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Mini review

# Emerging roles for ADAMTS5 during development and disease

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## 1. Introduction

Since its discovery in 1999 the chondroitin sulphate proteoglycanase ADAMTS5 (aggrecanase-2, ADAMTS11) has emerged as a major drug target in osteoarthritis. However, until recently little was understood regarding its potential role in other pathologies, and in physiology. Advancements beyond the arthritis field have provided valuable new insights into ADAMTS5 biology from both developmental biology and biochemistry standpoints, whilst emerging roles in pathologies such as

*Abbreviations:* ADAMTS, A Disintegrin-like and Metalloproteinase with Thrombospondin-1 motifs; CSPG, chondroitin sulphate proteoglycan; ECM, extracellular matrix; GAG, glycosaminoglycan; PACE, paired basic amino acid cleaving enzyme; SNP, single nucleotide polymorphism.

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cancer are becoming apparent. Since the targeting of zinc-dependent metalloproteinases such as ADAMTS5 continues to be of great therapeutic interest, the accumulation of knowledge surrounding such specific drug targets will assist greatly in assessing efficacy and the potential side-effects of those targeting strategies. Herein we discuss those recent discoveries and advancements in the context of the ADAMTS proteoglycanases, and their potential impact on the future of ADAMTS5 research into pathology and physiology.

## 2. The substrate specificity and activation mechanisms of ADAMTS5

### *2.1. ADAMTS5 is a chondroitin sulphate proteoglycanase*

ADAMTS (A Disintegrin-like and Metalloproteinase with Thrombospondin-1 motifs)5 (aggrecanase-2, ADAMTS11) (Abbaszade et al., 1999; Hurskainen et al., 1999) (Fig. 1) is a member of the evolutionary conserved proteoglycanase clade of the larger ADAMTS superfamily (recently reviewed in (Apte, 2009)). Together, the proteoglycanases represent a unique group of zinc-dependent, extracellular matrix (ECM) degrading enzymes that show proteolytic activity toward the hyalectan group of chondroitin sulphate proteoglycans (CSPGs), which comprise: aggrecan, versican, brevican and neurocan (Schaefer and Schaefer, 2010) (Table 1). The hyalectan CSPGs, so-called because of their hyaluronan and lectin binding properties, share an N-terminal G1 (immunoglobulin-like) domain with a signal peptide, an intermediate CS modifiable region, and a C-terminal G3 domain (Wu et al., 2005). The G1 domain of the hyalectans contains a high affinity hyaluronan binding region, allowing the formation of aggregates along a hyaluronan scaffold. Aggregating hyalectans are thought to provide their respective tissue with a rigidly structured, yet flexible ECM (Iozzo and Murdoch, 1996), that is able to be dynamically remodelled during homeostasis and disease.

Proteoglycanase cleavage within the hyalectans occurs at Glu-Xaa recognition motifs located throughout their core protein. Perhaps the most notable cleavage events mediated by ADAMTS5 are those occurring at the N-terminus of aggrecan and versican, generating G1-EGE (Chockalingam et al., 2004) and G1-DPEAAE (Longpre et al., 2009; McCulloch et al., 2009b) fragments respectively. The cleavage of aggrecan by ADAMTS5 particularly at this site is thought to be the most detrimental to articular cartilage function as it compromises the collective aggregating properties of the aggrecan–hyaluronan complex, releasing the entire CS containing C-terminus of aggrecan from the joint, whilst the G1-EGE fragments remain apparently attached to hyaluronan via the G1 domain (Sawaji et al., 2008). Loss of the highly sulphated GAG chain from articular cartilage reduces the tissue's load-bearing properties due to a loss of water retention that confers rigidity upon the tissue, causing loss of joint function in arthritis sufferers.

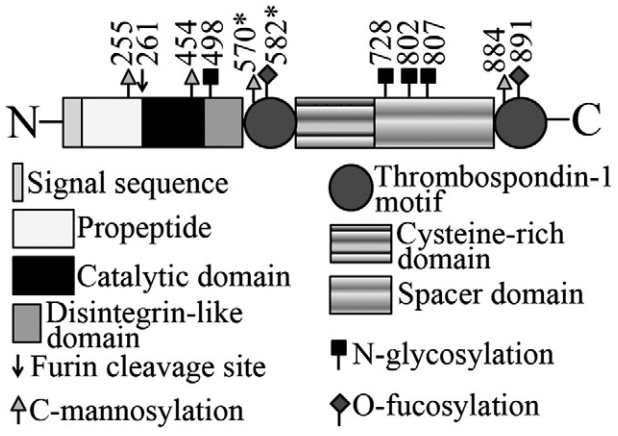


**Fig. 1.** Domain structure and organisation of ADAMTS5 with post-translational modification sites. * indicates confirmed C-mannosylation and O-fucosylation sites (Wang et al., 2009). Enumerated amino acids correspond to human ADAMTS5 annotation (Uniprot: Q9UNA0).

