Cartilage matrix degradation: an appropriate therapeutic target in osteoarthritis

"Hopefully, better, more affordable methodologies and protocols will be developed for clinical trials so that cartilage-preserving DMOADs can become an important part of the arsenal of treatments to manage OA."

KEYWORDS: aggrecan ■ articular cartilage ■ collagen ■ disease-modifying osteoarthritis drugs ■ matrix metalloproteinase ■ osteoarthritis

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Osteoarthritis (OA) is a complex disease, now recognized to involve all structural elements of the articulating joint. Different therapies will be required to tackle different aspects of the condition. Cartilage loss associated with OA is a major determinant for joint replacement surgery. Preventing, or even reversing, articular cartilage matrix degradation in OA has long been considered an important therapeutic aim by the research community and the pharmaceutical industry. There are still a number of hurdles to leap before blocking cartilage matrix breakdown becomes a standard part of OA therapy, but there are good grounds to argue that the cartilage matrix is a relevant, worthwhile target for therapeutics that will improve patient outcomes.

Articular cartilage degradation associated with OA is an enzyme-driven process, and is, therefore, an excellent candidate for the development of inhibitory, disease-modifying OA drugs (DMOADs). Research has concentrated on the two major components of articular cartilage, collagen type II and aggrecan. Collagen II provides cartilage with its tensile strength and aggrecan is responsible for its weight-bearing properties. Together these molecules make up 70–80% of the dry weight of the tissue. The loss of collagen II and aggrecan in OA cartilage is well documented [1]. Cartilage loss associated with OA is likely to be irreversible due to the poor ability of the tissue to repair the collagen framework. The importance of aggrecan degradation in cartilage erosion was confirmed in a genetically modified mouse strain, in which aggrecan was made resistant to enzymatic degradation; these mice had less aggrecan loss and cartilage erosion in a model of OA [2]. A wealth of *in vitro* and *in vivo* data from both human tissues and animal models have identified specific zinc metalloproteinases as the major mediators of both collagen II and aggrecan loss; matrix metalloproteinase (MMP)-13 is the major collagenase [3], and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and -5 are the major aggrecanases [4]. The importance of these enzymes is underlined by targeted deletion of either MMP-13 [5] or ADAMTS-5 [6] in mice, which are both resistant to cartilage erosion in a model of OA. One limitation of using 'knockout' mice to identify the role of specific proteinases is that enzymatic activity is completely blocked at disease onset, a situation unlikely to be replicated in the treatment of human OA. However, in many patients, the disease remains stable for long periods of time before progressing [7,8], and DMOADs could be used to prevent further cartilage loss. An alternative is to give these drugs prophylactically to patients with acute traumatic joint injury that is likely to lead to OA.

Cathepsin K has been implicated in collagen degradation [9], and calpain [10] and HtrA1 [11] degrade human aggrecan *in vivo*, but the significance of these enzymes in OA remains to be determined. An alternative therapeutic target is tissue inhibitor of metalloproteinase-3, a potent endogenous inhibitor of MMP-13, and ADAMTS-4 and -5 [12]. In the tissue, inhibitor of metalloproteinase-3 knockout mouse, there is significant, spontaneous cartilage degradation, characterized by both collagen and aggrecan loss [13].

A number of small-molecule inhibitors have been developed that target MMP-13 and ADAMTS-4 and -5. The results of previous clinical trials of MMP inhibitors for the treatment of arthritis and cancer were disappointing, as there were side effects, such as muscle

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soreness and tendonitis, or the drugs showed no benefit [14]. However, the early MMP inhibitors blocked a number of metalloproteinases, whereas now there are more promising drugs that are more specific for MMP-13 [15]. Cartilage matrix degradation has recently fallen out of favor as a target of OA therapy, even with the development of these potentially useful new DMOADs. A recent review of the Clinical Trials Data Bank revealed only one Phase I clinical trial of an aggrecanase inhibitor (NCT00454298) and no trials involving MMP inhibitors [16]. As of September 2010, this situation had not changed. In the past few years, several OA discovery programs in large pharma have closed down. This is not due to a lack of progress but rather due to difficulties in determining the efficacy of DMOADs on cartilage loss in clinical trials. The major American (US FDA) and European (EMEA) licensing authorities specify joint space narrowing (JSN), caused by cartilage loss, as the primary end point. However, the rate of JSN is very slow, it can also be caused by meniscal displacement and there are problems with current radiological methods of measuring it [17], so that improvements can only be determined using very large clinical trials over long time periods that are impractical and prohibitively expensive for the pharmaceutical industry. In response to these issues, the Osteoarthritis Research Society International OMERACT initiative has devised "time to fulfillment of criteria for total joint replacement" [18] as an alternative end point, specifically for use in clinical trials, as a way of making trials of DMOADs more feasible.

