

Interactions between subchondral bone and cartilage in OA.

Cells from osteoarthritic bone can alter cartilage metabolism

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Keywords: Osteoarthritis, Subchondral Bone, Cartilage, Joint Destruction

Osteoarthritis (OA) is characterised by increased subchondral bone activity and focal loss of articular cartilage. However, whether these changes occur independently or are linked by biochemical interactions between the two structures is not clear. Almost 40 years ago Johnson¹ observed changes in bone remodelling and suggested that such changes might precipitate irregularities in the integrity of articular cartilage. Some time later Sokoloff² showed that bony changes in the human hip could not be dissociated from cartilage fibrillation even in early disease. However, it was Simon et al.³ who promoted the notion that OA begins in the bone by demonstrating that stiffening of subchondral bone, attributed to healing microfractures, preceded cartilage damage in guinea pigs. Similar healing microfractures, resulting in increased subchondral bone stiffness were reported to be the primary cause of OA in humans. Bone, stiffened by callus formation during repair processes, was hypothesised to be less pliable so that the impact of loading was borne principally by the cartilage, which then degenerated.

Further evidence in support of this hypothesis was lacking in humans until relatively recently. Increased subchondral bone activity, as judged by enhanced uptake of technetium labelled diphosphonate, was shown to predict cartilage loss⁴. More importantly, the results suggest that cartilage lesions did not progress in the absence of significant subchondral activity. This notion gained credence from histological and histomorphometric analysis of tibial condyles that showed cartilage degeneration to be influenced by remodelling of underlying subchondral bone⁵. Moreover, several animal species exhibit spontaneous OA-like changes consistent with those seen in human disease. For example, guinea pigs of the Dunkin-Hartley strain⁶ and cynomolgus macaques⁷ develop age-related changes in bone that precede those in cartilage.

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Accepted 1 August 2002

In animal models of OA, changes in both bone and cartilage occur as a result of mechanical or surgical alteration of joint loading. For example, impulsive loading of rabbit knees, resulting in increased bone volume, is followed by progressive changes in articular cartilage during the following 6 months⁸. Taken together, these results demonstrate that subchondral bone remodelling is linked to cartilage destruction in both man and animals. However, the mechanism by which changes in subchondral bone result in damage to articular cartilage is not readily apparent.

In OA, high body mass index, together with increased bone density, suggests new bone synthesis exceeds degradation in susceptible individuals. In support of this contention, measurements of osteocalcin (marker of bone formation) in synovial fluids from patients with severe scintiscan abnormalities were higher than patients with only mildly altered knee scans⁹. Similarly, serum concentrations of osteopontin, a bone specific matrix protein, were significantly higher in patients with bone scan abnormalities than in those without. These results suggest bone cell activity is increased in OA and, together with observations that osteopontin measurements increase quickly following trauma, also imply that alterations in bone cell activity may occur early in disease. Moreover, synovial fluid markers of bone and cartilage turnover are associated and related to scintigraphic scan abnormalities in patients with OA⁹. If altered bone cell activity is linked to changes in cartilage metabolism, then it would be predicted that cells from osteoarthritic bone, but not non-arthritis bone, should alter cartilage metabolism.

To test this hypothesis, we devised a co-culture system to determine the effects of osteoblast-like cells on cartilage metabolism. We showed for the first time that cells derived from the bone of some OA patients increased glycosaminoglycan (GAG) release from cartilage, whereas similar cells obtained from NA bone did not¹⁰. Attempts to identify the soluble mediator of the effects of bone cells on cartilage revealed the presence of various cytokines in medium from cultured bone cells, although none of those measured were significantly associated with glycosaminoglycans loss from cartilage.

These results suggest either that the effects of bone cells on cartilage were mediated by an unidentified cytokine(s), or by other molecules. Other findings suggested enzymic activity in co-culture supernatants¹¹, and demonstration of aggrecanase-generated catabolites that increased with time in supernatants from cartilage incubated in the presence of bone cells¹² lend support to this contention. These findings therefore imply that either bone cells produce aggrecanase(s) that directly degrades cartilage aggrecan, or that bone cell-derived cytokines act indirectly by inducing chondrocytes to produce aggrecanase.

