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Chondrocytes

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Cartilage is a skeletal tissue largely consisting of extracellular matrix populated by a small number of cells—the chondrocytes. All hyaline cartilages consist of about 75% water while collagen fibres and proteoglycan molecules make up a large proportion of the dry mass. Elastic cartilage contains elastic tissue in addition to collagen fibres, while in fibrocartilage the amounts and proportions of collagen and proteoglycan are such that the fibres are visible to the naked eye and accessible to routine histological stains. The matrix is responsible for the rigidity and resilience of the tissue, the mechanical properties reflecting the physicochemical organisation of the matrix macromolecules. The chondrocytes produce the matrix during growth and, despite their small numbers, maintain the tissue during adult life. Since cartilage lacks blood vessels, lymphatics, and nerves—except in cartilage canals during growth—the cells must be sustained by nutrient and gas diffusion over large distances compared with vascular tissues.

Cartilage is easily recognised histologically in normal circumstances, with its scattered cells in lacunae lying in basophilic matrix. The chondrocyte itself has many typical features but nevertheless the cell type is difficult to define in structural terms. Identification in practice often depends on recognising its synthetic and secretory products. The histologist is prone to rely ultimately on the pericellular localisation of metachromatic material or, in electron micrographs, of banded collagen fibres in amorphous electron-lucent ground substance. The biochemist can use more specific criteria to characterise the phenotype, such as the secretion of type II 'cartilage' collagen (Miller and Matukas, 1974) and of proteoglycans that can aggregate with hyaluronic acid (Muir, 1977). Recent immunofluorescent techniques for type II collagen (Von der Mark *et al.*, 1976) may offer a more precise means of histological identification. However, changes can occur in the types of collagen and proteoglycan secreted by chondrocytes *in vitro*, depending on the culture conditions. Similar changes may occur in osteoarthrosis (Muir, 1977).

Ultrastructure

Typical chondrocytes are ovoid cells ranging in maximum diameter from about 10 μm in articular cartilage to about 30 μm in other hyaline cartilages (Stockwell and Meachim, 1973). The pericellular matrix is usually of a finer texture than the coarsely fibrous tissue more remote from the cell (Fig. 1). The junction is often sharply demarcated and constitutes the lacunar rim. The cell has a scalloped surface which increases the surface area:volume ratio. Projecting cell processes are occasionally several micrometres long and may reach beyond the lacuna. A monocilium is sometimes found in adult cartilage (Fig. 2) but more commonly in immature tissue. While it is difficult to identify a glycocalyx in the presence of ground substance, chondrocytes enzymatically stripped of their matrix carry major histocompatibility antigens (Elves, 1976).

The cell nucleus in older chondrocytes is often irregular and lobated, a feature which once appeared to substantiate the old erroneous view that chondro-

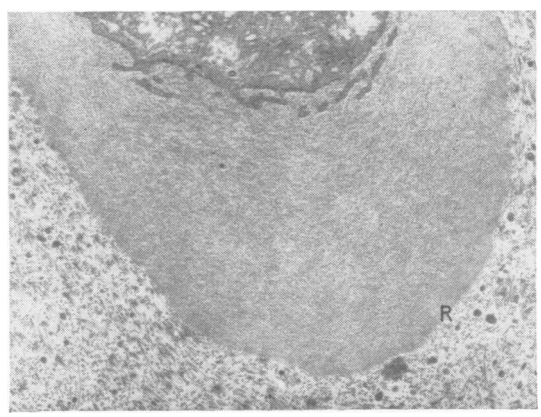

Fig. 1 *Human femoral condylar cartilage, 56 years. Part of chondrocyte with finely textured pericellular matrix* (× *8000*). *R = lacunar rim.*

cytes replicated by amitosis. The predominant cytoplasmic organelles are the granular endoplasmic reticulum and the Golgi complex (Fig. 2), both associated with the synthesis and secretion of collagen and proteoglycans (Revel and Hay, 1963; Horwitz and Dorfman, 1968; Ross, 1975). Golgi vacuoles are more numerous in the cells of growing cartilage. Lysosomes function in the removal of effete intracellular material but in chondrocytes they are also concerned with the turnover of the extracellular matrix. After endocytosis the digestion of partly degraded macromolecules is completed in the lysosomal vacuole (Dingle, 1975). Mitochondria are quite numerous in chondrocytes of immature tissue but in the adult become scarcer, smaller, and dense with few cristae. This accords with the low respiratory activity of chondrocytes. However, in the degenerate chondrocytes of the metaphyseal side of the growth plate mitochondria are often the only organelles that are well-preserved.

