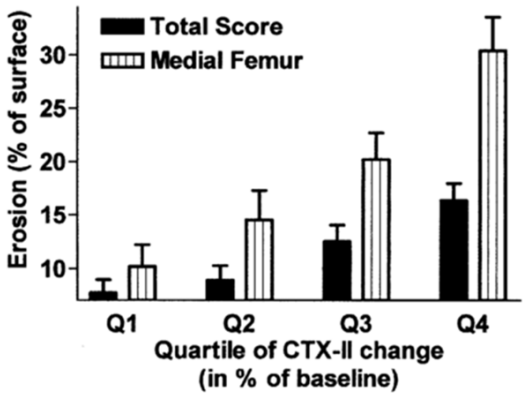

Figure S1. Association between cartilage erosion and C-telopeptide fragments of collagen type II (CTX-II). Animals from the cohort of the estrogen-SERM (selective estrogen-receptor modulator) intervention experiment were stratified into quartiles of the 4-week change in CTX-II. The range of ΔCTX-II in each quartile was as follows. Q1: -78.8% to -39.5%; Q2: -36.8% to -6.0%; Q3: -5.8% to 40.1%; Q4: 41.0% to 256.4%. Average erosion score for the medial femur as well as the total score for all four compartments of the knee is shown for each quartile. Error bars represent SEM. P = 0.001 by nonparametric ANOVA. (Adapted from Christgau S *et al.* [1]).

Table S1. Correlations between histologically assessed cartilage erosion scores and markers of bone (CTX-I) and cartilage (CTX-II) turnover in the knees of female Sprague-Dawley rats. (Adapted from PernilleHøegh-Andersen *et al.* [2])

			Changes in CTX-I		Changes in CTX-II	
Cohort[a] (treatment)		Age at start (months)	From weeks 0-4	At week 4	From weeks 0-4	At week 4
A (OVX or sham[b]) (*n*=18)		5				
Cartilage erosion:	Total		0.10	0.15	0.50	0.27
	Medial femur		0.47	-0.02	0.64*	0.51*
B (OVX or sham) (*n*=17)		7				
Cartilage erosion:	Total		0.24	0.25	0.74**	0.54*
	Medial femur		0.24	0.41	0.70**	0.63**
C (OVX + intervention or sham) (*n*=56)		5				
Cartilage erosion:	Total		0.40**	0.34*	0.50***	0.43**
	Medial femur		0.35*	0.33*	0.37**	0.45**

Values are Spearman's rho. [a]Cohorts: C, intervention with either estrogen or SERM. [b]Sham operation. *P<0.05, **P<0.01, ***P<0.001. CTX-I, collagen type I fragments; CTX-II, collagen type II fragments.

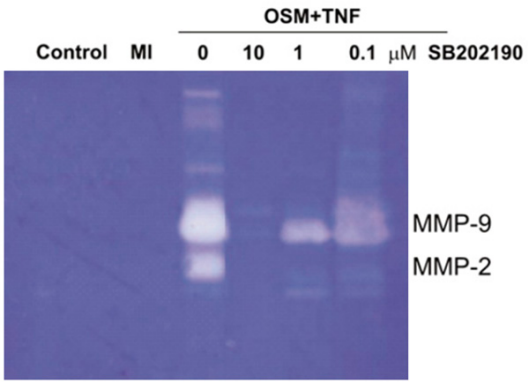

Figure S2. Expression of pro- and active MMP-9 and -2. Conditioned medium from bovine articular cartilage explants stimulated with the cytokines OSM + TNF-α (O + T) and co-cultured with the SB-202190 inhibitor of MAPK P38, was investigated by gelatinase zymography. MI, metabolic inactivated cartilage. (Adapted from Bodil C. Sondergaard *et al.* [3]).

