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Anti-ADAMTS5 monoclonal antibodies: implications for aggrecanase inhibition in osteoarthritis

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Abstract

The extracellular matrix of articular cartilage is structurally specialized for efficient absorption of mechanical impact. In particular, giant aggregates of the large chondroitin sulfate proteoglycan, aggrecan, with the glycosaminoglycan, hyaluronan, allow cartilage to resist compressive load. Proteolysis of aggrecan by members of the proteinase family ADAMTS (A disintegrin-like and metalloproteinase domain with thrombospondin type 1 motif), was identified as an early step in the inexorable destruction of cartilage in osteoarthritis (OA). Of the investigated proteinases, ADAMTS5 has emerged as a principal mediator of aggrecan loss in OA, convincingly so in mouse models, and with high probability in humans. ADAMTS5 has a bipartite organization, comprising a proteinase domain and an ancillary domain containing exosites for interaction with aggrecan and other substrates. In a recent issue of this journal, Santamaria et al. characterized anti-ADAMTS5 monoclonal antibodies isolated from a phage display library. By blocking the catalytic site of the ADAMTS5 immunogen with a synthetic inhibitor, the authors of the paper biased selection of antibodies to the ancillary domain. This work, together with other antibodies targeting ADAMTS5, offers diverse, high-affinity and, as far as can be determined, selective aggrecanase inhibitors. Mapping of their epitopes provided novel insights into ADAMTS5 interactions with aggrecan. These monoclonal antibodies deserve continued investigation for potential arthritis therapy, although their successful use will require a comprehensive understanding of the physiological roles of ADAMTS5, and its regulation, intrinsic properties and intermolecular interactions.

Keywords

ADAMTS proteinase; aggrecan; arthritis; articular cartilage; metalloproteinase; osteoarthritis

Osteoarthritis (OA) is a common ‘degenerative’ disorder of synovial joints resulting from loss of articular cartilage, reactive changes in subchondral bone and varying degrees of synovial inflammation. Its manifestations are joint pain, joint stiffness and, periodically, joint swelling, which reduce mobility and adversely affect the quality of life. Although it can affect any synovial joint, OA of the hip, knee, spine and hands commands the most clinical attention. OA is a progressive, irreversible condition that is common in both sexes after the

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fifth decade of life. Its incidence and severity within the population increase steadily thereafter, portending epidemic proportions as life expectancy improves globally. Current pharmacological treatment addresses the symptoms of OA without modifying the disease itself. Definitive resolution of OA is provided only by joint arthroplasties, which are major, expensive, surgical procedures requiring advanced medical facilities, unavailable in many parts of the world.

These imperatives, especially the prospect of a large ageing population, have driven investigation of OA mechanisms as a gateway to the development of disease-modifying therapy. The current view of OA pathobiology is that it is a disease of the entire joint, but arises from progressive loss of articular cartilage, with secondary effects on underlying bone and articular soft tissues. Articular cartilage comprises chondrocytes, present at a relatively low cell density, and an abundant extracellular matrix, the components and networks of which have evolved specifically to absorb mechanical impact. Aggrecan, a large sulfated proteoglycan that forms giant supramolecular aggregates with the glycosaminoglycan (GAG) hyaluronan (HA) [1,2], is a major cartilage constituent. Aggrecan core protein comprises three globular domains – G1, G2 and G3 – and the region between the G2 and G3 domains is modified by attachment of the GAGs keratan sulfate (KS) and chondroitin sulfate (CS) [3] (Figure 1). Extensive sulfation of KS/CS and aggregation with HA generates a substantial fixed negative charge that renders the aggregates highly hydrated, and the resulting swelling pressure confers the desired viscoelastic properties to cartilage. HA is bound by the G1 domain in a ternary complex which includes a cartilage link protein, whereas the G3 domain interacts with several matrix molecules such as fibulin-1 and -2, fibrillin-1, and tenascin-C and -R [3]. Thus, aggrecan contributes unique intrinsic properties and is an indispensable component of a crucial network in cartilage matrix.