Most chondrocytes contain fine filaments 7-10 nm in diameter in the cytoplasm. Large masses of them (Fig. 3) are thought to be a sign of cell degeneration (Meachim and Roy, 1967). While actin-like filaments have been identified in cultured chondrocytes (Ishikawa *et al.*, 1969) the chemical nature of the 10 nm filaments is not known. They are unlikely to be interconvertible to microtubules (De Brabander *et al.*, 1975), as has been suggested. Glycogen and lipid are common inclusions of the chondrocyte. Glycogen may be one of many sources of organic phosphate for calcification in the epiphyseal growth plate as well as providing the raw material for matrix synthesis. The large amounts of lipid in chondrocytes has never been explained satisfactorily. Fat is a normal inclusion (Fig. 4), but there is little evidence that it is used either by the cell itself or by the whole organism. However, as in the aorta (Buddecke *et al.*, 1973), utilisation of NADH for fat synthesis might be an important factor in the reoxidation of the coenzyme, helping to stabilise the NAD/NADH ratio in the chondrocyte. Fat globules increase in size during maturation and are smaller in articular than other hyaline cartilages. Recent investigations of lipoarthrosis show that the superficial articular chondrocytes become engorged with lipid and that cell death and cartilage fibrillation ensue (Ghadially *et al.*, 1970; Sprinz and Stockwell, 1977). Seemingly the cells selectively incorporate fatty acids (Fig. 5) rather than the glycerol

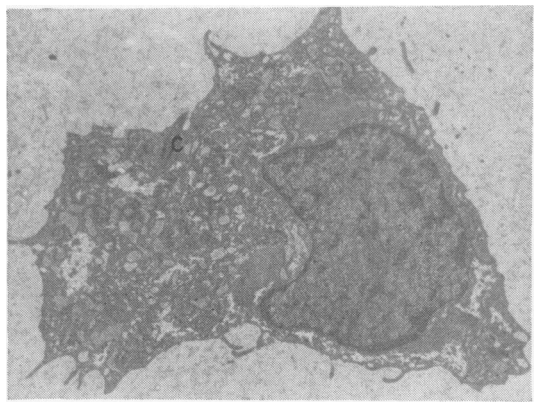

Fig. 2 *Human femoral condylar cartilage, 21 years. Chondrocyte with profuse endoplasmic reticulum and Golgi membranes* (× *7000*). *C = single cilium.*

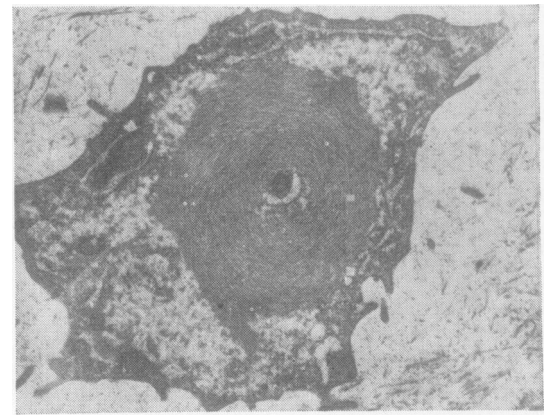

Fig. 3 *Human femoral condylar cartilage, 21 years. Chondrocyte with large whorl of filaments* (× *12 000*).

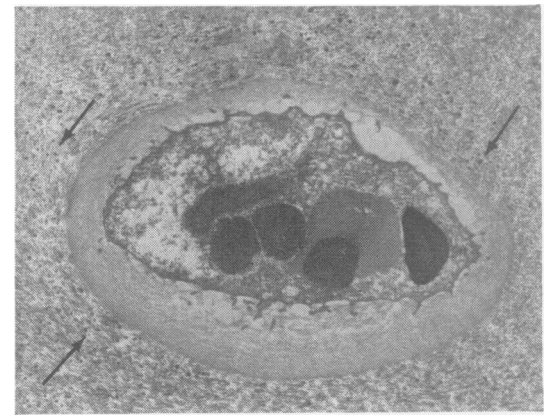

Fig. 4 *Human femoral condylar cartilage, 56 years. Chondrocyte with several lipid globules. Note numerous dense bodies (extracellular lipid) (arrows) near distinct lacunar rim* (× *4000*).