> *"Preventing, or even reversing, articular cartilage matrix degradation in OA has long been considered an important therapeutic aim … There are still a number of hurdles to leap … but there are good grounds to argue that the cartilage matrix is a relevant, worthwhile target for therapeutics that will improve patient outcomes."*

Given the difficulties in using imaging techniques to monitor drug efficacy, there is an urgent requirement for biomarkers to chart the progression of articular cartilage damage and the effectiveness of DMOADs; none are currently available. Recently, two new assays [19,20] have been devised that detect aggrecan fragments in serum and urine. Using these assays, increased levels of aggrecan fragments were seen in OA patients [19,20]. It remains to be determined if aggrecan fragments are accurate biomarkers of OA disease progression, but if so, these assays will be valuable not only for clinical trials but for diagnosis and management of the disease.

Pain and loss of joint function are the clinical symptoms of most concern to patients. There is conflicting evidence over the relationship between cartilage loss (as measured by JSN) and pain. A recent review of the literature concluded that JSN is an imprecise guide to the presence of pain [21]. However, a subsequent study of two cohorts with a total of over 1000 patients, which minimized confounding factors, showed a strong link between JSN and pain [22]. Recently, intriguing links have been made between matrix degradation and pain in animal models. In the mouse, deletion of ADAMTS-5 activity reduced mechanical allodynia in a model of OA [23]. The mechanism remains unclear but a drug that blocks ADAMTS-5 could improve this major clinical symptom. Similarly, inhibition of cathepsin K in a guinea pig model of spontaneous OA reduced collagen degradation and joint nociception [24]. There is also a suggestion from the trialing of new MMP-13 inhibitors in a rat OA model that pain was reduced [15]. Some tantalizing evidence is therefore emerging that blocking cartilage loss could alleviate pain.

Inhibiting MMP-13, and ADAMTS-4 and -5 could have beneficial effects on joint tissues other than articular cartilage. All three enzymes cleave a number of extracellular matrix and cell surface proteins *in vitro* [25,26], and all are expressed in bone [27,28] and synovium [29,30], two tissues that are affected in OA and are very likely to be major drivers of the disease [31,32]. In a mouse model of OA, there was less thickening of the subchondral bone plate in ADAMTS-5-deficient mice compared with wild-type mice [33]; this effect could be due to a lack of ADAMTS-5 activity in the bone. There is evidence that the degradation of cartilage matrix proteins (e.g., collagen II [34] and fibronectin [35]) produces bioactive fragments. For example, fibronectin fragments have biphasic effects on the release from articular cartilage of IL-1 and TNF-α [35], proinflammatory cytokines that may play important roles in OA [36,37]. Although research in this area has focused on the effects of bioactive matrix protein fragments in cartilage, these fragments readily diffuse from the tissue and are detected in human OA synovial fluid [38,39]. It is interesting to speculate that these fragments might contribute to OA symptoms that could therefore be alleviated by blocking metalloproteinase action.

The past decade has seen the interest in cartilage as an OA therapeutic target wane, concomitant with increasing evidence that changes in subchondral bone precede, and might even cause, cartilage erosion [31]. However, the concept that subchondral bone changes drive cartilage loss remains controversial, and both processes could happen independently or influence each other. In the same time period, the research community has made major progress in identifying drug targets and demonstrating in animal models the potential effectiveness of DMOADs directly targeting cartilage breakdown. Hopefully, better, more affordable methodologies and protocols will be developed for clinical trials so that cartilage-preserving DMOADs can become an important part of the arsenal of treatments to manage OA.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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