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Emerging roles of ADAMTS metalloproteinases in regenerative medicine and restorative biology

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Abstract: ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) proteinases degrade proteoglycans and thereby have the potential to alter tissue architecture and regulate cellular function. Recent studies about the roles of these enzymes have produced new perspectives for the molecular mechanisms behind regenerative biology with clinical potential to generate therapeutic targets to resolve tissue injury. ADAMTS enzymes play an important role in the turnover of extracellular matrix proteins in various tissues and their dysregulation has been implicated in disease-related processes such as inflammation and fibrosis. Increasing evidence indicates that they may be of key significance in the physiological and pathological central nervous system. In this review, we summarize what is currently known about the roles of ADAMTS proteins in tissue repair and regeneration as well as in the pathogenesis of other important biological processes and diseases including arthritis, atherosclerosis, and cancer.

Key words: Regenerative biology, ADAMTS, extracellular matrix, nervous system, chronic disease

1. Introduction

Regeneration is the process of renewal and restoration of damaged tissues with identical cells. It is also known as the ability of the cleavage of cells replacing the damaged tissues of the species ranging from bacteria to humans (Goss, 1992). In mammals, some human organs (liver and uterus) have the ability to regenerate themselves after injury. The regeneration of tissues or organs impaired as a result of many reasons such as congenital defects and diseases involves a healing process of active tissue and organs (Mimeault et al., 2007; Daar, 2013). The cells and tissues damaged by injuries go into motion to initiate their own healing processes. In healthy tissues, regeneration and reparation of cells occur after practically any injury that causes tissue destruction, and this is essential for the survival of the organs (Daar, 2013). Frequently, reparation consists of a combination of regeneration and wound healing with the deposition of collagen. Moreover, extracellular matrix (ECM) growth factors and cytokines are critical for the healing process (Werner and Grose, 2003; Daley et al., 2008). This requires some knowledge of ECM components and their functions as well as matrix metalloproteinase and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) to grasp the mechanisms of healing and regeneration. ADAMTS members, many of which bind to each other and modulate ECM proteins, form a family having 19 members and sharing many common features, and they are secreted out of the cell (Apte, 2004). In this mini-review, we summarize what is currently known about the roles of ADAMTS proteases in tissue repair and regeneration as well as their other important roles in biological processes. We searched for English-language studies published between June 2002 and May 2015 by using the MEDLINE/PubMed and Google Scholar databases. In general, studies used as references in this article were selected with an approach based on a comprehensive literature review through April 2015. For each database, the review terms used were 'ADAMTS', 'Extracellular matrix', 'Wound healing', and 'Regenerative or restorative biology'.

2. ADAMTS genes

ADAMTS constitutes a family of 19 secreted enzymes, of which the first member, ADAMTS-1 (Figure 1), was described in 1997 (Kuno, 1997). Members of this family are widely seen in mammals and they engage in different biological processes including ovulation, spermatogenesis, coagulation, neurogenesis, and extracellular matrix turnover (Reiss and Saftig, 2009). Furthermore, ADAMTS genes and their enzymes are also involved in diverse

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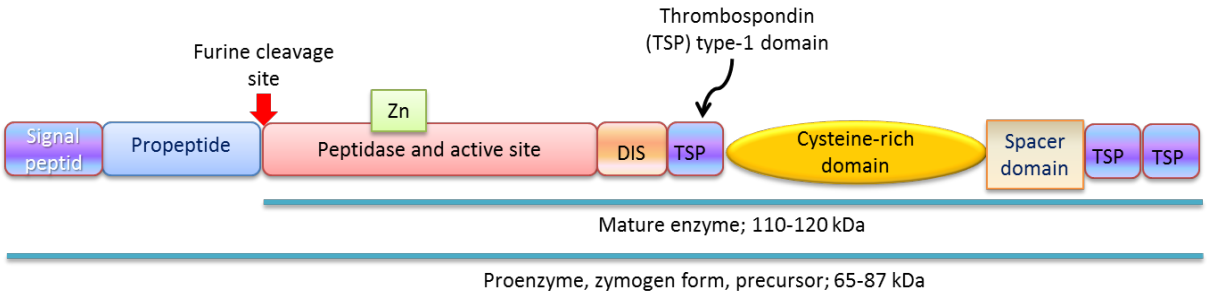

Figure 1. Structure and schematic representation of the domain organization of ADAMTS-1 proteinase. ADAMTS-1 is composed of a propeptide, a metalloproteinase domain, a disintegrin domain, a thrombospondin type 1-like motif, a cysteine-rich domain, and a spacer domain followed by two additional thrombospondin type 1-like motifs.