The swelling pressure exerted by HA–aggrecan is constrained by a network of collagen II-rich fibrils, associated with small leucine-rich proteoglycans [4]. Through the compressive resilience provided by HA–aggrecan aggregates, and the resistance to shear and tension provided by the fibrils, cartilage efficiently absorbs multiaxial loads. Loss of aggrecan, an early hallmark of OA, results not from physical ‘wear and tear’, but from an active, protease-mediated catabolic process, the instigating factors of which include joint trauma, joint malalignment or genetic variations that weaken cartilage extracellular matrix. Aggrecan depletion is believed to expose surface molecules on collagen fibrils and, subsequently, the collagen II fibrils themselves to proteolytic degradation [5,6], by which point the disease process is well nigh irreversible. Evidence also exists for feedback loops in which the products of cartilage catabolism potentiate joint damage [7–9]. For these reasons, aggrecan catabolism became a major focus of many academic and pharmaceutical laboratories.

The paper by Santamaria et al. [10] in the *Biochemical Journal*, as well as other recent successes in developing selective, high-affinity, inhibitory antibodies [11,12], is the culmination of almost three decades of intense research on mechanisms of aggrecan proteolysis. The sequence of discoveries tells a remarkable scientific story. The concept of ‘aggrecanase’ as a catabolic entity distinct from known matrix-degrading proteinases, then chiefly the matrix metalloproteinases (MMPs), first arose in the early 1990s. Sandy et al. [13,14] noted that the bulk of aggrecan found in OA synovial fluid had the N-terminus

A^{374}RGS (mature human/bovine aggrecan sequence enumeration), and attributed cleavage at the Glu^{373}–Ala^{374} peptide bond in the 'interglobular domain' (IGD), i.e. between G1 and G2, to a putative novel proteinase (Figure 1). In contrast, cartilage matrix contained the remnant N-terminal, hyaluronan-binding region of aggrecan (Figure 1). The development of antibodies specifically detecting the new IGD N- and C-termini (neoepitope antibodies) [15], and other neoepitopes within the CS-bearing domain [16], was a major advance, enabling the discovery of aggrecanase. Anti-A^{374}RGS neoepitope antibodies identified aggrecanase-derived cleavage products in OA synovial fluid and showed intense staining in OA cartilage. Staining was also evident in histologically normal cartilage, suggesting that OA could be incipient with a long latency, although the staining could also have arisen from physiological matrix turnover in the chondrocyte pericellular matrix [17]. The Glu^{373}–Ala^{374} cleavage was detectable in aggrecan fragments released from retinoic acid or interleukin-1-treated cartilage explants and chondrocytes, providing a system for *in vitro* manipulation, characterization and finally isolation of the putative aggrecanase(s) [18,19]. The identity of aggrecanase remained a mystery for a while, because cognate matrix-degrading enzymes such as MMPs were unable to reproduce the activity efficiently, until Tortorella et al. [20] identified a disintegrin-like and metalloproteinase domain with thrombospondin type 1 motif 4 (ADAMTS4) as aggrecanase-1. Subsequently, ADAMTS5 (redundantly numbered ADAMTS11), which was concurrently cloned in a search for novel metalloproteinases, was identified as aggrecanase-2 [21,22]. Joint protection in mice that had an aggrecan knock-in mutation to prevent cleavage of Glu^{373}–Ala^{374} provided compelling justification for targeting ADAMTS-mediated aggrecanolysis [5]. The resistance of *Adamts5*- but not *Adamts4*-mutant mice to mechanical instability or inflammation-induced cartilage aggrecan loss was a pivotal discovery that pointed to ADAMTS5 as the major aggrecanase in mice [23,24].

