Introduction. One of the earliest features of cartilage degradation, a hallmark of both inflammatory and degenerative joint diseases, is proteolysis and loss of the proteoglycan aggrecan, which severely impairs the load dissipating properties of the tissue. In the inflammatory arthropathies, it is widely accepted that IL-1 and TNF are key mediators in disease pathogenesis. These cytokines act both by increasing synovial inflammation and pannus formation as well as by directly stimulating chondrocytes to degrade the cartilage matrix. There is extensive evidence that proinflammatory cytokines potently stimulate aggrecan degradation through upregulation of chondrocyte-derived aggrecanase and matrix metalloproteinase (MMP) activity [reviewed in 1]. However, the role of cytokines in osteoarthritic (OA) disease progression and more particularly cartilage destruction, is less clear. Transection of the cranial cruciate ligament (CCL) in dogs induces progressive cartilage degradation particularly cartilage destruction, is less clear. Transection of the cranial cruciate ligament (CCL) in dogs induces progressive cartilage degradation. Only OSM and LIF significantly increased aggrecan synthesis and stimulation of MMP-1 and ADAM-TS5 mRNA expression was not coupled with increased proteoglycan degradation in the canine CCL model. In contrast MMP-3 mRNA was expressed in control and all stimulated canine cartilage cultures. ADAM-TS4 mRNA was not detected in any canine cartilage. ADAM-TS5 mRNA was not expressed in control cartilage but was induced by all catabolic stimuli in canine cartilage irrespective of their effect on GAG release. Taken together, these results demonstrate that canine chondrocytes were responsive to, and activated by, all the catabolic agents tested. However, the inhibition of proteoglycan synthesis and stimulation of MMP-1 and ADAM-TS5 mRNA expression was not coupled with increased proteoglycan degradation in all cases.

Results and Discussion. None of the agents tested had a detrimental effect on chondrocyte metabolism as there was no significant difference in media lactate compared with control cultures. Canine and bovine cartilage were cultured in the presence of RA released significantly more GAG (3.7-fold) into the medium compared with control cultures (P < 0.01 for both analyses; Fig 1). Bovine cultures stimulated with RA released 6.7 times more GAG than controls compared with a 4.4 fold increase in canine cartilage. Surprisingly, there was no increase in GAG release from canine cartilage cultured with IL-1, TNF, IL-6 ± sIL-6R ± IL-1, or LPS (Fig 1). In contrast, an increase in GAG release from bovine cartilage was induced by these agents (P < 0.008 for all analyses; Fig 1). In canine cartilage GAG release was significantly increased by both OSM (P < 0.0001) and LIF (P = 0.03), while only OSM stimulated GAG release from bovine cartilage when compared with controls (P = 0.005), although the percentage increase was significantly less than in canine cartilage.

Canine articular cartilage therefore, differed significantly from bovine tissue in its catabolic responsiveness to inflammatory cytokines. However, Western blot analysis indicated that similar degradative mechanisms were induced in cartilage from both species, as any agent that stimulated GAG release from canine or bovine cartilage cultures, increased the BC-3 positive (but not BC-14) positive aggrecan metabolites in the medium. These results indicated that aggrecanases rather than MMPs were responsible for the induced proteoglycan release as has been reported in other tissues [4].

To determine if the lack of catabolic response of canine cartilage to a number of inflammatory cytokines was due to failure of signalling of these molecules, proteoglycan synthesis and mRNA expression of several proteolytic enzymes was evaluated. In canine articular cartilage, IL-1 (10ng/ml), LPS, LIF, OSM and RA (but not TNF (100ng/ml)), significantly reduced proteoglycan synthesis compared with controls (P < 0.006 for all analyses). MMP-1 mRNA was not expressed in control cultures of canine articular cartilage but was induced by stimulation with IL-1, TNF, LPS, IL-6 ± sIL-6R + IL-1, LIF and OSM. In contrast MMP-3 mRNA was expressed in control and all stimulated canine cartilage cultures. ADAM-TS4 mRNA was not detected in any canine cartilage. ADAM-TS5 mRNA was not expressed in control cartilage but was induced by all catabolic stimuli in canine cartilage irrespective of their effect on GAG release. Taken together, these results demonstrate that canine chondrocytes were responsive to, and activated by, all the catabolic agents tested. However, the inhibition of proteoglycan synthesis and stimulation of MMP-1 and ADAM-TS5 mRNA expression was not coupled with increased proteoglycan degradation in all cases.

Conclusions. Canine articular cartilage differs significantly from other species in its response to catabolic cytokines that induce aggrecan degradation. Only OSM and LIF significantly increased aggrecan degradation in canine cartilage. Modulation of cartilage destruction in canine CCL transection by anti-cytokine therapies may be primarily due to reducing synovial inflammation rather than by direct effects on chondrocyte mediated catabolism.


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