Compensation and decompensation of articular cartilage in osteoarthritis

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Abstract

Although contemporary descriptions of the pathology of osteoarthritis emphasize the loss of articular cartilage, in the earlier stages a marked increase in synthetic activity of the chondrocytes can lead to an increase in proteoglycan concentration and commonly, to cartilage hypertrophy. Thus, osteoarthritis exhibits a biphasic course, with an initial “compensatory” phase, during which homeostatic mechanisms may maintain a reasonable articular surface until the second phase, “decompensation” (joint failure), develops. Salicylates interfere with homeostatic repair mechanisms and can markedly truncate the compensatory phase. Polysulfated glycosaminoglycans and tetracyclines prolong the compensatory phase, thereby protecting against joint breakdown.

Although progressive loss of articular cartilage is the pathologic hallmark of osteoarthritis (OA), the typical biochemical, metabolic and histologic changes of OA which develop in OA cartilage of the unstable knee of dogs subjected to anterior cruciate ligament transection are accompanied by increases in total cartilage mass, net rate of proteoglycan synthesis, in proteoglycan concentration [1–4]. Furthermore, this cartilage hypertrophy persists for 3 years or more [5] before full-thickness cartilage loss occurs. (Based upon average life expectancy, one year in the life of the dog is equivalent to approximately 7 years in the life of a human; development of cartilage ulceration in a patient 20 years after rupture the anterior cruciate ligament is, therefore, temporally consistent with the natural history of this form of secondary OA in humans).

The earlier stages of OA represent a homeostatic compensatory phase, with a sharp increase in the synthetic activity of the chondrocytes in the articular joint, resulting in hypertrophic repair of the articular cartilage. Progressive cartilage loss occurs only subsequently and represents a stage of “decompensation,” i.e., chondrocyte failure. Why the cartilage fails is unclear, but may be related to inability of the chondrocytes to sustain indefinitely the increased level of proteoglycan synthesis, or to progressive thickening and stiffening of the subchondral plate [6, 7].

A marked synthetic response, leading to hypertrophy of OA cartilage, is not unique to the canine cruciate-deficiency model. It is seen also in a lapine model of OA [4] and in cartilage from Rhesus macaque monkeys developing OA spontaneously [8, 9]. An increase in proteoglycan concentration has been found in mildly involved areas of human hip cartilage from patients undergoing total joint replacement for severe OA [10]. Observations of
cartilage thickening in early human OA were made as long ago as 1937 [11], and have been confirmed [12].

Any study of the effects of pharmacologic intervention in OA must be viewed in the context of the dynamic pathophysiologic changes described above. When the in vivo effect of aspirin was examined in the canine cruciate-deficiency model of OA, consistent with in vitro data [13], cartilage degeneration in the unstable knee of dogs that were fed aspirin in daily doses sufficient to maintain the serum salicylate concentration at 20–25 mg/dl was much more marked than that in the unstable knees of dogs that did not receive the drug [14]. In addition, the proteoglycan concentration of the cartilage matrix was significantly lower when dogs were fed aspirin than when they were not, and the augmentation of proteoglycan synthesis in the OA cartilage, reflecting repair activity, was virtually eliminated. Similarly, oral administration of aspirin markedly accelerated development of OA in C57 black mice, a strain genetically predisposed to the disease [15]. Thus, salicylate administration truncates the compensatory phase of OA.

A number of reports have suggested that various NSAIDs might slow the progression of articular cartilage breakdown in OA and hence serve as “chondroprotective” agents. Such claims, which have occasionally been promoted extensively by pharmaceutical manufacturers, have been based largely on in vitro effects of the drug on, e.g., cytokine production, release or activity of cartilage matrix-degrading proteases, inhibition of the production of toxic oxygen metabolites, etc. [1, 16]. There are no data from well controlled clinical trials in humans, however, to indicate that any NSAID favorably influences the progression of joint breakdown in OA.

On the other hand, we have shown that oral administration of doxycycline retards the progression of articular cartilage breakdown in an accelerated canine model of OA [17]. The effect was most striking when the drug was administered prophylactically but was apparent even when treatment was delayed until after the initiation of cartilage lesions [18]. In conjunction with this “chondroprotective” effect, levels of collagen and gelatinase in extracts of OA cartilage were strikingly reduced. Notably, reductions in the levels of total collagenase and gelatinase was much more pronounced than reductions in the levels of active enzyme.

To examine the effect of doxycycline on activation of the proenzyme, we recently activated recombinant human neutrophil procollagenase in vitro in the presence or absence of clinically relevant concentrations of doxycycline and assayed collagenase activity on a small peptidyl substrate. Enzyme activity was strongly inhibited by doxycycline (IC_50 = approx. 10 μM). In the absence of doxycycline, Western blots showed that most of the proenzyme (55 kDa) was converted to active enzyme (44 kDa). In the presence of doxycycline, however, the proenzyme was cleaved to a prominent 31 kDa fragment and additional smaller fragments and little active enzyme accumulated. Similar results were obtained after activation with aminophenylmercuric acetate (APMA). These results indicate that doxycycline alters the conformation of procollagenase during activation and increases its susceptibility to proteolysis, resulting in irreversible denaturation of the proenzyme. By this mechanism, doxycycline appears to be capable of prolonging the compensatory phase of OA.

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