Similar to other ADAMTS proteinases, ADAMTS5 (see Figure 1) has a proteinase domain and a large non-catalytic (or ancillary) domain [22,25]. The proteinase domain comprises the propeptide, which needs to be excised by proprotein convertases to reveal proteolytic activity [26,27], the catalytic module and the disintegrin-like module (see Figure 1). The crystal structure of ADAMTS5 has shown that the catalytic and disintegrin-like modules both participate in substrate engagement [28,29]. ADAMTS5 comprising only the proteinase domain cleaved native aggrecan inefficiently, implying the requirement for additional contacts between the ancillary domain (termed 'exosites') and aggrecan [30,31]. This finding was consistent with the role of the ancillary domains of other ADAMTS proteinases in cleavage of native substrates, e.g. cleavage of von Willebrand factor by ADAMTS13 [32] and procollagen I processing by ADAMTS2 [33]. Santamaria et al. [10] postulated that exosites could be specific for different ADAMTS5 substrates; thus, antibodies or other molecules targeting ADAMTS5 exosites required for aggrecan cleavage may spare catalytic activity towards other substrates.

Santamaria et al. [10] used recombinant ADAMTS5 which included the spacer module, and they blocked the catalytic cleft with the peptidomimetic, broad-spectrum, zinc-chelating, active-site metalloproteinase inhibitor GM6001 to enhance isolation of ancillary domain antibodies from a phage antibody library. They used surface plasmon resonance, domain-specific deletion constructs of ADAMTS5, spatial occlusion of the catalytic domain by the

endogenous inhibitor tissue inhibitor of metalloproteinases 3 (TIMP3) [34] and molecular modelling to define the epitopes for these antibodies [10]. The four selected antibodies showed inhibitory activity against ADAMTS5, but not against ADAMTS4 or a panel of selected metalloproteinases, and bound specifically to ADAMTS5 but not to ADAMTS4 in surface plasmon resonance assays. The antibodies 2D3 and 2D11 bound to distinct surfaces in the catalytic/disintegrin-like modules, the epitope for 2D5 was at the interface between the catalytic/disintegrin-like modules and TS type 1 module 1 (TSR1), and 2B9 bound to the ADAMTS5 spacer. Following their previous work [31], the paper by Santamaria et al. [10] shows that the spacer is crucial for cleavage of aggrecan, via interaction with the aggrecan core protein but not with the GAG chains, which bind to the ADAMTS5 cysteine-rich domain (see Figure 1). Interestingly, 2B9 did not inhibit aggrecan release from a chondrocyte monolayer because in this system the prevalent form of ADAMTS5 lacked the spacer, and hence the antibody's epitope [10]. This leads to legitimate concerns about inhibitory antibodies to the ancillary domain, and the need for a detailed knowledge of truncated ADAMTS5 isoforms in OA.

Although Santamaria et al. [10] did not test their antibodies in animal models, two recent publications demonstrated the efficacy of aggrecanase inhibition *in vivo* using monoclonal antibodies. Chiusaroli et al. [11] identified CRB0017, a recombinant ADAMTS5 monoclonal antibody of high affinity and selectivity against the spacer. Intra-articular injection of CRB0017 in STR/ort male mice, which spontaneously develop OA, resulted in significant chondroprotection [11]. Larkin et al. [12] developed selective high-affinity antibodies against ADAMTS4 and ADAMTS5. They demonstrated that the ADAMTS5 antibody GSK2394002 was chondroprotective in both mice and cynomolgus monkeys, and could reduce pain-associated allodynia in mice [12]. GSK2394002 recognizes an epitope spanning the catalytic and disintegrin-like modules and appears to work by an 'allosteric lock effect' on ADAMTS5's active site [12]. Molecular imaging demonstrated its successful targeting to cartilage after intraperitoneal injection. Although ADAMTS5 is unequivocally implicated as the chief aggrecanase in mice, the identity of the major human aggrecanase is somewhat controversial [35,36]. Larkin et al. [12] suggest that ADAMTS5 is the primary target for human OA as well, because anti-ADAMTS5 antibodies effectively suppressed release of the ARGS epitope from human knee cartilage explants.

