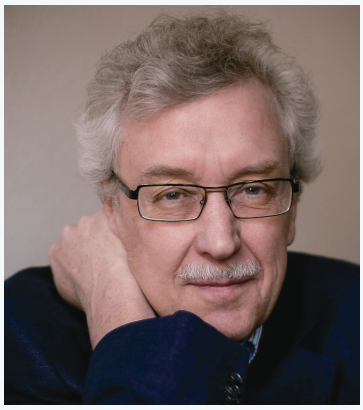

Proteoglycans, cartilage and osteoarthritis – a story in translation

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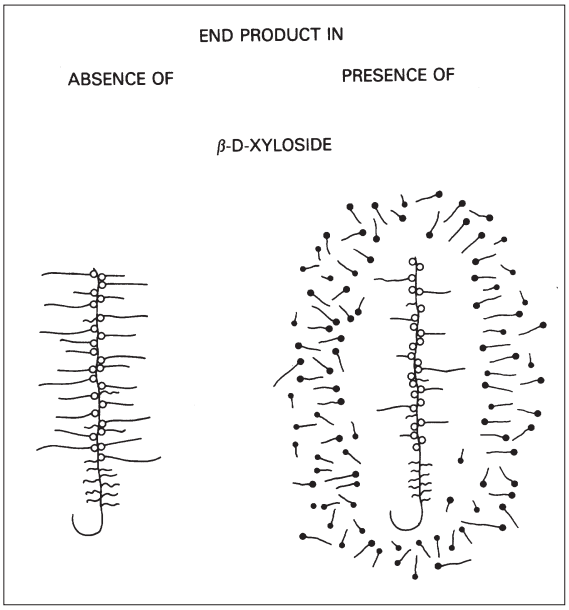
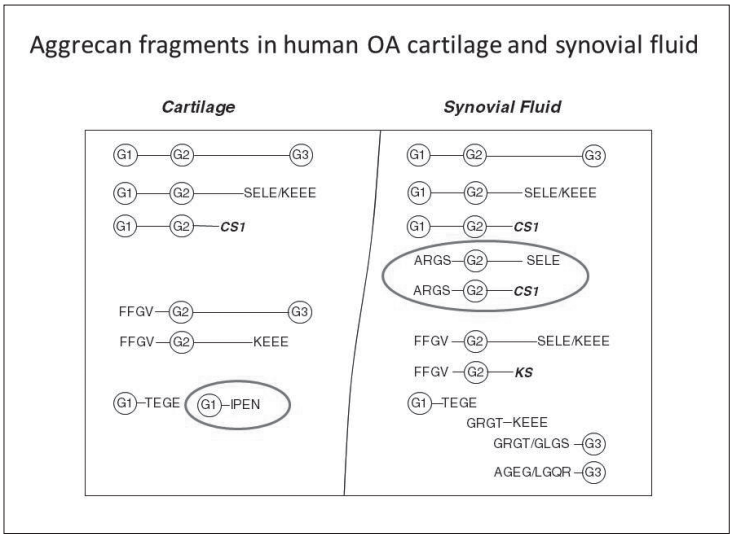
The story of proteoglycans is connected with our growing understanding of the function and malfunction of joint cartilage. This abstract presents a subjective selection of some attempts to translate our understanding of a complex molecule into a better understanding of the common complex human disease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

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