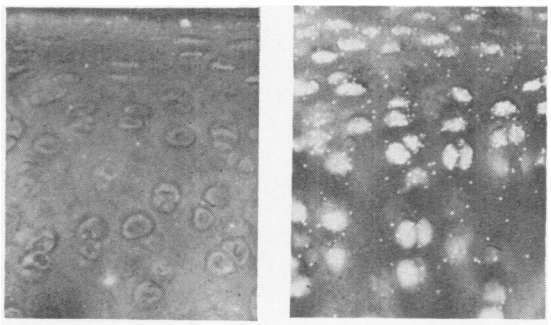

Fig. 5 *Rabbit femoral condylar cartilage, 3 months. After intra-articular injection of* (a) *glyceryl-2-H³ trioleate,* (b) *glyceryl tri (oleate-9,10-H³). Frozen section autoradiographs, incident light* (× 280).
(from Sprinz and Stockwell (1976), by permission of the Editor and publishers of the Journal of Anatomy)

moiety of intra-articular triglyceride (Sprinz and Stockwell, 1976).

Metabolism

Oxygen tension in the middle of small blocks of cartilage is only one-third of that in vascular tissues (Silver, 1975). The chondrocyte is remarkable for its ability to synthesise and secrete matrix components in an avascular environment. Nevertheless, while they tolerate very low oxygen tensions more successfully than do fibroblasts, chondrocytes do not thrive under such conditions. Synthetic activity is also reduced by very high oxygen tensions (Marcus, 1973; Brighton *et al.*, 1974).

Since cartilage cellularity varies over a wide range the glycolytic and respiratory rates (Table 1) of the whole tissue tend to reflect cell density. This factor accounts for much of the greater activity of immature compared with mature cartilage. While the glycolytic rate per cell is comparable to that in other tissues, oxygen utilisation is much lower than in vascular organs (Bywaters, 1937). Species differences in cartilage also reveal greater variation in cellular oxygen uptake than in glycolytic rate. There is an age-related diminution of chondrocyte respiration though not of glycolysis; this is associated with loss of cytochromes (Rosenthal *et al.*, 1941). However it is not known whether these age changes affect synthetic activity significantly.

Manufacture of collagen and proteoglycans depends on an adequate supply of precursors such as amino-acids and sugars. Proteoglycan formation can be studied using ^{35}S-sulphate and collagen by using ^{3}H-proline. In collagen synthesis hydroxylation, important both for stability of the collagen molecule and for intermolecular cross-linkage, requires factors such as atmospheric oxygen and vitamin C. In proteoglycan synthesis the production and interconversion of the nucleotide sugar donor molecules are affected by the redox state of the cell, particularly the NAD/NADH ratio (Phelps and Stevens, 1975). Such requirements for synthesis depend ultimately on adequate diffusion of nutrients, itself affected by the physicochemical state of the matrix (Maroudas, 1973). The availability of proteoglycan core-protein and the intracellular levels of enzyme inhibitors—for example, UDP-xylose —also affect rates of synthesis. Secretion occurs via the Golgi complex, although steric effects may hinder the extracellular passage of large proteoglycans through the matrix. Proteoglycans influence collagen fibrogenesis by electrostatic interactions.

Endogenous mechansims for the degradation of collagen in cartilage are ill-understood, although chondrocytes produce cathepsin B1 capable of cleaving collagen fibres at an acid pH (Dingle, 1975). However, little or no turnover of collagen occurs in adult cartilage. Proteoglycan degradation is achieved most effectively by disrupting the protein core; a number of cathepsins (B1, D, and F) have been implicated. Initial partial cleavage of macromolecules occurs in the extracellular matrix by release of degradative enzymes. There are, however, biochemical (Dingle, 1975) and anatomical difficulties

Table 1 *Glycolytic and respiratory rates of whole cartilage samples*

	Oxygen uptake (*μl/mg dry weight/h*)	*Anaerobic glycolysis* (*μg lactic acid produced /mg dry weight/h*)	*Cell density* (*cells × 10⁴/mm³*)	*Authors*
Rat costal cartilage	0·22, 0·68	5·44, 7·40	25	Dickens and Weil-Malherbe (1936)
Rabbit articular cartilage	0·15	2·56	12·8	Bywaters (1937); Hills (1940)
Bovine articular cartilage	0·024	1·75	4·7	Rosenthal *et al.* (1941)
Rabbit liver	7·7	13·6	62	Bywaters (1937)
Rabbit kidney	10·8	20·8	110	Bywaters (1937)

regarding the turnover of matrix, at least in regions remote from the cell.