By any measure, the story of aggrecanase leading up to its selective targeting is a notable success of modern biomedical research, and a fine example of academic–industrial collaboration and synergy. How does one build on this success while being mindful of the wisdom accrued from previous failure? The aggrecanase armamentarium available for prospective OA therapy also includes several small-molecule, active-site inhibitors (reviewed in Dancevic and McCulloch [37]). Small-molecule, active-site inhibitors are cheaper than antibody drugs and orally bioavailable, but often lack the exquisite specificity of well-characterized monoclonal antibodies, a lesson learned from failed attempts to treat cancer with MMP inhibitors [38]. In addition to the lack of fine specificity of active-site inhibitors, this failure revealed how little was known about the complex biology of proteinases in cancer and normal tissue turnover [38]. The human genome carries little dead weight, and ADAMTS5, which has evolved over millennia, is required for cardiovascular and limb development, widely expressed in adult mice, and potentially involved in wound

healing via processing of versican and/or other substrates [39–44]. All inhibitors have potential side effects. Santamaria et al. [10] suggest that exosite-specific antibodies could be one way of selectively inhibiting proteolysis of aggrecan, which is located primarily in cartilage, fibrocartilage of tendons and menisci, and the brain, which is protected by the blood–brain barrier. What is needed now is an in-depth understanding of the physiological roles of ADAMTS5, including comprehensive understanding of its substrate repertoire, which currently includes aggrecan, versican and brevican, located in the brain. The blockage of the turnover of versican, which is present in the cardiovascular system and elsewhere, is probably inadvisable and may lead to collateral damage. Consideration could be given to dosing or delivery methods that maximize the effect on cartilage, but spare other tissues. Some possibilities include intra-articular delivery, intermittent infrequent dosing and combinations of low-dose anti-ADAMTS5 with drugs targeting other OA pathways. The catabolic effect of cartilage breakdown products [7–9] makes a case for early treatment to interrupt a feed-forward cycle of joint destruction, an approach that could be facilitated by advances in OA biomarkers.

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Abbreviations

ADAMTS	adamalysin-like metalloproteinases with TS motif
CS	chondroitin sulfate
GAG	glycosaminoglycan
HA	hyaluronan
IGD	interglobular domain
KS	keratan sulfate
MMP	matrix metalloproteinase
OA	osteoarthritis
TS	thrombospondin

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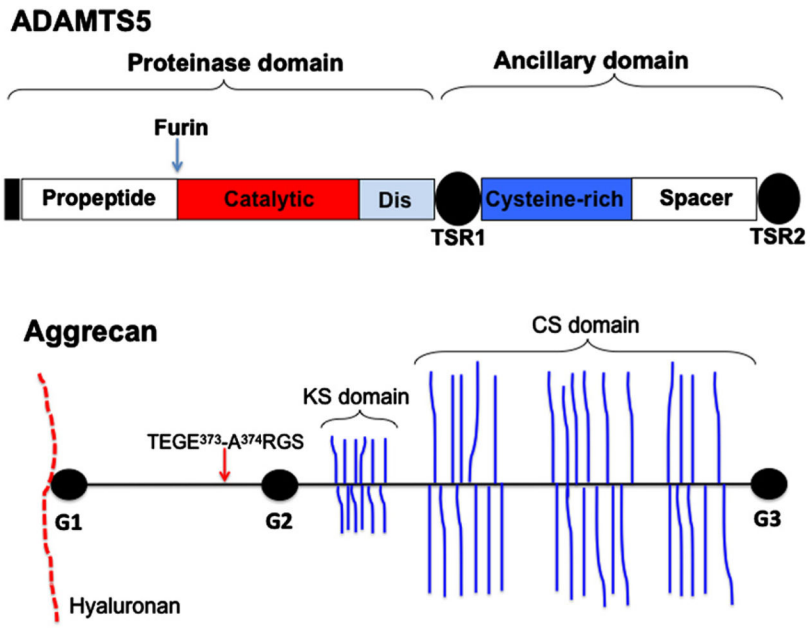

Figure 1. ADAMTS5 and aggrecan, the protagonists of this commentary

The schematic shows the domain structure of ADAMTS5 and aggrecan. The furin cleavage site in ADAMTS5 and the interglobular domain cleavage site for ADAMTS5 in aggrecan are shown. Dis, disintegrin-like module.