

The Structure And Function Of Cartilage Proteoglycans

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All hyaline cartilages are characterized by their high content of the proteoglycan aggrecan, which exists in the form of proteoglycan aggregates in association with hyaluronan (HA) and link protein (LP). The proteoglycan aggregates provide the osmotic properties needed for tissue turgidity. Cartilages also contain a variety of small leucine-rich repeat proteoglycans (SLRPs), including decorin, fibromodulin and lumican, which help maintain the integrity of the tissue and modulate its metabolism.

Aggrecan is a modular proteoglycan with multiple functional domains. The amino terminal G1 domain is responsible for the interaction of aggrecan with HA, whereas the adjacent structurally related G2 domain presently has no known function. The carboxy terminal G3 domain is essential for normal posttranslational processing of the aggrecan core protein and subsequent aggrecan secretion. The intervening keratan sulfate (KS) and chondroitin sulfate (CS)-attachment domains provide the high anionic charge density needed for the unique osmotic properties of aggrecan. In the human, the first of the two CS-attachment domains (CS1) exhibits size polymorphism due to a variable number of 19 amino acid repeats. This results in different individuals possessing aggrecan core proteins of different length and different CS content. Those individuals with the shortest core protein length and lowest CS substitution may possess functionally inferior aggrecan and be at risk for cartilage degeneration.

Link proteins are structurally related to the G1 domain of aggrecan and also possess the ability to interact with HA. Mammals possess four link protein genes of which one is predominantly expressed in cartilage. The cartilage LP serves several functions in the proteoglycan aggregate. First, by virtue of its ability to interact with both HA and the G1 domain of aggrecan it stabilizes the proteoglycan aggregate and prevents its dissociation under physiological conditions. Second, it participates in a phenomenon termed delayed aggregation, in which it interacts with newly secreted aggrecan and promotes subsequent interaction with HA. Third,

together with the G1 domain of aggrecan, LP forms a protein coat covering the surface of HA, which helps protect the HA from undesirable degradation by both hyaluronidases and free radicals.

HA is synthesized at the plasma membrane of the cell via a hyaluronan synthase (HAS). Mammals possess three HAS genes, with HAS2 expression predominating in cartilage. HA is present as a coat surrounding all chondrocytes and it is likely that proteoglycan aggregate formation occurs in this pericellular location. The mechanism whereby the proteoglycan aggregates are released from this environment and move to the more remote parts of the extracellular matrix is not clear. Studies on knockout mice have demonstrated that the absence of HAS2 in cartilage is catastrophic; resulting in a severely abnormal skeleton and perinatal death, confirming the essential role of the HA and proteoglycan aggregates in normal cartilage function.

SLRPs are characterized by multiple adjacent domains bearing a common leucine-rich motif. In the case of decorin, fibromodulin and lumican there are ten leucine-rich repeats. Decorin possesses a CS chain in the amino terminal region of its core protein, whereas fibromodulin and lumican possess KS chains within their central leucine-rich repeat region. The CS and KS can interact with a variety of growth factors and provide a sink for growth factor accumulation within the extracellular matrix, so modulating chondrocyte metabolism. The core proteins allow the SLRPs to interact with the collagen fibrils, and in so doing they help regulate fibril diameter and fibril-fibril interaction. They also limit the access of the collagenases to their unique cleavage site on each collagen molecule, and help protect the fibrils from proteolytic damage.

All cartilage proteoglycans are essential for normal tissue function, and perturbation in their abundance or structure can have dire consequences.

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