pathological processes including arthritis, atherosclerosis, fibrosis, and wound healing. Since the first description of prototype ADAMTS-1, there has been a quickly expanding literature related to the definition of this gene family and the proteins encoded (Porter et al., 2005). The more the roles of ADAMTS family members are clearly known in organogenesis, inflammation, and fertility, the more articles are published on the role of ADAMTS family members in angiogenesis and cancer (Kumar et al., 2012). These extracellular multidomain enzymes can be classified (Table 1) into subgroups in respect to their functions as follows: procollagen processing (ADAMTS-2, -3, and -14), proteoglycan degradation (ADAMTS-1, -4, -5, -8, -9, and -15), blood coagulation (ADAMTS-13), and cartilage oligomeric matrix protein (COMP) degradation (ADAMTS-7 and -12). The functions of several neglected ADAMTS members including ADAMTS-6, -16, -17, -18, and -19 are still unknown (Porter et al., 2005; Kumar et al., 2012).

3. Mechanisms of tissue regeneration

Reparation or healing is involved in the restoration process of living tissue structure and gaining its function after an injury; the reparation of a wound occurs as a result of two types of reactions: regeneration by proliferation of uninjured cells and maturation of tissue stem cell, and the deposition of connective tissue to form a scar (Gurtner et al., 2008). In all organ systems, the response of normal mammalian tissue to an injury occurs in three overlapping but distinctive stages: inflammation, new tissue formation, and remodeling/reshaping. The sequence of events that follows a myocardial infarction is remarkably similar to the one seen in a spinal-cord injury (SCI). Interestingly, the human liver is one of the few organs in the body to able to regenerate up to 70% of itself without scar formation, as demonstrated after partial hepatectomy (Hernandez-Gea and Friedman, 2011). However, reparation by connective tissue deposition consists of sequential stages following tissue damage such as the inflammatory response, angiogenesis, formation of granulation tissue, and remodeling of connective tissue. Although regeneration is a basic property of life, there are many varieties of regeneration and posttraumatic tissue loss is associated with a variety of physiological and pathological events in the tissue regeneration process (Table 2). The loss of cells through normal attrition is replaced on a continuous basis by processes described as physiological regeneration (Gurtner et al., 2008). The third stage of wound repair is

Table 1. Classification of ADAMTS proteoglycanases according to their functions.

Physiological function	Proteoglycanases
Aggrecanases	ADAMTS-1, -4, -5, -8, -9, -15, -16, and -18
Procollagen peptidases	ADAMTS-2, -3, and -14
COMP-ADAMTS	ADAMTS-7 and -12
GON-ADAMTS	ADAMTS-9 and -20
Anti-angiogenics	ADAMTS-1, -8, and -9
vWECP	ADAMTS-13
ORPHAN ADAMTS	ADAMTS-6, -10, -17, and -19

Table 2. General consecutive physiopathological events series in tissue regeneration process.

Trauma (mechanical, chemical, thermal…)
Localized posttraumatic ischemia and edema
Local inflammation and the removal of damaged tissues by phagocytosis
Activation of the cellular precursors of regeneration
Revascularization of the traumatized region
The extracellular matrix as a substrate for regeneration
Increase in the number of regenerating cells by proliferation
Differentiation of the regenerating tissue
Morphogenesis of the regenerating tissue
Functional restoration

implemented with matrix metalloproteinases secreted by fibroblasts, macrophages, and endothelial cells, and it strengthens the repaired tissue. Different patterns of fibrosis growth have been accounted for in terms of their etiology, the location of the injury, the source of the fibrogenic cells involved, and the predominant fibrogenic mechanism. On the other hand, multiple growth factors initiate the cleavage of the cells assigned in reparation (Gurtner et al., 2008; Hernandez-Gea and Friedman, 2011). Macrophages play a central role in reparation not only by clearing off the disruptive agents and dead tissue by means of providing growth factors for the proliferation of various cells but also by secreting cytokines that stimulate fibroblast proliferation and connective tissue synthesis and deposition. Almost simultaneously, the presence of macrophages is associated with the activation of precursor cells for regeneration. Fibroblasts are the prototypical mesenchymal cells that exist in many tissues (e.g., liver, kidneys, skin, and lungs) and get activated during repair processes (Kalluri and Zeisberg, 2006). Epithelial-mesenchymal improvement has been associated with tissue regeneration and fibrosis processes (Lee et al., 2006). The ECM constitutes the largest component of the damaged tissue and its synthesis is a key property of wound healing, especially when there has been a significant loss of tissue that inhibits closure. It is known that the ECM has both structural and regulatory functions in respect to cells and tissues. On the other hand, it has been proved that ECM is particularly vital for the regulation of transforming growth factor-beta (TGF-β), which is a pivotal agent in fibrosis and inflammation. ECM deposition depends on the balance between fibrogenic agents, metalloproteinases (MMPs) that digest the ECM, and the tissue inhibitors-MMPs (TIMPs) (Page-McCaw et al., 2007; Hubmacher and Apte, 2013). Progress in understanding the effects of the ECM thanks to proteinases has both provided a new insight to cell regulation and identified useful disease biomarkers, including ADAMTS proteinases.

