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Review

ADAMTS and ADAM metalloproteinases in osteoarthritis – looking beyond the 'usual suspects'

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SUMMARY

Introduction: Matrix metalloproteinases (MMPs) and 'aggrecanase' a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) are well established to play key roles in osteoarthritis (OA) through degradation of extracellular matrix (ECM) type II collagen and aggrecan, and are thus potential targets for development of OA therapies.
Objective: This paper aims to provide a comprehensive review of the expression and potential roles of other, lesser-known ADAMTSs and related adamalysins (or a disintegrin and metalloproteinases (ADAMs)) in cartilage, with a view to identifying potentially protective or homeostatic metalloproteinases in the joint and informing consequent selective inhibitor design.
Design: A comprehensive literature search was performed using PubMed terms 'osteoarthritis' and 'ADAMTS' or 'ADAM'.
Results: Several ADAMTSs and ADAMs were identified as having reportedly increased expression in OA. These include enzymes likely to play roles in cartilage matrix anabolism (e.g., the procollagen N-proteinases ADAMTS-2, ADAMTS-3 and ADAMTS-14), chondrocyte differentiation and proliferation (e.g., ADAM9, ADAM10, ADAM12), as well as enzymes contributing to cartilage catabolism (e.g., Cartilage oligomeric protein (COMP)-degrading ADAMTS-7 and ADAMTS-12).
Conclusions: In addition to the well-characterised MMPs, ADAMTS-4 and ADAMTS-5, many other ADAMTSs and ADAMs are expressed in cartilage and several show significantly altered expression in OA. Studies aimed at elucidating the pathophysiological roles of these enzymes in cartilage will contribute to our understanding of OA pathogenesis and enable design of targeted inhibitors that effectively target metalloproteinase-mediated cartilage degradation while sparing cartilage repair pathways.

Introduction

Osteoarthritis (OA) is a common degenerative joint disease characterised by cartilage loss, subchondral bone remodelling and osteophyte development. These structural changes are accompanied by impaired movement, stiffness and chronic joint pain. Primary risk factors for OA include age, obesity and joint injury, which alter the mechanical loading of the joint and initiate dysregulated cellular signalling and activation of catabolic pathways.

The role of matrix metalloproteinases (MMPs) in osteoarthritic degradation of the extracellular matrix (ECM) has been well documented. In particular, the collagenase matrix metalloproteinase 13 (MMP-13) plays a central role in degrading type II collagen[1,2], and the two 'aggrecanases', namely a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and -5, degrade aggrecan[3,4]. Collagen and aggrecan are the primary structural components of the cartilage ECM, and their degradation correlates with progression of OA. Collagenases and aggrecanases are thus potential targets for the development of disease-modifying OA drugs (DMOADs). For such an approach to be successful, it is vital that we learn lessons from previous attempts to develop metalloproteinase inhibitors as anti-cancer therapies[5]. These drugs failed due to limited specificity and consequent off-target inhibition of other metalloproteinases with homologous catalytic domains. Only by understanding the full spectrum of metalloproteinases expressed in the joint and their biological function(s) in this location will it be possible to design

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strategies to selectively target pathological tissue destruction. Several ADAMTSs other than ADAMTS-4 and -5 are expressed in cartilage, but little is known about whether they are required for joint health or whether they contribute to OA pathogenesis. The roles of the related adamalysin (a disintegrin and metalloproteinase, ADAM) family of metalloproteinases in cartilage are similarly poorly understood. Here, we review studies examining the role of ADAMTSs and ADAMs in cartilage, and compare microarray studies examining their expression in murine models of OA[6–8] and human normal and osteoarthritic cartilage[9–17]. This review thus highlights ADAMTSs and ADAMs that are expressed in cartilage and whose expression is altered in OA, with a view to developing a broader understanding of the contribution of the metalloproteinase family to joint health and disease.

ADAMTSs

The ADAMTSs are a family of 19 secreted metalloproteinases (Fig. 1) involved in various developmental and homeostatic processes[18]. The 'aggrecanases' ADAMTS-4 and -5 have been extensively reviewed elsewhere[19,20], and will not be covered here. Several other ADAMTSs are expressed in cartilage, and have emerging roles in joint pathophysiology.

ADAMTS-1

ADAMTS-1 is expressed in cartilage and synovium[18] and has been shown to cleave aggrecan and versican[21]. Several studies show that ADAMTS-1 expression is significantly upregulated in OA cartilage[7,10–12,14,22], though some studies indicate reduced expression in late-stage human OA[9,13,17] (Fig. 2). Immunohistochemical analysis indicates that in normal cartilage, ADAMTS-1 is primarily expressed in the superficial zone, with OA cartilage showing increased staining in the middle zone and in osteophytes[22].

Adamts1-null mice display unaltered susceptibility in the antigen-induced model of inflammatory arthritis and there is also no change in the level of aggrecan degradation in response to interleukin 1 (IL-1) stimulation of cartilage explants *in vitro*[23]. The susceptibility of these mice to surgical destabilisation of the medial meniscus (DMM), a model that more closely resembles human OA, has not been reported. Given that *Adamts1*-null mice show developmental abnormalities[24], conditional deletion may be required to establish the role of the enzyme in cartilage homeostasis.

