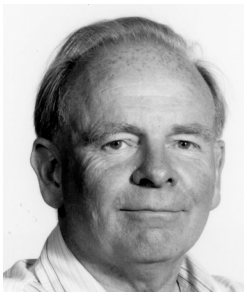
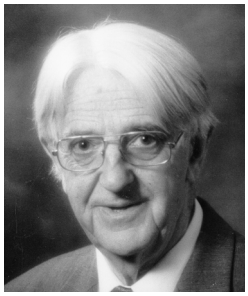
Editorial

Cartilage Is Held Together by Elastic Carbohydrate Strings. Implications in Osteoarthrosis





Clefts, fissures, and erosions all indicate that something is breaking down in osteoarthritic (OA) cartilage. But what is the initial event that leads to cartilage failure? Vast resources have been invested in the study of proteins and proteases in the quest for the basic defect, without the hoped-for payoff[1]. New techniques, however, have allowed visualization of other macromolecules, disclosing a vista of intriguing simplicity.

Scott and Stockwell[2], using electron microscopy, atomic force spectroscopy[3], and rheo-nuclear magnetic resonance (NMR)[4], raise fundamental questions about structure/function relationships between proteoglycans and collagen in cartilage, and how the shape of tissues such as cartilage is preserved or may fail in OA. The shape of connective tissue extracellular matrices is maintained by collagen fibrils held in place by decoran proteoglycans, so-called because they "decorate" collagen fibrils at regular ~60 nm intervals. Decoran proteoglycans are ubiquitous in corneal stroma, skin, intervertebral discs, and even in remote primitive animals such as echinoderms, suggesting a fundamental role throughout animal evolution. They were proposed to be tissue organizers, holding collagen fibrils at characteristic separations and in register, determining the intrinsic geometry of extracellular matrices and hence the shape of the organism. This vital role was confirmed when cells from an electively aborted fetus that were unable to express decoran were found to be incapable of forming normal extracellular matrix[5].

Although this "shape module" system ensures that basic building blocks are correctly positioned to produce recognizable tissue, there must be built-in elasticity. In 2005 the polysaccharide of decoran, dermochondan sulfate, was proved directly by atomic force spectroscopy[3] on single molecules to have elastic sugar units (i.e., iduronic acid), and a further mechanism based on a sliding filament model also provides reversible deformability, as shown *in vitro* by rheo-NMR[4].

Therefore, extracellular matrices (and through them the whole organism) are held together by elastic carbohydrate strings. Until very recently it was not clear that this applied to cartilages. Now, using ultrastructural techniques that were successful with tendons, etc., articular and nasal septal cartilages are seen to contain shape modules like those in all other extracellular matrices. Moreover, by analyzing the expected behavior of shape modules under compressive and tensile stresses, it is possible to account for the anisotropic (elasticity differing in directions at right angles) behavior of articular cartilage under these stresses[2].

For the first time, a physiological framework for the elastic behavior of cartilage is available based on findings at the molecular level. Cartilage is tendon-like in the sense that it has similar elastic interfibrillar proteoglycan bridges in similar amounts at similar specific binding sites on the fibrils, with the addition of expansile aggrecan-rich reservoirs of aqueous shock-absorber fluid[2]. Indeed, tendon expresses aggrecan when under constant pressure, as in rabbit "knee joints." Cartilage, like all other extracellular matrices, is thus seen to be constructed on a fundamental shape modular pattern, modified and developed to meet specific physiological and local requirements[2].

Rupture or loss of interfibrillar ties would allow expansile proteoglycan to force the matrix apart, increasing swelling and fissuring, which are characteristic manifestations of OA. The occurrence of clefts parallel to the fibrils in OA cartilages implies that relevant interfibrillar shape module bridges have been disrupted. It is also apparent that cleavage or disappearance of these bridges removes the cohesion between fibrils, which prevents passive swelling of the cartilage matrix driven by the expansile properties of aggrecan and decoran. The increased hydration of OA cartilage and its capacity to swell in isotonic solutions, characteristics that are not shared by normal cartilage, is thus accounted for by failure of the interfibrillar carbohydrate strings (Figure 1).

This new understanding of cartilage structure/function and its dependence on decoran interfibrillar bridges provides a new etiological framework for OA. What is it that disrupts these bridges? Is it enzymatic [J. Sandy showed that cathepsin D attacks decoran (personal communication cited in[2])], free radical, metabolic, genetic — or mechanical

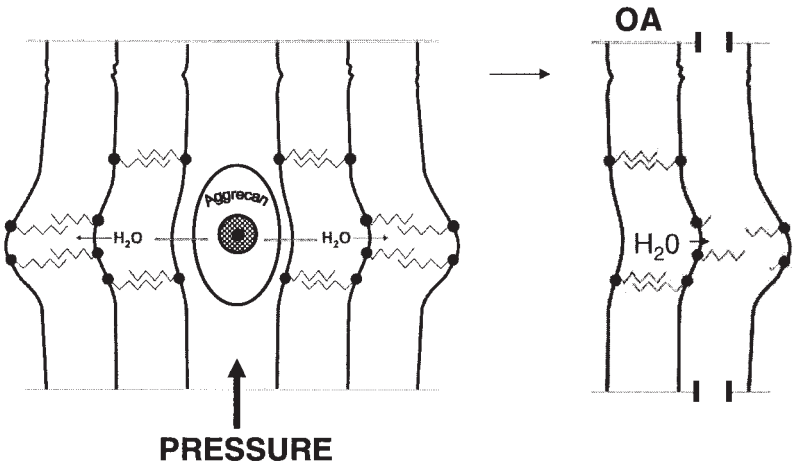


Figure 1. Predicted responses of cartilage shape modules to compressive mechanical stress, and postulated effect in OA cartilage. Collagen fibrils (vertical black lines) are linked by antiparallel decoran polysaccharide bridges (zigzag lines) attached noncovalently via protein cores (closed circles) to the fibrils. Crimps and bends in the fibrils are shown (arrows). Under pressure, the pericellular aggrecan-rich reservoir (the territory) of aqueous fluid loses water into the shape modules of the interterritory against elastic resistance. The compressed aggrecan domains exert swelling pressure, sucking water back from the shape modules, helped by the decoran bridge elasticity, which ensures that the tissue organization stays intact. In OA cartilage (right) the decoran bridges between the fibrils are postulated to be disrupted or lost, depriving the tissue of reversible deformability and permitting swelling, increased water content, softening, and fissuring (see Scott JE, Stockwell RA[2]).

— breakdown due to occupational overload? Or just *avoirdupois* and old age? High physiological use in athletics does not seem to induce OA[6], but there is increasing evidence that continued overload results in OA[7-9], providing opportunities for primary prevention.

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