4. ADAMTS expression in the nervous system and related disorders

One of the characteristics of the central nervous system (CNS) is that the ECM is composed mainly of proteoglycans. It is thought to play important roles in the CNS by modulating cell–matrix and cell–cell interactions, and by binding to various cellular components. The ECM is rich in hyaluronan, chondroitin sulfate proteoglycans (CSPGs), lecticans (e.g., aggrecan, brevican, neurocan), link proteins, and tenascins and can regulate cellular migration and axonal growth, thus actively getting involved in the development and maturation of the CNS (Zimmermann and Dours-Zimmermann, 2008; Gottschall et al., 2015). Studies on human diseased tissues and experimental analyses using molecular biology techniques have demonstrated the expression and function of ADAMTS proteases in various tissues including the lungs, liver, kidneys, and brain (Shiomi et al., 2010). Several members of the ADAMTS family including ADAMTS-1, -4, -5, and -9, or more precisely the proteoglycanases subgroup, are characterized by their routine ability to degrade CSPGs (Stanton et al., 2011). The CSPGs, a family of ECM macromolecules, have been extensively investigated for understanding their involvement in inflammation-induced osteoarthritis (OA), and an increasing amount of evidence indicates that they could have a crucial role physiologically and pathologically in the CNS (Lemarchant et al., 2013). Digestion of CSPGs is known to accelerate healing after neural injury, therefore indicating the modulating of

aggrecan function and cleavage related to perineuronal net formation and maintenance in the CNS (Cicanic et al., 2012). In addition, brain-derived link protein 1 (Bral1) is a link protein that stabilizes the binding between lecticans and hyaluronic acid and thus protects the ECM assembly in the CNS (Morawski et al., 2012). ADAMTS members are seen in the CNS (cortex, hippocampus, striatum, brain stem, and spinal cord) and detected by means of direct immunohistochemistry, western blot, and RT-PCR by using ADAMTS-specific neoepitope antibodies to check the changes in the fragments of various lectican substrates. According to the recent literature, the proliferation of lecticans appears to play an increasingly key role in neural plasticity (Gottschall et al., 2015). After CNS injury, CSPGs are rapidly upregulated within the glial scar and cause both fusing and cleaning effects in the place where the injury occurs. For example, their contribution to the establishment of a dense glial scar initially constitutes a protective barrier not only to limit the expansion of damage but also to prevent the formation of a harmful barrier to subsequent neurorepair and neuroplasticity (Rolls et al., 2009). Comprehensive data indicate that ADAMTS members increase their impacts on the therapy of CNS disease, CNS disorders, and the restoration of damaged tissues (Lemarchant et al., 2013; Gottschall et al., 2015). Additionally, recent advancements in cellular and molecular biology have provided a promising approach for disc regeneration that focuses on the migration of necessary cells to the degenerative disc (Wei et al., 2014). In the degenerated disc the catabolic activity of MMPs, disintegrins, ADAMTS members, and TIMPs alters, resulting in enhanced breakdown of ECM proteins, unlike that of normal disc tissue. These proteins facilitate tissue remodeling in normal disc tissue, and at least they are regulated to a certain extent by biomechanical pressure stimuli (Pockert et al., 2009; Vo et al., 2013). In another study, Tauchi et al. (2012) reported that for 7 days after injury the spinal cord lysate shows a significant increase in the aggrecan-degradation activity of ADAMTS-4, and they claimed that improvements in axonal regeneration/sprouting and subsequent functional recovery after SCI were witnessed. Similarly, several studies suggest that the ADAMTS members make a big contribution to SCI recovery, helping the formation of a glial scar that is rich in growth inhibitory molecules including lecticans, which diminish during functional recovery. In the aftermath of SCI, mRNA was upregulated, and this change was accompanied by increasing proliferation of aggrecan, brevican, and versican thanks to ADAMTS-1, -5, and -9 (Demircan et al., 2013). On the other hand, the expression of key ECM components aggrecan and collagen decreases in the degenerated disc tissues (Mern et al., 2013).