How feasible is this mechanism *in vivo*? Cartilage destruction in OA proceeds from the articular surface down¹³. It is therefore unlikely that bone cell-derived aggrecanases contribute greatly to focal loss of cartilage. By contrast, cytokines act at specific receptors on chondrocytes and signals are only transduced in the presence of sufficient cytokine. As a wide variety of cytokines are produced by cells from OA bone, cytokines produced during bone remodelling could serve as signals to modulate chondrocyte activity. Regional differences are apparent within and between joints in chondrocyte cytokine receptor expression¹⁴, whilst zonal differences in sensitivity to cytokines suggest that chondrocytes near the articulating surface are more responsive than those in deeper zones. Thus, if bone cell-derived cytokines contribute to cartilage destruction *in vivo*, only cartilage in areas where chondrocytes are sensitive to cytokines will be affected. Recent data show a higher proportion of bone cells (79%) could degrade cartilage when osteoblast-like cells were derived only from the weight-bearing regions of OA joints (Westacott, unpublished). Moreover, mechanical loading enhances cytokine production by osteoblasts^{15,16} whilst pressure can alter cytokine receptor expression¹⁷. Taken together, these observations suggest that in overloaded joints, conditions exist whereby molecules produced by bone could exacerbate cartilage damage.

Can bone cell products gain access to cartilage? Indirect communication between cartilage and bone is suggested by the existence of stress microfractures in bony trabeculae of the normal ageing skeleton. Fissures observed in histological preparations of undecalcified bone, originally considered to be artefacts, were later defined as two different types¹⁸. Most frequent were fine hairline microcracks in the calcified layer of cartilage that began just below the tidemark and proceeded toward the junction with bone. These occurred most often in the weight-bearing regions and were attributed to mechanical fatigue. Associated with microcracks were microfractures which were broader and protruded through gaps in the tidemark into the junction with the subchondral plate. Plugs of fibro-vascular tissue containing newly proliferated chondrocytes were often found in the microfractures that interrupted the calcified layer of cartilage. Thus, microdamage that transcends the tidemark initiates repair mechanisms, presumably via vascular invasion from the subchondral region, as suggested by the greater abundance of blood vessels in the load-bearing regions of articular cartilage. If similar microfractures occur in the load-bearing regions of the OA joint, mol-

ecules produced in the bone may gain access to cartilage.

Whilst bone is well vascularised, the avascularity of articular cartilage has been acknowledged for over two hundred years. That adult articular cartilage received its nutrition from joint fluid was a commonly held belief until relatively recent times, when observations in animals gave rise to suggestions that nutrients from the medullary cavity in bone may nourish cartilage¹⁹. These findings were confirmed in human femoral heads initially by perfusion studies demonstrating the presence of channels running from cancellous bone through the subchondral bone plate into the basal layer of articular cartilage. Since then refinements in imaging techniques have allowed better visualisation of the channels that connect bone with cartilage as well as the blood vessels contained within them²⁰. However, the relative importance of subchondral nutrition compared with the topical route via synovial fluid is not known.

To address this question, Malinin and Ouellette performed a long-term study of subchondral bone/cartilage autographs in mature primates²¹. Osteochondral plugs from femoral condyles were either replaced immediately into the original sites, or into sites lined with non-toxic cement to prevent direct contact with the underlying bone. Abrogation of the contact between subchondral bone and autograft had little effect on cartilage during the first 5-12 months. However, by 3 years, cartilage on autografts in the cement lined wells showed degenerative changes compatible with OA. By contrast, cartilage on autografts placed in unlined wells was smooth and glistening and united with the surrounding articular cartilage. Of particular note were the presence of channels between deep layers of the cartilage and subchondral bone in autografts approximately 1 year after transplantation. These were not found in normal cartilage, suggesting channel formation may be an attempt to augment cartilage nutrient supply. These results suggest that interruption of the contact between articular cartilage and vascularised subchondral bone results in cartilage degeneration, the time course of which appears to be comparable to the slow degeneration of cartilage characteristic of OA. Moreover, they emphasise that interactions between the two structures are essential for healthy cartilage.

In summary, subchondral bone remodelling and cartilage destruction are associated in man and animals. Evidence suggests bone cell metabolism is different in OA, possibly due to an altered osteoblast phenotype. Subchondral circulation, important for maintenance of cartilage integrity, provides a link between metabolic activities in cartilage and bone. Potential for further exchange of biochemical information is provided by fissures that transcend the tidemark. *In vitro*, cells from OA bone can alter cartilage metabolism. Taken together, these observations suggest a mechanism by which products of altered bone cell metabolism may influence cartilage integrity in OA and identifies pathways by which such interactions may occur. These observations therefore reinforce the notion that the joint should be considered as a whole organ. Furthermore, they suggest that biochemical interactions between bone and cartilage warrant further attention.

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