

Cleavage of CD44 and generation of intracellular domain fragment alters CD44 function in chondrocytes

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Articular chondrocytes exhibit an extensive hyaluronan (HA) and proteoglycan-rich pericellular matrix that is tethered to the cell surface via interactions with the HA receptor, CD44. We have found that disruption of this cell-matrix interaction results in the induction of cell signaling that includes both the stimulation of genes involved in matrix degradation such as matrix metalloproteinases as well as matrix repair genes including collagen type II, aggrecan, and HAS-2. Loss of cell-matrix can sometimes be observed in sections of normal human cartilage from donors with no known history of disease. This suggests that in vivo episodes of cell-matrix loss likely do occur. We have examined a variety of approaches to experimentally mimic a loss of HA/PG-cell interactions. These approaches include; the use of small HA oligosaccharides, hyaluronidase, CD44 antisense or DN-pCD44. Although our experimental approaches are useful to examine events downstream of cell-HA matrix loss, we have not determined the naturally-occurring agents responsible for this loss. We have not detected extracellular hyaluronidase activity in chondrocytes, we have not detected HA oligosaccharides and, a decrease in overall CD44 expression is rare. Interestingly, some investigators have described the enzymatic cleavage and shedding of CD44 from the surface of various tumor cells. Additionally, Sugahara *et al.* found that addition of HA oligosaccharides induced CD44 cleavage. In our previous studies, CD44 shedding in normal bovine chondrocytes was not observed. However, while exploring the loss of pericellular matrix in de-differentiated chondrocytes and human osteoarthritic (OA) chondrocytes, naturally-occurring CD44 cleavage was readily apparent. Thus, we speculated that the CD44 cleavage could be the first step of OA pathogenesis.