An increasing amount of evidence suggests that ADAMTS members may play a role in neuroplasticity. Lemarchant et al. (2014) claimed that the use of tPA, a drug for the treatment of stroke, or of the recombinant human ADAMTS-4 when it is applied in the subacute phase of injuries in the CNS may promote plasticity and provide long-term functional recovery. Overall, ADAMTS-4 may be a potentially promising therapeutic agent in order to increase plasticity and maintain functional recovery in the aftermath of SCI, especially when it is delivered soon after the injury. A study supporting this hypothesis demonstrated that recombinant active ADAMTS-4 promotes neurite growth of cortical neurons in vitro by degrading CSPGs via its proteolytic activity (Hamel et al., 2008). Additionally, after testing ADAMTS-4 proteoglycanases in cultures of astrocytes, Hamel et al. (2005) suggested that TGF-β may play a role in neural plasticity and regeneration via its regulation of brevican and the activity of the ADAMTS members. Furthermore, Krstic et al. (2012) claimed that ADAMTS-4 and ADAMTS-5, as the proteases being capable of cleaving reelin and the extracellular molecules, are also involved in synaptic plasticity and in neurodevelopment, which induces learning and memory processes. Interestingly, ADAMTS-induced cleavage of reelin is considered to partly improve its reproduction during aging and to restore the well-known synaptic plasticity defects in elderly CNS tissues (Figure 2). Considering both of them together, the majority of data suggest that the ADAMTS members are involved in the activation of plasticity mechanisms possibly on neurites and synapses and highlight that they play a key role, which is not surprising since the CSPGs can inhibit both neurite outgrowth and synaptic plasticity (Lemarchant et al., 2013; Gottschall et al., 2015). However, more studies are needed to determine whether or not ADAMTS proteoglycanases have unnecessary expressions and functions in the physiological and pathological CNS.

5. Effects of ADAMTS in the other pathological conditions

ADAMTS proteases are not only utilized in ECM assembly and degradation in morphogenesis, the physiology of female reproductive system biology, and many organ systems and processes, but they have been incriminated in the pathological destruction of joint tissues in rheumatoid arthritis and OA as well (Murphy and Nagase, 2008; Demircan et al., 2014). These enzymes degrade ECM macromolecules and modulate factors governing cell behavior; therefore, they participate in tissue reparation. Recent studies indicate that ADAMTS members are likely to be beneficial in the understanding of many diseases such as the pathogenesis of nervous system disorders, arthritis, and liver fibrosis (Gurtner et

