expression and synthesis of NF-κB inhibitors, IκBα and I-κB-β. (4) DTF downregulates IL-1β-induced IκB kinase (IKK) activation in cells treated with DTF/rest for 4/20, 8/16, 12/12, and 16/8.
Conclusions: This is the first study to demonstrate persistent effects of biomechanical signals in the surrounding proinflammatory environment. Furthermore, biomechanical signals suppress NF-kB signaling cascade. These signals act in two ways: (i) inhibit mRNA expression and synthesis of NF-κB, I-κBα and I-κBβ, and (ii) downregulate IKKb activation and thus I-κB degradation. The studies show the necessity of using adequate time intervals of physical therapies for the optimal management of arthritic joints.
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ACTIVIN A IS AN ANTI-CATABOLIC CYTOKINE PRODUCED BY INJURED CARTILAGE VIA RELEASE OF FIBROBLAST GROWTH FACTOR-2 AND ACTIVATION OF NUCLEAR FACTOR KAPPA B

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Purpose: Direct or indirect injuries to articular cartilage predispose to osteoarthritis. We have previously shown that injury to cartilage such as simple dissection causes the release of FGF-2 from a pericellular pool and activation of inflammatory signalling pathways such as the mitogen activated protein kinases and NFκB. Following such injury, the TGF β family member activin A is synthesised by human articular cartilage. We investigated **a)** how injury regulates the production of activin A by articular cartilage and **b)** whether this molecule has an important function in cartilage. Because TGF β has anti-inflammatory actions, the effect of activin A on IL-1-induced breakdown of the proteoglycan aggrecan in cartilage was assessed.
Methods: Activin A production was measured by ELISA of porcine or human cartilage explant culture medium. mRNA induction in cartilage explants or primary chondrocyte monolayers was by RT-PCR for genes of interest. The effect of exogenous activin A on IL-1 induced cleavage of aggrecan was determined by western blotting medium from human cartilage explant culture for the aggrecan cleavage neoepitope ARGSV.
Results: Activin A mRNA and protein were induced by simple dissection of human or porcine cartilage from the articular surface. Its production was due to an active cellular process. Activin A mRNA in cartilage explants was induced by FGF-2. Activin A production following injury was reduced by 80% by the FGF receptor inhibitor PD173074 and 70% by the IKK inhibitor BMS345541. FGF appeared to induce activin A production via ERK and src family kinases. Low concentrations of exogenous activin A suppressed the IL-1 induced aggrecanase-mediated cleavage of aggrecan in human articular cartilage. Osteoarthritic cartilage was noted to produce significantly more activin A than normal cartilage.
Conclusions: Activin A is produced by chondrocytes in response to injury of articular cartilage in an FGF and NFκB-dependent manner. This molecule appears to be anti-catabolic for cartilage by preventing aggrecan breakdown, and its production is enhanced in osteoarthritic tissue. Activin A may therefore be an endogenous chondroprotective cytokine, whose actions might be exploited therapeutically.

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METABOLIC ACTIVITY IN OSTEOARTHRITIC KNEES CORRELATES WITH BODY MASS INDEX

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Purpose: Osteoarthritis (OA) is the most common form of arthritis in the United States and has been linked to obesity. It is hypothesized that obesity, defined as a body mass index (BMI) over 30 kg/m^2, increases the incidence of OA through increased joint pressure and disruption of normal metabolism. Studies have identified factors in obese patients that may function as regulators of chondrocyte metabolism. However, metabolic changes resulting from obesity that may precede OA have not been thoroughly investigated. The purpose of this study was to identify the relationship between chondrocyte metabolism and BMI in osteoarthritic tissue.
Methods: Grade 0 or 1 cartilage was removed from the medial and/or lateral femoral condyles after total knee arthroplasty and was digested in collagenase. The chondrocytes were then resuspended in alginate beads at 2x10^6 cells/mL. The beads were equilibrated in media containing 10% fetal bovine serum for 7 days (37°C) and then separated into wells (8 beads/well) with 1 mL media. Media was replaced every 48 hours. At day 5, 9, and 13, beads were dissolved in 55 mM sodium citrate and centrifuged into their cell matrix and alginate portions. Glycosaminoglycan (GAG) content was measured in the cell pellet, alginate, and saved media using the dimethylmethylene blue (DMMB) assay. The DMMB results were normalized to DNA content. To assess differences in GAG content between obese and non-obese group, a Wilcoxon rank sum test was used. $P < 0.05$ was used as the criterion for significance. All procedures were approved by the University of Wisconsin - Madison, Institutional Review Board.
Results: At day 5, the average normalized GAGs from the obese group (BMI >30 kg/m^2) was >4-fold higher than the average normalized GAGs in the non-obese group (BMI <30 kg/m^2). Table 1 displays the normalized GAG averages from the 3 study days.
Fig. 1 shows a significant and linear relationship between BMI and normalized GAGs at day 9 (p=0.0003).
The 4-fold difference in normalized GAGs between obese and non-obese groups continued at day 9 with significance (p=0.0087) and widened at day 13, without significance. Fig. 2 displays the day 9 averages of normalized GAG content from the obese and non-obese groups.
Some osteoarthritic knees had less tissue quality, therefore GAG testing was limited to earlier study days resulting in variable sample numbers for each study day.

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	Day 5 GAGs (μg)/DNA (μg) (n)	Day 9 GAGs (μg)/DNA (μg) (n)	Day 13 GAGs (μg)/DNA (μg) (n)
Non-Obese Group (BMI < 30 kg/m^2)	31.8 (3)	53.3 (6)	34.9 (2)
Obese Group (BMI > 30 kg/m^2)	140.6 (6)	205.6 (6)	323.8 (3)