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OSTEOARTHRITIS and CARTILAGE

Chondroitin sulfate and joint disease

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Summary

Chondroitin sulfate is an important and major component of articular cartilage, where it occurs as part of the large proteoglycan, aggrecan. In the early stages of joint disease, both in animal models and in man, there are changes in chondroitin sulfate that affect the chain length and the pattern of sulfation. These changes can be detected by monoclonal antibodies and appear to reflect part of the cellular response by the chondrocytes to damage to the articular cartilage matrix. The specificity of the changes show that the biosynthesis of chondroitin sulfate is under tight cellular control in chondrocytes and suggests that selected patterns of sulphation within chains are expressed to suit different biological functions.

Key words: Chondroitin sulfate, Joint disease, Glycosaminoglycans, Collagen.

Chondroitin sulfate is an important component of most vertebrate tissues. It is present predominantly in the extracellular matrix surrounding cells and is most abundant in those tissues with a large extracellular matrix such as those that form the connective tissues of the body, cartilage, skin, blood vessels and also bone, ligaments and tendons. These tissues also contain large amounts of fibrillar proteins, mainly collagen, and their properties are determined by the content and orientation of the fibrillar collagen and the content of glycosaminoglycans such as chondroitin sulfate. Where the collagen has a single predominant orientation, such as in ligaments and tendons, the tissues are tensile and the chondroitin sulfate content is quite low, but where there is no predominant orientation of the collagen, such as in skin, there is a high content of chondroitin sulfate and the tissue stretches in tension, but is resilient and resists compression.

How does chondroitin sulfate contribute to the functions of these tissue? Chondroitin sulfate is a sulfated glycosaminoglycan and is composed of a long unbranched polysaccharide chain with a repeating disaccharide structure of N-acetylgalactosamine and glucuronic acid [1]. The chains are long and vary in length from 10 to 40 kDa. Most of the N-acetylgalactosamine residues are sulfated and this varies with tissue source, but is predominantly in the 4- or 6-position, with a few non-sulfated residues and occasional di-sulfated residues. Chondroitin sulfate is thus a polyanion and some of its properties are because it is so strongly charged and thus draws water into tissues and hydrates them.

Chondroitin sulfate chains are synthesized by cells covalently attached to proteins, which are secreted into the extracellular matrix as proteoglycans. Each chain is attached to the proteoglycan by a trisaccharide linkage (CS chain-gal-gal-xyl-serine). The chains are synthesized on intracellular pathways common to other secreted glycoproteins and they are assembled on the protein as it passes through the vesicular compartments of the medial/trans Golgi, immediately prior to secretion. Several families of proteoglycans bearing chondroitin sulfate chains have been characterized. These include two of the most prominent families of proteoglycans found in the extracellular matrix of connective tissues, the aggrecan family and the leucine-rich repeat family [2]. The aggrecan family are high molecular weight (> 500 kDa) and aggregate extracellularly by binding to hyaluronan. The leucine-rich repeat family are of smaller size (< 200 kDa) and contain two members, decorin and biglycan, that contain chondroitin sulfate/dermatan sulfate chains. Of these, decorin binds to collagen fibrils, whereas biglycan has a more pericellular distribution, but the full range of their tissue functions have yet to be determined (Fig. 1).

Articular cartilage is a very specialized tissue with a particularly large expanded extracellular matrix with more than 98% of its volume matrix and less than 2% cells. It is the structure and

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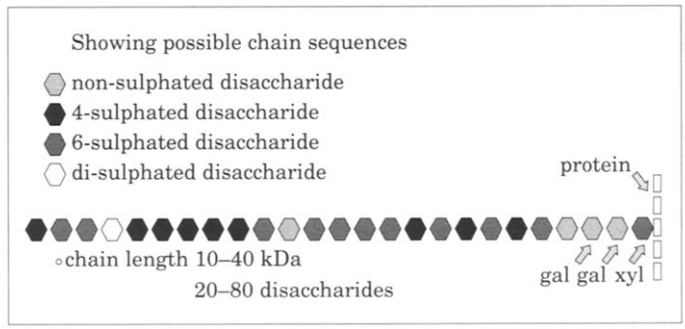

FIG. 1. Chondroitin sulfate structure.

integrity of the matrix that is essential to the tissues load-bearing properties [3]. The physical properties of the tissue can be understood largely in terms of the contribution made by fibrillar collagen and nonfibrillar proteoglycans. The collagen network is of fine fibers which have no preferred orientation in the mid zone of the cartilage and provides an essential framework that gives shape and form to the tissue. The structure of collagen gives it impressive tensile properties and this is utilized in cartilage in a special way to produce a tissue that is not only strong in tension but also resistant to compression by filling the interfibrillar matrix with a very high content of chondroitin sulfate-rich proteoglycan, primarily aggrecan. The aggrecan at high concentration draws water into the tissue as it creates a large osmotic swelling pressure, which swells and expands the matrix. This places the collagen network under tension, and a balance is achieved when tension in the collagen network prevents further entry of water. At this equilibrium, with the tissue swollen with water, it has good compressive resilience. Another feature of the composite collagen–aggrecan organization is also important, as aggrecan is not only largely immobilized within the matrix, but it also offers great resistance to any fluid flow and redistribution of water. The tissue thus behaves largely as a stiff elastic polymer to sudden impact loading, but shows some slow inelastic deformation with sustained loads. However, removal of all loads leads to a redistribution of water and a return to the pre-loading equilibrium position. The articular cartilage thus forms a tough but compliant load-bearing surface, and these characteristics depend on the integrity of the collagen network and the retention within it of a high concentration of aggrecan rich in chondroitin sulfate.

In degenerative joint diseases, such as osteoarthritis, there is damage and loss of the articular cartilage. A key stage in the degenerative process is the loss of proteoglycan from the cartilage and the exposure of its collagen network to mechanical disruption. However, the results from studies of experimental osteoarthritis suggest that early in the process, before there is any fibrillation, there is a hypermetabolic repair response in articular cartilage with increased synthesis of matrix components and increased matrix turnover [4]. The increased synthesis of aggrecan in cartilage is accompanied by interesting changes in the chondroitin sulfate, which shows a longer chain length and the chains contain more epitopes recognized by specific antibodies [5]. Although chondroitin chains are typically very poorly antigenic it has been possible to produce monoclonal antibodies that recognize some specific sequences within the chains. These appear to be infrequently found in normal healthy tissue, but their expression increases in cartilage during the early hypermetabolic response in experimental OA. This change has been observed in several different experimental animal systems and an increase in chondroitin sulfate epitopes has also been observed on the aggrecan fragments in the joint fluid of some patients following major joint trauma, which frequently results in the joint developing OA in later life [6].

The biological reason for these changes in chondroitin sulfate in cartilage in early OA is not yet clear, but it may suggest that there are specific biological functions of selected sequences within chondroitin sulfate chains that may be important to the processes of tissue repair. There is thus considerable interest in gaining a better understanding of what controls the sulphation pattern within chondroitin sulfate chains [7] and how it changes in response to the effects of cellular mediators and biomechanical forces acting on the cells in which the chains are synthesized.

Acknowledgments

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