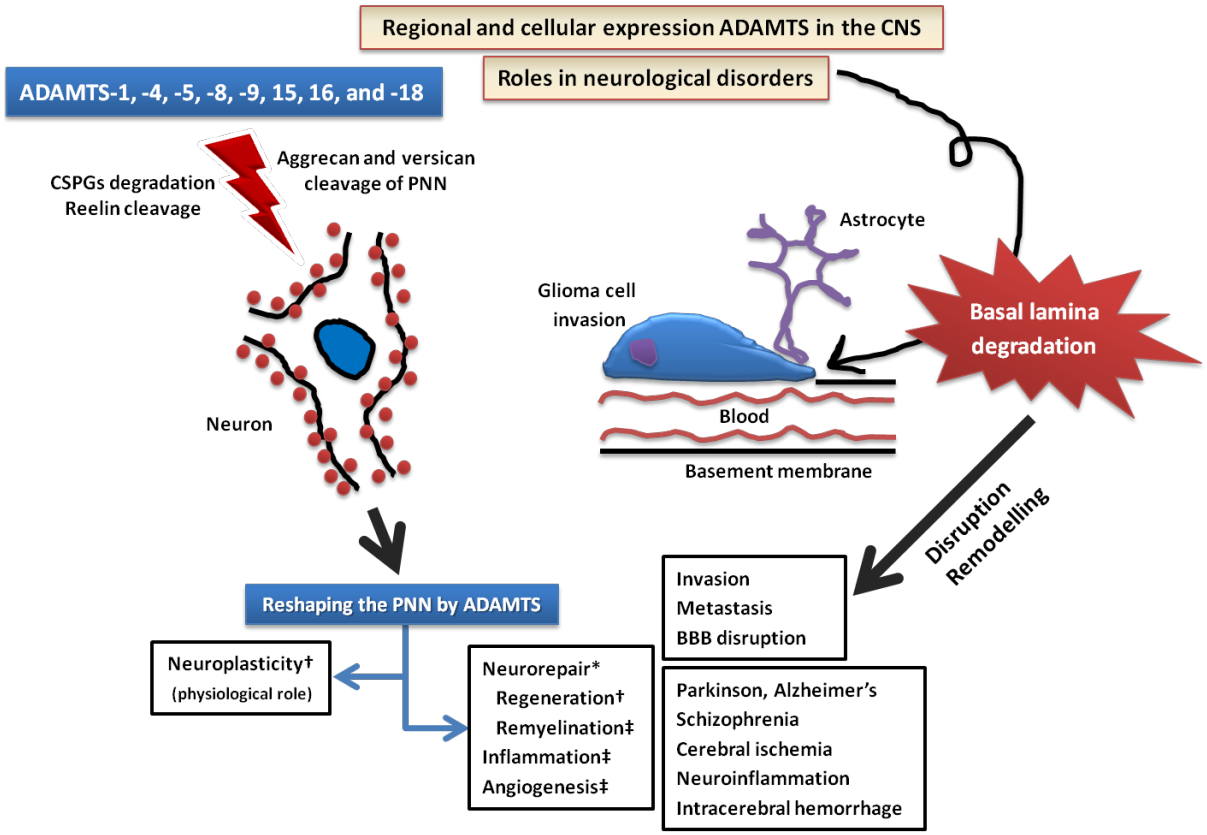

Figure 2. A schematic presentation on the roles and importance of ADAMTS proteoglycanases in the CNS and neurological disorders (CSPGs, chondroitin sulfate proteoglycans; PNN, perineuronal net; BBB, blood–brain barrier; *pathological role; †described, ‡hypothetical).

al., 2008). Certain members of the ADAMTS family of proteins have been demonstrated to cleave aggrecan in vitro at the aggrecanase cleavage site. ADAMTS-4 and ADAMTS-5 are closely related aggrecanases due to their implications in proteolytic destruction of aggrecan in osteoarthritic joint cartilage (Majumdar et al., 2007). In addition, the inhibition of these enzymes is in line with the prevention of aggrecan degradation in vitro (Malfait et al., 2002). They are considered the primary enzymes that are responsible for the cleavage of aggrecan; therefore, they are potential targets for therapeutic intervention in OA (Fosang and Little, 2008). In one study, Wylie et al. (2012) investigated the distribution and activation of ADAMTS-5, a vital aggrecanase in OA, in a mouse explant model with inflammatory arthritis. The occurrence of less severe osteoarthritis-like cartilage destruction in syndecan-4 deficient mice and syndecan-4 specific antibody-treated wild-type mice happens as a result of a considerable decrease in ADAMTS-5 activity. Syndecan-4 regulates the activation of ADAMTS-5 via its direct interaction with the protease and through regulating mitogen-activated protein kinase (MAPK)-dependent synthesis of matrix metalloproteinase-3 (Echtermeyer et al., 2009). On the other hand, the versican processing with ADAMTS versicanases makes contributions to muscle fiber formation. ADAMTS-5 was also proved to contribute to versican proteolysis in the fibroblast pericellular matrix and to reduce the versican amount in ADAMTS-5-deficient fibroblasts, leading to a substantial myofibroblast transition (Hattori et al., 2011). Establishing the versican remodeling may increase the regenerative capacity of muscle fiber fusion during regeneration (Stupka et al., 2013). For example, ADAMTS-1 takes part in versican proteolysis during myocardial compaction, a process in which cardiac myocytes form a functional myocardium during embryogenesis (Stankunas et al., 2008). ADAMTS-7, another protease, associates with granulin-epithelin precursor (GEP), a growth factor implicating in tissue regeneration, tumorigenesis, and inflammation. ADAMTS-7 functions as a new GEP convertase and neutralizes GEP-stimulated endochondral bone formation. In addition, COMP and GEP growth factor, two binding partners of ADAMTS-7, were also perceived to be primary intracellular factors in the growth

plate chondrocytes. Diverse localization of ADAMTS-7 and GEP in various chondrocytes suggests that they could play key roles at different levels in skeletogenesis (Bai et al., 2009). Moreover, the fusion and cleavage of COMP (a partner for ADAMTS-7 and -12) may also make contributions to put forward the pathogenesis of atherosclerotic disease. Wagsater et al. (2008) indicated that not only are ADAMTS-4 and -8 expressed in macrophages and in atherosclerotic plaques but also that the expression is accelerated during atherogenesis. ADAMTS-13 is the most extensively studied of all ADAMTS proteases. Its essential substrate is von Willebrand's factor (vWF), an important component of the clotting cascade and vascular basement membrane. Although the unclear contributions of ADAMTS-13 in angiogenesis and neovascularization are also reported, it has no direct relationship with the ECM (Rodríguez-Manzaneque et al., 2015). It is known that angiogenesis, the growth of new blood vessels from preexisting vasculature, is very crucial in physiological processes (growth and tissue remodeling in the menstrual cycle) and pathological conditions such as cancer, synovitis, and aberrant wound healing. Hsu et al. (2012) reported that ADAMTS-4, like ADAMTS-1, is expressed by endothelial cells, and it has antiangiogenic activity.