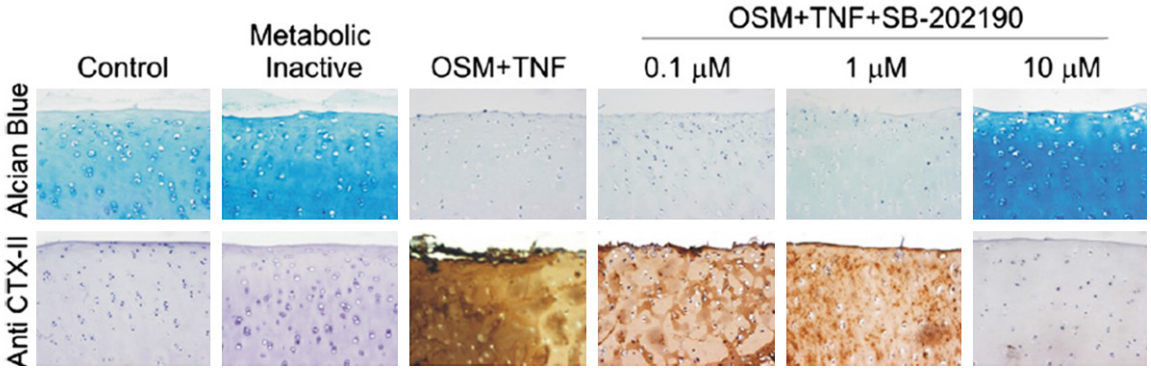

Figure S3. Histology and immunohistochemistry. Articular cartilage was cultured with catabolic cytokines OSM + TNF-α for 3 weeks to investigate the effect of MAPK P38-inhibition, by three doses of SB-202190. In order to visualize the retained proteoglycans in the cultured cartilage, the formaldehyde fixed, paraffin embedded and sectioned slides were stained with Alcian blue. Other sections were used for immunolocalization by the CTX-II antibody, which recognizes the CTX-II neoepitopes in cleaved collagen type II molecules and is visualized in the panel by the brown color. 20X magnification. (Adapted from Bodil C. Sondergaard *et al.* [3]).

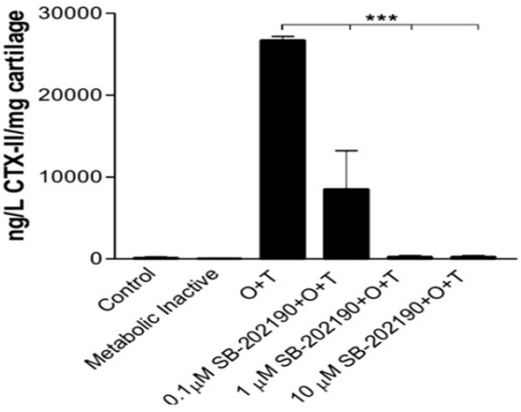

Figure S4. The effect of P38-inhibition on the degradation of collagen type II (CTX-II). Bovine articular cartilage explants were cultured in the presence of cytokines OSM + TNF (O + T) and P38 inhibitors (SB-202190). The CTX-II level in the conditioned medium from day 21 was dose-dependently inhibited by SB-202190. All bars represent the mean value of six replicates and were adjusted for the weight of the individual cartilage explants, presented with the standard error of the mean (S.E.M.). The asterisks represent the level of statistically significant difference from the O + T treatment, ***P<0.001. (Adapted from Bodil C. Sondergaard *et al.* [3]).

References

[1] Christgau S, Tankó LB, Cloos PA, Mouritzen U, Christiansen C, Delaissé JM and Høegh-Andersen P. Suppression of elevated cartilage turnover in postmenopausal women and in ovariectomized rats by estrogen and a selective estrogen-receptor modulator (SERM). Menopause 2004; 11: 508-518.

[2] Høegh-Andersen P, Tankó LB, Andersen TL, Lundberg CV, Mo JA, Heegaard AM, Delaissé JM and Christgau S. Ovariectomized rats as a model of postmenopausal osteoarthritis: validation and application. Arthritis Res Ther 2004; 6: R169-R180.

[3] Sondergaard BC, Schultz N, Madsen SH, Bay-Jensen AC, Kassem M, Karsdal MA. MAPKs are essential upstream signaling pathways in proteolytic cartilage degradation-divergence in pathways leading to aggrecanase and MMP-mediated articular cartilage degradation. Osteoarthritis Cartilage 2010; 18: 279-288.