Topographical differences in proteoglycan metabolism in articular cartilage are well documented (Collins and McElligott, 1960; Maroudas, 1975). The synthetic activity of the superficial cells is much less than in the deeper tissue. Such zonal variations occur in other cartilages. There is some evidence also of local functional heterogeneity among chondrocytes, superimposed on the zonal variation. Results indicate that some cells produce chondroitin sulphate-rich rather than keratan sulphate-rich proteoglycans (Kincaid *et al.*, 1972), that in immature cartilage some are more active in collagen than in proteoglycan synthesis (Mazhuga and Cherkasov, 1974), and that there is also heterogeneity in degradative enzyme release (Poole, 1975). Variability in activity could be either cyclical or permanent. It is not known if the same cell produces at the same time both hyaluronic acid and the proteoglycan 'subunit' molecules which bind together to produce the aggregates characteristic of cartilage matrix.

Control of cartilage metabolism is not well understood. Low oxygen tension and mechanical compression favour chondrocyte expression (Bassett and Herrmann, 1961). Little is known about the mode of action of mechanical forces on chondrocyte metabolism although calcium ions and cyclic AMP may be involved (Norton *et al.*, 1977). Proteoglycans stimulate (Nevo and Dorfman, 1972) and hyaluronic acid inhibits (Wiebkin and Muir, 1975) proteoglycan synthesis through interactions at or near the cell surface. Local cation concentration also affects synthesis (Shulman and Opler, 1974). A number of hormones, particularly growth hormone (via somatomedin) and thyroxin, stimulate chondrocyte metabolism. Corticosteroids depress synthesis and degradation of ground substance.

Apart from their main products and associated enzymes, chondrocytes have an active role in cartilage calcification. Matrix vesicles 0·1-1·0 μm diameter containing alkaline phosphatase (Ali *et al.*, 1970) are deposited in the longitudinal septa of the growth plate by chondrocyte cell processes. They appear to act as vectors for calcium by virtue of their membrane lipids (for example, phosphatidylserine) and other factors, thereby nucleating apatite crystals (Wuthier, 1977). The chondrocytes also mediate the removal of proteoglycan-hyaluronate complexes (thought to be inhibitory to calcification) from the hypertrophic zone by producing the enzyme lysozyme which disaggregates them (Kuettner *et al.*, 1975).

Chondrocytes also have a positive role in the exclusion of blood vessels from the tissue. A factor which prevents endothelial proliferation is produced by cartilage. This antagonises the angiogenic factors produced by tumours (Brem and Folkman, 1975; Eisenstein *et al.*, 1975) and lymphocytes and may be a protease inhibitor.

Cellularity

Cartilage increases in size both by appositional and interstitial growth. Chondrocyte mitotic rates in the epiphyseal growth plates are important factors in the rate of increase in length of long bones (Kember and Sissons, 1976). Most other cartilages are thought to be dependent on appositional rather than interstitial cell proliferation in the later stages of growth. Mitotic rates in articular cartilage are only 1/20th of those in the growth plate during development and no thymidine-labelling can be detected in the normal adult (Mankin, 1964). Cell proliferation is resumed if tissue damage occurs, as in cell cluster formation in fibrillated cartilage (Dustmann *et al.*, 1974) or if cells freed from their matrix are grown in culture (Sokoloff, 1976).

Cellularity in human cartilage is reduced sevenfold during maturation from birth to adult life (Stockwell, 1967). A major factor is the secretion and interposition of new matrix between cells, but the contribution made by cell death has never been measured. Cell distribution is not uniform within the adult tissue. At a microscopically local level cells lie either singly or in isogeneous groups, while decreasing gradients of cell density are observed from the tissue periphery to its centre. Such gradients also occur wherea perichondrium is lacking—for example, at articular surfaces—but the tissues near most osteochondral boundaries (though not in the intervertebral disc) show little change in cellularity. The maximum cell density found in the superficial zone of articular cartilage must be attributed to proximity to synovial fluid and its nutrient and other contents.