Previously, Malfait et al. (2002) claimed that ADAMTS-4 and ADAMTS-5 represent a potential target for the treatment of OA, and then Larkin et al. (2015) generated and tested the first selective ADAMTS-5 inhibitor named GSK2394002. They developed fully selective high-affinity monoclonal antibodies (mAb) for inhibition of aggrecanase activity, which is the hallmark of OA. Based on their studies, ADAMTS-5 is a significant proteoglycanase involved in cartilage degradation in human OA patients. Humanized mAb dose-dependently inhibited ADAMTS-5-mediated proteolysis of aggrecan and brevican via an allosteric lock mechanism. They also found that the mice treated with ADAMTS-5 mAb were protected from mechanical allodynia (a pain-related behavior) during a medial meniscus model of OA. In this way, ADAMTS-5 may be candidate of pain-related factors in OA and provides the first evidence for the treatment of both cartilage regeneration and pain symptoms caused by OA-associated algesia in OA. All these results suggest that ADAMTS proteases could be beneficial in the therapy of chronic degenerative diseases, not only because of its protective effects on the matrix but also because it has no interference with chondrogenesis. Thanks to its regenerative impacts it could make regenerative processes based on endogenous progenitor cells come into action.

6. Conclusion

During the last 15 years studies have demonstrated that ADAMTS proteinases are involved in a surprisingly diverse range of biological processes, from organogenesis to fertility and from regulation of angiogenesis to blood coagulation, with clear links to ECM assembly and ECM degradation. In the approach of investigative molecular mechanisms, they have been noticed to have regulatory functions on propeptide processing and posttranslational modification. Recent clinical and laboratory data show that not only do ADAMTS proteases play a key role in tissue reparation but that the destruction of ECM components impairs wound healing processes as well. The role of the ADAMTS members in the CNS continues to expand; more and more evidence demonstrates that they have a crucial role in neuroplasticity and neurorepair. ADAMTS family members, when taken together naturally, may be utilized to support other therapies for CNS injuries and neurodegenerative disorders such as Alzheimer disease. In addition to their proteolytic functions, ADAMTS proteases can potentially accelerate tissue regeneration (after the destruction of joint tissues and vascular-related damages) in the field of restorative biology and medicine. In spite of the management of larger lesions by using tissue engineering, many cartilage defects may be repaired, providing biologic solutions thanks to cartilage regeneration in the near future. Although many investigations have been carried out regarding ADAMTS in a wide spectrum of fields ranging from CNS disorders and arthritis to tumor pathobiology in recent years, more mechanistic and functional studies are required to be conducted to fully understand the benefits of the enzyme dynamics.

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References

Apte SS (2004). A disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motifs: the ADAMTS family. Int J Biochem Cell Biol 36: 981–985.

Bai XH, Wang DW, Kong L, Zhang Y, Luan Y, Kobayashi T, Kronenberg HM, Yu XP, Liu CJ (2009). ADAMTS-7, a direct target of PTHrP, adversely regulates endochondral bone growth by associating with and inactivating GEP growth factor. Mol Cell Biol 29: 4201–4219.

Cicanic M, Sykova E, Vargova L (2012). Bral1: "Superglue" for the extracellular matrix in the brain white matter. Int J Biochem Cell Biol 44: 596–599.

Daar AS (2013). The future of replacement and restorative therapies: from organ transplantation to regenerative medicine. Transplant Proc 45: 3450–3452.

Daley WP, Peters SB, Larsen M (2008). Extracellular matrix dynamics in development and regenerative medicine. J Cell Sci 121: 255–264.

Demircan K, Cömertoğlu I, Akyol S, Yigitoğlu BN, Sarikaya E (2014). A new biological marker candidate in female reproductive system diseases: matrix metalloproteinase with thrombospondin motifs (ADAMTS). J Turk Ger Gynecol Assoc 15: 250–255.

Demircan K, Yonezawa T, Takigawa T, Topcu V, Erdogan S, Ucar F, Armutcu F, Yigitoglu MR, Ninomiya Y, Hirohata S (2013). ADAMTS1, ADAMTS5, ADAMTS9 and aggrecanase-generated proteoglycan fragments are induced following spinal cord injury in Mouse. Neurosci Lett 544: 25–30.