ADAMTS-2, ADAMTS-3 and ADAMTS-14

ADAMTS-2, ADAMTS-3 and ADAMTS-14 are procollagen N-proteinases, responsible for removing the N-terminal propeptide of

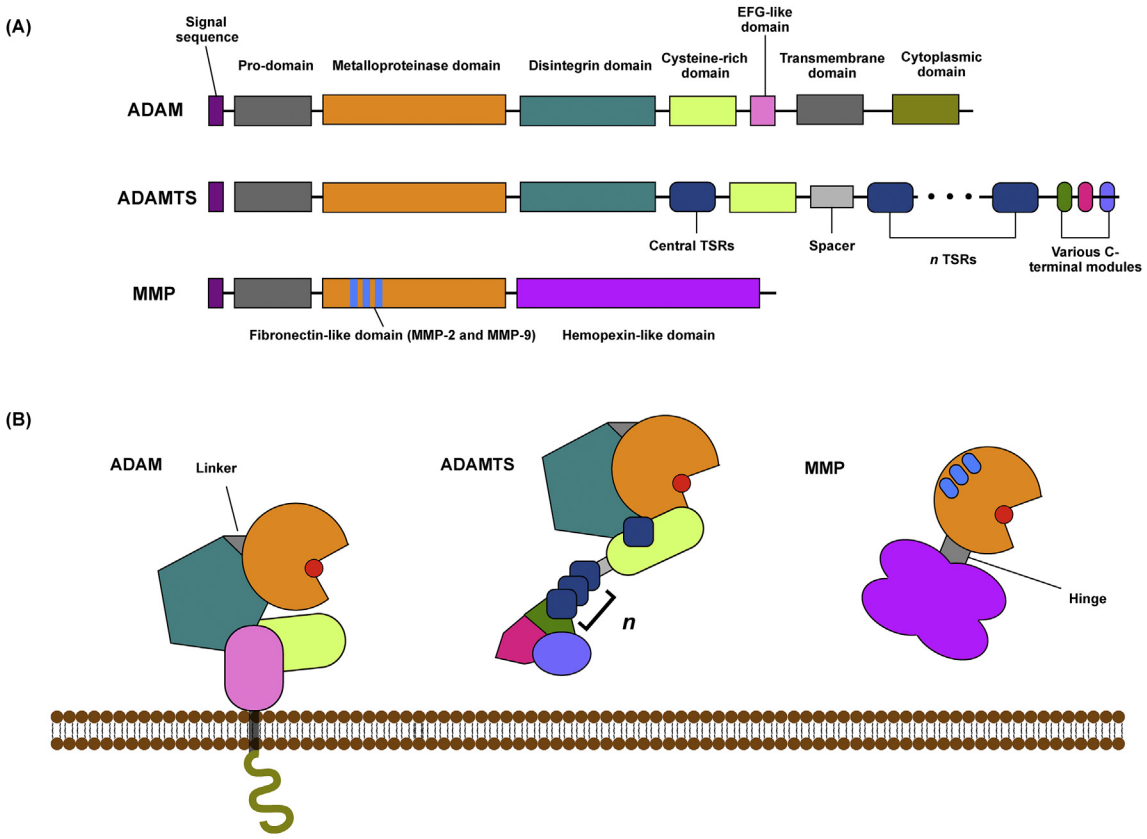

Fig. 1. Schematic representation of ADAM and ADAMTS topography. ADAMs and ADAMTSs are metzincin metalloproteinases whose catalytic domains share homology with those of the MMPs, and contain a zinc ion (red circle) that is essential for their proteolytic activity. All three groups of enzymes have a prodomain that keeps them in an inactive zymogen form until they are activated. The families differ in their C-terminal ancillary domains, which mediate interaction with substrates and other proteins. *ADAM ancillary domains*: ADAMs contain C-terminal disintegrin-like domains, thought to regulate cell–cell and cell–matrix adhesion, as well as conserved cysteine-rich domains and EGF-like domains[102]. The cytoplasmic domains are the most diverse, and vary in sequence and length. Some ADAM cytoplasmic domains contain proline-rich Src homology (SH)-2 and/or SH-3 binding sites, indicating that they may participate in intracellular signalling. Some also contain potential serine–threonine and/or tyrosine phosphorylation sites, making them plausible adaptors for conveying signals between the cell and its surroundings. *ADAMTS ancillary domains*: In contrast to the ADAMs, ADAMTSs are secreted metalloproteinases that lack transmembrane and cytoplasmic domains. In addition to their catalytic and pro-domains, the enzymes contain a variable number of thrombospondin type 1 sequence repeat (TSR) motifs, which are homologous to thrombospondins[18], as well as a cysteine-rich domain and spacer domain. Some members of the family contain additional C-terminal domains[18]. For example, ADAMTS-9 and -20 contain GON-1 domains, ADAMTS-2, -3 and -14 contain a procollagen N-propeptidase (PNP) domain, and ADAMTS-7 and -12 contain a PLAC domain.