Overall cell density of the tissue varies enormously between different adult cartilages. This is easiest to investigate in joint cartilage where the articular surface is not covered by a perichondrium. Femoral condylar cartilage shows a 25-fold difference between small species (mice) which have very cellular cartilage and large species such as man (Table 2). On the other hand, a similar range of cellularity is found between the small and large joints of a single large species. Similar observations apply to other non-articular cartilages. Hence a scale effect is involved: the overall cellularity of the tissue is inversely related to the common factor, cartilage thickness (Fig. 6). It follows from such a relationship that the total number of chondrocytes nourished by diffusion from unit area of tissue boundary (for example, the synovial fluid bathing the articular surface) is of the same order in all cartilages and that the degree of

Table 2 *Cellularity of femoral condylar cartilage (from Stockwell, 1971)*

Source of cartilage	*Cartilage thickness (mm)*	*Cell density (cells × 10^4/mm³)*	*No. of cells (× 10^4) deep to 1 mm² articular surface*
Man	2·26	1·4	3·1
Cow	1·68	2·0	3·3
Sheep	0·84	5·3	4·2
Dog	0·67	4·4	2·7
Rabbit	0·21	18·8	3·7
Cat	0·33	10·8	3·2
Rat	0·07	26·5	1·9
Mouse	0·06	33·4	1·9

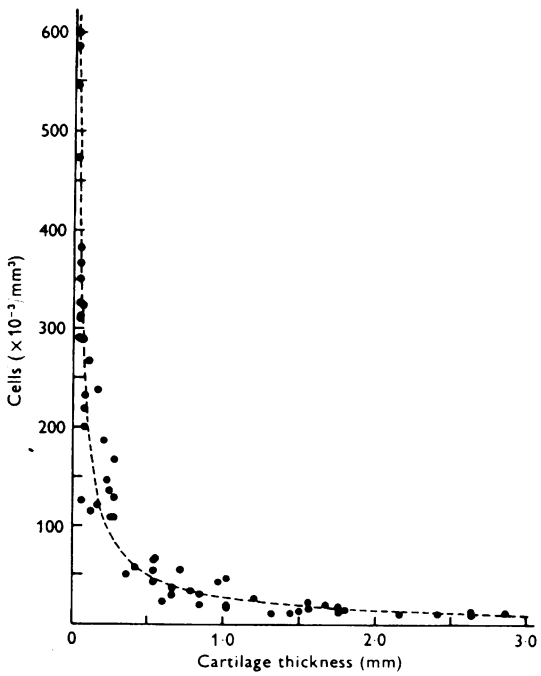

Fig. 6 *Relationship of articular cartilage thickness to cell density.* $y = 27\,900\ x^{-0.88}$. *(from Stockwell (1971), by permission of the Editor and publishers of the* Journal of Anatomy)

separation of the cells is probably due to other, mechanical, factors.

It is commonly believed that the cell content of cartilage falls during adult life. Cell density in non-articular cartilage shows a steady and constant decline of about 25% after growth has ceased. This is not always so in articular cartilage. When present, the principal age-related changes are in the superficial zone. Cell death *in situ* can occur in the knee and hip in the presence of an unbroken articular surface as judged by naked eye inspection or by light microscopy. Superficial cell density in such joints falls by 30-50% during adult life, but in normal humeral head cartilage no such changes are observed (Meachim and Collins, 1962; Stockwell, 1967; Vignon *et al.*, 1976). In the femoral head, though not the condylar cartilage, the superficial zone losses are large enough to cause a change in the overall cell density of the whole thickness of the tissue. Probably in arthritis-prone joints such as the hip and knee the age-related cell loss of the superficial zone is associated with ultrastructural fissures and other aberrations seen in surfaces judged intact by light microscopy. The lack of change in the shoulder suggests strongly that the cell loss in other joints is an abnormal phenomenon rather than a physiological age change. Whether superficial cell loss is a primary event or secondary to other defects is not known, but it must reduce the capacity of the cartilage to resist harmful agents.

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