Echtermeyer F, Bertrand J, Drejer R, Meinecke I, Neugebauer K, Fuerst M, Lee YJ, Song YW, Herzog C, Theilmeier G et al. (2009). Syndecan-4 regulates ADAMTS-5 activation and cartilage breakdown in osteoarthritis. Nat Med 15: 1072–1076.

Fosang AJ, Little CB (2008). Drug insight: aggrecanases as therapeutic targets for osteoarthritis. Nat Clin Pract Rheumatol 4: 420–427.

Goss RJ (1992). Regeneration versus repair. In: Cohen IK, Diegelman RF, Lindblad WJ, editors. Wound Healing: Biochemical and Clinical Aspects. Philadelphia, PA, USA: WB Saunders, pp. 20–39.

Gottschall PE, Howell MD (2015). ADAMTS expression and function in central nervous system injury and disorders. Matrix Biol 44–46C: 70–76.

Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008). Wound repair and regeneration. Nature 453: 314–321.

Hamel MG, Ajmo JM, Leonardo CC, Zuo F, Sandy JD, Gottschall PE (2008). Multimodal signaling by the ADAMTSs (a disintegrin and metalloproteinase with thrombospondin motifs) promotes neurite extension. Exp Neurol 210: 428–440.

Hamel MG, Mayer J, Gottschall PE (2005). Altered production and proteolytic processing of brevican by transforming growth factor β in cultured astrocytes. J Neurochem 93: 1533–1541.

Hattori N, Carrino DA, Lauer ME, Vasanji A, Wylie JD, Nelson CM, Apte SS (2011). Pericellular versican regulates the fibroblast–myofibroblast transition: a role for ADAMTS5 protease-mediated proteolysis. J Biol Chem 286: 34298–34310.

Hernandez-Gea V, Friedman SL (2011). Pathogenesis of liver fibrosis. Annu Rev Pathol 6: 425–456.

Hsu YP, Staton CA, Cross N, Buttle DJ (2012). Anti-angiogenic properties of ADAMTS-4 in vitro. Int J Exp Pathol 93: 70–77.

Hubmacher D, Apte SS (2013). The biology of the extracellular matrix: novel insights. Curr Opin Rheumatol 25: 65–70.

Kalluri R, Zeisberg M (2006). Fibroblasts in cancer. Nat Rev Cancer 6: 392–401.

Krstic D, Rodriguez M, Knuesel I (2012). Regulated proteolytic processing of reelin through interplay of tissue plasminogen activator (tPA), ADAMTS-4, ADAMTS-5, and their modulators. PLoS One 7: e47793.

Kumar S, Rao N, Ge R (2012). Emerging Roles of ADAMTSs in angiogenesis and cancer. Cancers 4: 1252–1299.

Kuno K, Kanada N, Nakashima E, Fujiki F, Ichimura F, Matsushima K (1997). Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene. J Biol Chem 272: 556–562.

Larkin J, Lohr TA, Elefante L, Shearin J, Matico R, Su JL, Xue Y, Liu F, Genell C, Miller RE et al. (2015). Translational development of an ADAMTS-5 antibody for osteoarthritis disease modification. Osteoarthritis Cartilage 23: 1254–1266.

Lee JM, Dedhar S, Kalluri R, Thompson EW (2006). The epithelial-mesenchymal transition: new insights in signaling, development, and disease. J Cell Biol 172: 973–981.

Lemarchant S, Pruvost M, Hebert M, Guberti M, Hommet Y, Briens A, Maubert E, Gueye Y, Feron F, Petite D (2014). tPA promotes ADAMTS-4-induced CSPG degradation, thereby enhancing neuroplasticity following spinal cord injury. Neurobiol Dis 66: 28–42.

Lemarchant S, Pruvost M, Montaner J, Emery E, Vivien D, Kanninen K, Koistinaho J (2013). ADAMTS proteoglycanases in the physiological and pathological central nervous system. J Neuroinflammation 10: 133–141.

Majumdar MK, Askew R, Schelling S, Stedman N, Blanchet T, Hopkins B, Morris EA, Glasson SS (2007). Double-knockout of ADAMTS-4 and ADAMTS-5 in mice results in physiologically normal animals and prevents the progression of osteoarthritis. Arthritis Rheum 56: 3670–3674.

Malfait AM, Liu RQ, Ijiri K, Komiya S, Tortorella MD (2002). Inhibition of ADAM-TS4 and ADAMTS-5 prevents aggrecan degradation in osteoarthritic cartilage. J Biol Chem 277: 22201–22208.

Mern DS, Fontana J, Beierfuss A, Thome C, Hegewald AA (2013). A combinatorial relative mass value evaluation of endogenous bioactive proteins in three-dimensional cultured nucleus pulposus cells of herniated intervertebral discs: identification of potential target proteins for gene therapeutic approaches. PLoS One 8: e81467.

