland J: Osteoarthritis: Positive feedback between ADAMTS-7 and TNF in OA. Nat Rev Rheumatol 9: 566, 2013.
36. Li S, Wang L, Xing Z, Huang Y and Miao Z: Expression level of TNF-α in decidual tissue and peripheral blood of patients with recurrent spontaneous abortion. Cent Eur J Immunol 42: 156-160, 2017.
37. Bauer RC, Tohyama J, Cui J, Cheng L, Yang J, Zhang X, Ou K, Paschos GK, Zheng XL, Parmacek MS, et al: Knockout of Adamts7, a novel coronary artery disease locus in humans, reduces atherosclerosis in mice. Circulation 131: 1202-1213, 2015.
38. Patel RS and Ye S: ADAMTS7: A promising new therapeutic target in coronary heart disease. Expert Opin Ther Targets 17: 863-867, 2013.
39. Hanby HA and Zheng XL: Biochemistry and physiological functions of ADAMTS7 metalloprotease. Adv Biochem 1, 2013.
40. You L, Tan L, Liu L, Shen R, Chaugai S, Wang DW and Cui W: ADAMTS7 locus confers high cross-race risk for development of coronary atheromatous plaque. Mol Genet Genomics 291: 121-128, 2016.
41. Du Y, Gao C, Liu Z, Wang L, Liu B, He F, Zhang T, Wang Y, Wang X, Xu M, et al: Upregulation of a disintegrin and metallo-proteinase with thrombospondin motifs-7 by miR-29 repression mediates vascular smooth muscle calcification. Arterioscler Thromb Vase Biol 32: 2580-2588, 2012.
42. Müller G, Michel A and Altenburg E: COMP (cartilage oligomeric matrix protein) is synthesized in ligament, tendon, meniscus, and articular cartilage. Connect Tissue Res 39: 233-244, 1998.
43. Tan K and Lawler J: The interaction of Thrombospondins with extracellular matrix proteins. J Cell Commun Signal 3: 177-187, 2009.
44. Lin WD, Chou IC, Wang CH and Tsai FJ: Novel mutations in the cartilage oligomeric matrix protein gene identified in two Taiwanese patients with pseudoachondroplasia and multiple epiphyseal dysplasia. Pediatr Neonatol: 1-3, 2017.
45. Englund E, Bartoschek M, Reitsma B, Jacobsson L, Escudero-Esparza A, Orimo A, Leandersson K, Hagerling C, Aspberg A, Storm P, et al: Cartilage oligomeric matrix protein contributes to the development and metastasis of breast cancer. Oncogene 35: 5585-5596, 2016.
46. Englund E, Canesin G, Papadakos KS, Vishnu N, Persson E, Reitsma B, Anand A, Jacobsson L, Helczynski L, Mulder H, et al: Cartilage oligomeric matrix protein promotes prostate cancer progression by enhancing invasion and disrupting intracellular calcium homeostasis. Oncotarget 8: 98298-98311, 2017.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.