The 24th Proteoglycan Forum (PG Forum)
Date: August 22, 2015

Understanding inter-α-trypsin inhibitor in healthy and diseased tissues

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Inter-α-trypsin inhibitor (IαI) is composed of heavy chains (HC) 1 and 2 that are covalently attached to the chondroitin sulfate (CS) chain of bikunin. IαI is noted for its ability to modify hyaluronan (HA) through the trans-esterification of its HCs onto HA in the presence of tumor necrosis factor-inducible gene 6 (TSG-6). This process is known to be elevated in conditions such as arthritis and inflammation, however has not been explored in cartilage development. The localization of IαI in developing human cartilage and human osteoarthritic cartilage and structurally characterized IαI from osteoarthritis (OA) and rheumatoid arthritis (RA) patients and compared it to that from subjects without clinical evidence of arthritis was examined.

IαI was immunolocalized to the terminally differentiating chondrocytes in developing human cartilage. The distribution of CS was more widespread including surrounding the terminally differentiating chondrocytes. In human OA cartilage, IαI was immunolocalized to the lacunae surrounding the chondrocytes in all zones of the cartilage even though fewer chondrocytes were found in the fibrillated surface and superficial zones than the deep zone. CS was immunolocalized to the deep zone of the OA cartilage.

IαI was isolated from urine, plasma and synovial fluid samples using anion-exchange chromatography. Plasma- and synovial fluid-derived IαI, together with urinary bikunin isolated from OA and RA patients, contained CS that was lower in sulfation levels compared with plasma IαI and urinary bikunin CS from control subjects. The IαI that contained the more highly sulfated CS chain was found to be more effective at promoting the formation of HC-HA complexes resulting in the stabilization of HA in the cartilage matrix. This suggests that TSG-6 interacts more effectively with the highly sulfated CS regions of IαI and that the presence of

low sulfated forms of IαI in OA and RA patients may indicate a reduced ability to form HC-HA complexes and stabilize HA in the cartilage.

These data support the role of IαI has in stabilizing HA in cartilage and that the sulfation levels of the CS decorating urinary bikunin is indicative of disease. This concept will be explored further with examples of bioengineering applications.

2015/8/22