Mimeault M, Hauke R, Batra SK (2007). Stem cells: a revolution in therapeutics-recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies. Clin Pharmacol Ther 82: 252–264.

Morawski M, Brückner G, Arendt T, Matthews RT (2012). Aggrecan: beyond cartilage and into the brain. Int J Biochem Cell Biol 44: 690–693.

Murphy G, Nagase H (2008). Reappraising metalloproteinases in rheumatoid arthritis and osteoarthritis: destruction or repair? Nat Clin Pract Rheumatol 4: 128–135.

Page-McCaw A, Ewald AJ, Werb Z (2007). Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol 8: 221–233.

Pockert AJ, Richardson SM, Le Maitre CL, Lyon M, Deakin JA, Buttle DJ, Freemont AJ, Hoyland JA (2009). Modified expression of the ADAMTS enzymes and tissue inhibitor of metalloproteinases 3 during human intervertebral disc degeneration. Arthritis Rheum 60: 482–491.

Porter S, Clark IM, Kevorkian L, Edward DR (2005) The ADAMTS metalloproteinases. Biochem J 386: 15–27.

Reiss K, Saftig P (2009). The "a disintegrin and metalloprotease" (ADAM) family of sheddases: physiological and cellular functions. Semin Cell Dev Biol 20: 126–137.

Rodríguez-Manzaneque JC, Fernández-Rodríguez R, Rodríguez-Baena FJ, Iruela-Arispe ML (2015). ADAMTS proteases in vascular biology. Matrix Biol 44–46C: 38–45.

Rolls A, Shechter R, Schwartz M (2009). The bright side of the glial scar in CNS repair. Nat Rev Neurosci 10: 235–241.

Shiomi T, Lemaitre V, D'Armiento J, Okada Y (2010). Matrix metalloproteinases, a disintegrin and metalloproteinases, and a disintegrin and metalloproteinases with thrombospondin motifs in non-neoplastic diseases. Pathol Int 60: 477–496.

Stankunas K, Hang CT, Tsun ZY, Chen H, Lee NV, Wu JI, Shang C, Bayle JH, Shou W, Iruela-Arispe ML et al. (2008). Endocardial Brg1 represses ADAMTS1 to maintain the microenvironment for myocardial morphogenesis. Dev Cell 14: 298–311.

Stanton H, Melrose J, Little CB, Fosang AJ (2011). Proteoglycan degradation by the ADAMTS family of proteinases. Biochim Biophys Acta 1812: 1616–1629.

Stupka N, Kintakas C, White JD, Fraser FW, Hanciu M, Aramaki-Hattori N, Martin S, Coles C, Collier F, Ward AC et al. (2013). Versican processing by a disintegrin-like and metalloproteinase domain with thrombospondin-1 repeats proteinases-5 and -15 facilitates myoblast fusion. J Biol Chem 288: 1907–1917.

Tauchi R, Imagama S, Natori T, Ohgomori T, Muramoto A, Shinjo R, Matsuyama Y, Ishiguro N, Kadomatsu K (2012). The endogenous proteoglycan-degrading enzyme ADAMTS-4 promotes functional recovery after spinal cord injury. J Neuroinflammation 9: 53–63.

Vo NV, Hartman RA, Yurube T, Jacobs LJ, Sowa GA, Kang JD (2013). Expression and regulation of metalloproteinases and their inhibitors in intervertebral disc aging and degeneration. Spine J 13: 331–341.

Wagsater D, Bjork H, Zhu C, Bjorkegren J, Valen G, Hamsten A, Eriksson P (2008). ADAMTS-4 and -8 are inflammatory regulated enzymes expressed in macrophage-rich areas of human atherosclerotic plaques. Atherosclerosis 196: 514–522.

Wei A, Shen B, Williams L, Ashish D (2014). Mesenchymal stem cells: potential application in intervertebral disc regeneration. Transl Pediatr 3: 71–90.

Werner S, Grose R (2003). Regulation of wound healing by growth factors and cytokines. Physiol Rev 83: 835–870.

Wylie JD, Ho JC, Singh S, McCulloch DR, Apte SS (2012). Adamts5 (aggrecanase-2) is widely expressed in the mouse musculoskeletal system and is induced in specific regions of knee joint explants by inflammatory cytokines. J Orthop Res 30: 226–233.

Zimmermann DR, Dours-Zimmermann MT (2008). Extracellular matrix of the central nervous system: from neglect to challenge. Histochem Cell Biol 130: 635–653.