Proteoglycans, cartilage and osteoarthritis – a story in translation

Stefan Lohmander
University of Lund, Sweden / University of Southern Denmark, Denmark

Stefan Lohmander, MD, PhD, is senior professor at the Department of Orthopedics at Lund University, Sweden, and professor at the Institute of Sports Science and Clinical Biomechanics, and the Department of Orthopedics and Traumatology, University of Southern Denmark, Denmark. He received his training and degrees at the Karolinska Institute, Stockholm, Sweden. After serving as a visiting scientist at the NIH in Bethesda USA, he moved to Lund University. His research focuses on basic and clinical aspects of cartilage and osteoarthritis.

Stefan Lohmander has served as Visiting Professor at Department of Orthopaedics, University of Iowa, at the Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, USA, and at the Departments of Rheumatology and Orthopedics and Kolling Research Institute, University of Sydney, Australia.

Stefan Lohmander is the editor-in-chief of ‘Osteoarthritis and Cartilage’ and past president of the Osteoarthritis Research Society International. In 1994 he received the OARSI Award for Clinical OA Research, in 2004 the ORS Steindler Award for significant international contributions to the understanding of musculoskeletal disease and injury. In 2006 he received the Marshall Schiff Award from the American College of Rheumatology for ‘research in the interface between rheumatology and orthopedics in musculoskeletal medicine’, and in 2007 the Bone and Joint Decade 2000-2010 Award for Research in Osteoarthritis.

The story of proteoglycans is connected with our growing understanding of the function and malfunction of joint cartilage. This abstract presents a subjective selection of some attempts to translate our understanding of a complex molecule into a better understanding of the common complex human disease called osteoarthritis.

The structure, fluid retention and function of joint cartilage is linked to the matrix content of aggrecan, and the amount of chondroitin sulfate bound to the intact core protein \(^1\). Aggrecan, with its complement of oligosaccharides and keratan and chondroitin sulfate chains is synthesized by the chondrocytes \(^2\)\(^3\). Although osteoarthritis involves changes in both synthesis and degradation of aggrecan and other cartilage molecules, our attention has focused on the pathways of aggrecan breakdown. Aggrecanase (ADAMTS-4/5) activity in human joints was first shown on the basis of ARG5-peptide fragments, resulting from cleavage of the glu373-ala374 bond of the aggrecan interglobular domain, being present in synovial fluids from patients with osteoarthritis, inflammatory arthritis or joint injury \(^4\)\(^5\). Subsequent work provided evidence for the proteolytic activity of matrix metallopro-
teinases against aggrecan as well, but with aggrecanase mainly responsible for the upregulated proteolysis after injury 6–8. Differences in aggrecan degradation patterns were found for different joint diseases 9,10. In animal models of joint injury, an aggrecanase inhibitor was shown to attenuate in vivo aggrecanase activity 11. However, the efficacy of this proof-of-principle of joint disease modification remains to be shown in humans.

In the continued search for agents to slow disease progression in osteoarthritis, biomarkers to predict progression and monitor treatment response are high on the wish list. The concentrations of aggrecan fragments released from joint cartilage to the synovial fluid are greatly increased in the acutely inflamed or injured joint 12. The ARGS-fragments are a more sensitive biomarker than non-specific aggrecan fragments 13. In patients with early-stage knee osteoarthritis, decreasing levels of ARGS-fragments in synovial fluid over time were associated with an increased risk of loss of joint space on X-ray images and a worsening of knee pain 14.

Major challenges remain in our efforts to understand the role of aggrecan synthesis and degradation in joint disease. How effective would inhibition of aggrecan degradation be in protecting the injured or diseased joint and alleviating symptoms? Can the synthesis of aggrecan and other matrix components be stimulated to regenerate a functional, load-bearing joint cartilage? Can sensitive and specific biomarkers be developed to aid future studies to show disease modification in osteoarthritis?

References

1) Lohmander S, Hascall V, Caplan A. Effects of 4-methyl umbellifer-
yl-β-D-xylopyranoside on chondrogenesis and proteoglycan syn-
3) Lohmander LS, Hascall VC, Yanagishita M, Kuettner KE, Kimura JH. Posttranslational events in proteoglycan biosynthesis: Kinetics of syn-
4) Sandy JD, Flannery CR, Neame PJ, Lohmander LS. The structure of aggrecan fragments in human synovial fluid: Evidence for the involve-
ment in osteoarthritis of a novel proteinase which cleaves the glu 373-
5) Lohmander LS, Neame P, Sandy JD. The structure of aggrecan frag-
7) Struglics A, Larsson S, Pratia MA, Kumar S, Lark MW, Lohmander LS. Human osteoarthritis synovial fluid and joint cartilage contain both aggrecanase- and matrix metalloproteinase-generated aggrecan frag-
8) Struglics A, Hansson M, Lohmander LS. Human aggrecanase gener-
ated synovial fluid fragment levels are elevated directly after knee inju-
ries due to proteolysis both in the interglobular and chondroitin sulfate domains. Osteoarthritis Cartilage 2011;19:1047-57.
9) Struglics A, Larsson S, Hansson M, Lohmander LS. Western blot quan-
tification of aggrecan fragments in human synovial fluid indicates dif-
10) Struglics A, Lohmander LS, Last K, Akikusa J, Allen R, Fosang AJ. Ag-
grecanase cleavage in juvenile idiopathic arthritis patients is minimal in the aggrecan interglobular domain but robust at the aggrecan C-
giadi KE, Morris EA. Elevated aggrecanase activity in a rat model of joint injury is attenuated by an aggrecanase specific inhibitor. Osteoar-
12) Lohmander LS, Hoerrner LA, Lark MW. Metalloproteinases, tissue in-
13) Larsson S, Lohmander S, Struglics A. Synovial fluid level of aggrecan ARGS fragments is a more sensitive marker of joint disease than gly-
14) Larsson S, Englund M, Struglics A, Lohmander LS. The association between changes in synovial fluid levels of ARGS-aggrecan and pro-