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Editorial

ADAMTS-5 takes centre stage in new developments for aggrecanase inhibitors

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It is a decade since genetically-modified mice, deficient in either ADAMTS-4 or ADAMTS-5, were used to identify ADAMTS-5 as the primary aggrecanase in models of inflammatory[1] and non-inflammatory[2] joint disease. However, the identity of the human aggrecanase has been less clear, with evidence on both sides of the debate informing the interim consensus that ADAMTS-4 and ADAMTS-5 might each play important roles in human aggrecanolysis. Using monoclonal antibodies (mAbs) that target the same structural domains within ADAMTS-4 and ADAMTS-5, Larkin and colleagues now describe anti-ADAMTS-5 mAbs that block aggrecan loss from cartilage in humans *ex vivo*, and non-human primates *in vivo*, and inhibit structural damage and mechanical allodynia in mouse models of OA[3]. The authors used ARGS neoepitope as a readout for ADAMTS-mediated aggrecan loss, to show that ADAMTS-5 mAbs were more effective than ADAMTS-4 or isotype control mAbs at reducing ARGS release from human cartilage explants in unstimulated conditions. Similarly, the levels of circulating ARGS epitope in cynomolgus monkeys that naturally develop an OA-like condition, were reduced by treatment with ADAMTS-5 mAbs and remained low following twice-monthly antibody administration. Although the release of ARGS from human cartilage explants was not inhibited by ADAMTS-4 mAbs in unstimulated conditions, in the presence of cytokine stimulation, ADAMTS-4 and ADAMTS-5 mAbs slowed release of ARGS neoepitope suggesting that both enzymes might have a role under certain conditions. This study advances OA research in several important directions.

New insights into the structure–function relationship of the catalytic and disintegrin-like domains of ADAMTS-5

One key finding is that the most effective ADAMTS-5 mAb is one that targets a conformational epitope spanning both the catalytic and the disintegrin-like domains. ADAMTS-5 mAbs targeting the catalytic site alone were ineffective inhibitors. The authors propose that inhibition induced by targeting both the catalytic and disintegrin-like domains might arise via an allosteric lock mechanism. This hypothesis is consistent with original reports of the ADAMTS-5 crystal structure showing that the catalytic and disintegrin-like domains form a single folding unit, and exist in both open and closed configurations[4]. The present results provide the first example within the metzincin family of targeting enzyme inhibition beyond the catalytic domain. Further investigation of the structure–function relationship between the catalytic and disintegrin-like domains of ADAMTS-5 are warranted.

Evidence that therapies designed to treat structural damage in joints might also ameliorate pain

Although it is pain that brings the patient to the physician, it is structural damage that leads to disability and failure of the joint. However the relationship between pain, and structural damage to joint tissues, is unclear. Malfait and colleagues have previously shown that ADAMTS-5 deficient mice fail to develop mechanical allodynia (a pain-related behaviour) associated with experimental OA[5]. Larkin and colleagues analysed the effect of treating mice with ADAMTS-5 mAbs prophylactically, and for 8-weeks post DMM surgery; they found that the mice were protected from mechanical allodynia during this time. This result appears to link structural damage with pain and provides the first tantalising evidence that therapies designed to treat joint structural damage might also have efficacy in ameliorating OA-related pain. The mechanisms underlying this relationship have yet to be fully explored, but are now possible with the availability of ADAMTS-4 and ADAMTS-5 mAbs.

Treatment with ADAMTS-5 mAbs post-DMM surgery might promote cartilage accrual

Histological analyses of cartilage damage in the mouse DMM model showed that not only did prophylactic administration of ADAMTS-5 mAbs prevent aggrecan loss and cartilage erosion, but that mice continuing to receive weekly treatments over an 8-week period appeared to accrue cartilage. Although this remarkable and unprecedented observation requires further investigation and quantitation, it does raise the possibility that ADAMTS-5 mAbs, at doses equal to or less than those reported by Larkin *et al.*, might have efficacy as cartilage-promoting as well as cartilage-sparing agents in certain clinical settings.

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Is inhibition of ADAMTS-5 activity *in vivo* compatible with ADAMTS-5 function in other tissues?

Following intra-peritoneal injections into mice, labelled ADAMTS-4 and ADAMTS-5 mAbs showed a systemic biodistribution and were readily detected in joint tissues when mice were harvested 4 days later. High power images confirmed mAb penetration into knee cartilage with staining in the superficial zone and pericellular region of chondrocytes. These results confirm that the ADAMTS-4 and -5 mAbs reach their molecular targets in joint tissues, and most likely in other tissues where the effects of ablating ADAMTS-5 activity have yet to be tested. Versican is a large aggregating proteoglycan, related to aggrecan, and is also a substrate for ADAMTS-5. Proteolysis of versican is essential in some developmental and homeostatic processes[6]. For example, failure to remodel versican in cardiac valves during development is associated with myxomatous valve disease[7]. In atherosclerotic disease, ADAMTS-5 deficiency is thought to impair proteolysis of versican and the small proteoglycan biglycan, and contribute to lipoprotein retention in the aorta[8] leading to atherosclerosis. Other studies suggest that ADAMTS-5 deficiency in tendon disturbs organisation of the tendon matrix and adversely affects its biomechanical properties[9]. Assessing the safety and tolerability of the ADAMTS-5 mAbs (GSK2394002) in other tissues is the next priority for Larkin and colleagues, ahead of clinical trials in OA patients.

Conflicts of interest

None declared.

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