Commentary

Usurped SLRPs: novel arthritis biomarkers exposed by catabolism of small leucine-rich proteoglycans?

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See related research by Monfort *et al*. in issue 8.1 [http://arthritis-research.com/content/8/1/R26] and Young *et al*. in issue 7.4 [http://arthritis-research.com/content/7/4/R852]

Abstract

Proteolytic degradation of articular cartilage macromolecules, including the large aggregating cartilage proteoglycan (aggrecan) and small leucine-rich proteoglycans (SLRPs), is a prominent pathophysiological feature of arthritic diseases such as osteoarthritis (OA). Molecular profiling and monitoring of soluble/circulating proteoglycan catabolites that may be released from the cartilage matrix therefore represents an attractive strategy for evaluating OA disease progression and intervention. The recent identification of discrete metalloproteinase-sensitive SLRP cleavage sites, and complementary neoepitope-bearing SLRP catabolites, extends decisive insight into the functional regulation of extracellular matrix integrity, and proffers poignant leads to assist in disclosing and appraising applicable biomarkers of cartilage degeneration during arthritis.

Proficient operativity of articular cartilage is effectively maintained via the specialized qualities of multiple macromolecular components, including a notable array of collagens and proteoglycans. Critical attributes of collagen organization and cytoregulatory sequelae are orchestrated in part through the interactive influences of a number of small leucine-rich proteoglycans (SLRPs), catabolism of which, for example during osteoarthritis (OA), may thereby detrimentally alter the biological and biophysical properties of the cartilage tissue. New findings reported in *Arthritis Research & Therapy* by Jordi Monfort and co-workers [1] provide an enhanced awareness of such processes by identifying a specific matrix metalloproteinase (MMP)-13 cleavage site in biglycan, and by assessing the ability of MMP-13 to degrade a number of SLRPs (biglycan, decorin, fibromodulin and lumican) present in normal and OA human cartilage extracts. Related studies also recently described in *Arthritis Research & Therapy* by Allan Young and colleagues [2] further highlight the susceptibility of cartilage SLRPs to proteolytic fragmentation during active progression of OA, thus concomitantly advocating the utility of monitoring SLRP catabolites as a promising biomarker strategy for evaluating OA disease status.

Members of the SLRP gene family play vital roles in a variety of tissues and extracellular matrices, comprising binding and regulation of collagen fibrils, as well as modulation of cellular responses [3]. As exemplified by knockout mice [4], SLRP deficiencies *in vivo* lead to the development of corneal, dermatological and musculoskeletal diseases (including OA), indicating that the connate functions of SLRPs could be profoundly impacted by post-translational (i.e. proteolytic) processing events. Indeed, and with pertinent regard to this tenet, cleavage of decorin by MMP-2, MMP-3 and MMP-7 can result in the release of sequestered transforming growth factor-β, conceivably leading to pathological consequences engendered by the soluble cytokine [5]. Decorin is physiologically catabolized in human skin via hydrolysis of the Phe170-Asn171 peptide bond located within the leucine-rich region of the core protein, although *in vitro* cleavage of decorin by MMP-3, or by 'a disintegrin and metalloproteinase with thrombospondin type I motifs-4' (ADAMTS-4), occurs amino-terminally distant at Glu154-Leu155 [6]. These observations emphasize the importance of correlating physiological processing events with those that can take place using isolated proteins, and highlight a key aspect to consider when designing assay reagents (i.e. antibodies) to track neoepitope elucidation and dispersion. In the case of fibromodulin, cleavage by MMP-13 between amino acid residues Tyr63 and Ala64 yields specific neoepitope-bearing fragments that are also detected in interleukin-1-stimulated bovine articular cartilage explant cultures, suggesting that such products may emanate in concert with joint disease progression [7]. Interestingly, ADAMTS-4 is also capable of

ADAMTS = a disintegrin and metalloproteinase with thrombospondin type I motifs; MMP = matrix metalloproteinase; OA = osteoarthritis; SLRP = small leucine-rich proteoglycan.

cleaving fibromodulin at Tyr63-Ala64 [8], exemplifying the possible contributions of disparate proteolytic activities in the degradation of available substrates.

In their recently described work, Monfort and colleagues [1] demonstrate that MMP-13 cleaves at Gly177-Val178 within the leucine-rich region of biglycan, generating fragments bearing the amino-terminal 'neoepitope' sequence 178VFSG.., and revealing a practicable new signature 'beacon' of SLRP catabolism. Recombinant MMP-13 was shown to degrade biglycan and fibromodulin (and to a lesser extent decorin and lumican) in cartilage extracts; however, it is important to appreciate that the proteolytic susceptibilities of these SLRPs may have become altered following their displacement from the cartilage matrix. Intriguingly, an endogenous biglycan degradation product similar in size to that generated *in vitro* by MMP-13 was in fact present in some of the cartilage specimens, although it remains to be definitively confirmed whether this fragment is produced as a result of cleavage at the MMP-13-sensitive Gly177-Val178 bond *in vivo*. Such corroboration is amenable to expeditious interrogation though the production and use of neoepitope antibodies directed toward cryptic amino or carboxyl termini exposed following proteolytic action, as have been successfully applied for the detection of aggrecan and type II collagen degradation products [9]. Furthermore, it will be constructive to determine whether additional (metallo)-proteinases (i.e. other MMPs or ADAMTSs) can also contribute to the turnover of accessible cartilage SLRPs through scission of either known or heretofore undiscerned cleavage sites.

Conclusion

The availability and persistence of cartilage-derived SLRP catabolites in synovial fluids and the peripheral circulation will be essential parameters to validate in order to establish efficacious assays for these potential biomarkers. Furthermore, and with respect to previously expressed circumspection [10], it is diligent to note that while proteolysis of SLRPs in articular cartilage may yield tenable markers of arthritis pathology, it is evident that SLRP degradation products (and indeed other putative arthritis biomarkers) could be generated in joints other than the index (affected) joint(s), and might in fact also originate from diverse tissue sources, including skin, intervertebral disc, meniscus and tendon [6,11-13]. Notwithstanding these caveats, it will nonetheless be of substantial interest to ascertain whether arthritis-associated alterations in usurped SLRP fragments correlate with disease severity, and to determine the contextual relationship of such levels within the repertoire of realizable biomarkers of OA [14].

Competing interests

The author declares that they have no competing interests.

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