**Table 1**
Hyalectan substrates reported to date for the ADAMTS proteoglycanases.

| ADAMTS Proteoglycanase | Aggrecan | Versican | Neurocan | Brevican |
|---|---|---|---|---|
| ADAMTS1 | Yes[a] | Yes[b] | Yes[c] | Yes[c] |
| ADAMTS4 | Yes[d] | Yes[b] | Yes[c] | Yes[e] |
| ADAMTS5 | Yes[f] | Yes[g] | Yes[c] | Yes[h] |
| ADAMTS8 | Yes[i] | Not known | Not known | Not known |
| ADAMTS9 | Yes[j] | Yes[j] | Not known | Not known |
| ADAMTS15 | Yes[k] | Not known | Not known | Not known |
| ADAMTS20 | Not known | Yes[l] | Not known | Not known |

[a] (Kuno et al., 2000).
[b] (Sandy et al., 2001).
[c] (Cross et al., 2006).
[d] (Tortorella et al., 1999).
[e] (Nakamura et al., 2000).
[f] (Abbaszade et al., 1999).
[g] (Longpre et al., 2009).
[h] (Nakada et al., 2005).
[i] (Collins-Racie et al., 2004).
[j] (Somerville et al., 2003).
[k] (Yamaji et al., 2000).
[l] (Silver et al., 2008).

In the case of versican cleavage, on the other hand, recent and past studies have noted a shift in localisation of DPEAAE immunoreactivity when compared with the immunoreactivity of the versican (V0/V1 isoform) GAG-beta domain (Kern et al., 2007; McCulloch et al., 2009b). These apparent shifts in localisation suggest either alternative cleavage sites upstream of DPEAAE, perhaps also mediated by ADAMTS proteoglycanases, and/or concordant hyaluronidase activity allowing a diffusible fragment of versican to be produced. Therefore, it is possible that versican fragments confer biological activity at sites distant to their hyaluronan-aggregating origins, highlighting the importance of remodelling these complexes by ADAMTS5 in potential cell-signalling events that mediate cell behaviour.

All members of the ADAMTS proteoglycanases have been shown to, or are predicted to, cleave aggrecan however ADAMTS5 has emerged as the most important "aggrecanase" (pathologically), at least in the mouse, whereby catalytically inactivated *Adamts5* (ΔCAT) homozygous allelic mice are protected from experimentally induced arthritis (Glasson et al., 2005; Stanton et al., 2005), which is not the case for *Adamts1* (Little et al., 2005) and *Adamts4* (Ilic et al., 2007) homozygous knockout mice. Most members of the ADAMTS proteoglycanases have also been shown to, or are predicted to, cleave versican (Sandy et al., 2001; Russell et al., 2003; Somerville et al., 2003; Westling et al., 2004; Silver et al., 2008; Longpre et al., 2009; McCulloch et al., 2009b) (Table 1) with ADAMTS5 showing the highest activity of all ADAMTS proteoglycanases characterised to date toward versican in vitro at the G1-DPEAAE cleavage site (*pers. comm.* Professor Suneel Apte and Smith and McCulloch, unpublished). ADAMTS5 has also been shown to have the highest aggrecan degrading activity (Gendron et al., 2007). A recent study highlighted the importance of this activity outside the context of arthritis; whereby in the dermis, a site of both aggrecan and versican expression during wound healing, ADAMTS5 activity towards aggrecan rather than versican, was shown to mediate cell signalling and cell behaviour during wound healing through the TGF-β signalling pathway (Velasco et al., 2011). This highlights the possibility of ADAMTS5 activity having targeted substrates in context-specific roles within tissues that may express multiple hyalectans in its presence.

### *2.2. Biosynthesis and activation mechanism of ADAMTS5 is unique amongst the proteoglycanases*

ADAMTS5 is synthesised as a zymogen, and like all proteoglycanases has a signal peptide sequence which directs it through the cellular