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INHIBITORY INTERACTIONS BETWEEN HMGB1 AND HEME OXYGENASE-1 PATHWAYS IN OSTEOARTHRITIC SYNOVIOCYTES

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Purpose: Extracellular high mobility group box 1 (HMGB1) has been demonstrated to participate in inflammatory processes in joint diseases. Activation of osteoarthritic synoviocytes by pro-inflammatory cytokines results in HMGB1 translocation and release. We have shown recently a potential modulation of HMGB1 by heme oxygenase-1 (HO-1). In this study, we have examined the interactions between both pathways in osteoarthritic synoviocytes.
Methods: Synovial tissue samples were obtained from 15 osteoarthritic patients undergoing total knee joint replacement. Synoviocytes were obtained by digestion with collagenase and cultured until third passage. Cells were treated with human recombinant HMGB1 (15 ng/ml) in the presence or absence of IL-1β (100 U/ml). HO-1 was induced by cobalt protoporphyrin IX (CoPP). Lentiviral HO-1.flag vector was also used for HO-1 overexpression. HO-1 gene silencing was achieved by using a specific siRNA. Gene expression was analyzed by quantitative PCR and protein expression by Western Blot and ELISA. HMGB1 translocation into the cytoplasm was studied by immunofluorescence.
Results: Treatment of synoviocytes with HMGB1 down-regulated HO-1. This effect was potentiated by IL-1β and accompanied by a significant increase in matrix metalloproteinase (MMP)-1 and MMP-3 gene expression and activity. Conversely, induction of HO-1 by CoPP in the presence of IL-1 β led to reduced expression of both protein and mRNA of HMGB1. These effects were accompanied by a significant reduction in gene expression of MMP-1 and MMP-3, and MMP activity. The consequences of HO-1 induction were counteracted by HO-1 gene silencing. Interestingly, we observed a marked reduction in the translocation of HMGB1 from the nucleus into the cytoplasm. Transfection with lentiviral HO-1.flag vector confirmed the inhibitory effect of HO-1 on HMGB1 translocation.
Conclusions: We have provided direct evidence that HO-1 inhibits the translocation of HMGB1 into the cytoplasm. Our data indicate a reciprocal negative regulation between HO-1 and HMGB1 pathways in osteoarthritic synoviocytes.

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RELATIONSHIP OF WEIGHT CHANGE WITH CHANGE IN KNEE PAIN AND FUNCTION IN PERSONS WITH SYMPTOMATIC RADIOGRAPHIC KNEE OSTEOARTHRITIS: ONE-YEAR FOLLOW-UP DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: Overweight is a major risk factor for the development and progression of knee osteoarthritis (OA) and weight loss is recommended as part of the non-pharmacologic management of patients with knee OA. This analysis examined the relationship between weight change and change in self-reported symptoms and function and physical performance in adults with symptomatic radiographic knee OA over one year.
Methods: Data for this analysis were obtained from the Osteoarthritis Initiative (OAI) public access database (http://www.oai.ucsf.edu). Specifically, we examined data from the baseline and 12-month follow-up visits for subjects with symptomatic radiographic knee OA enrolled in the OAI Progression subcohort. Subjects completed the Western Ontario McMaster Osteoarthritis Index (WOMAC) and Knee Osteoarthritis Outcome Score (KOOS) at both visits. Weight was measured with a balance beam scale and physical performance was measured with a timed 20-meter walk at both visits; height was measured with a stadiometer at baseline. Names and dosage of medications and supplements were recorded at both visits by trained personnel. Correlations between change in weight and change in outcomes were examined in unadjusted and multiple variable adjusted models using generalized estimating equations to control for the correlation between knees in subjects with both knees involved at baseline. In addition, subjects were categorized into tertiles based on weight change over one year and the change in outcomes was examined across the tertiles of weight change using analysis of variance.
Results: Of 1388 subjects enrolled in the Progression subcohort, 1189 (85.7%) attended the 12-month follow-up visit and were included in this analysis. The mean (SD) age at baseline was 61.4 (9.1) years; 658 (55.3%) were women and 862 (72.5%) were white. The mean weight and body mass index (BMI) at baseline were 86.1 (16.0) kg and 30.1 (4.8) kg/m^2, respectively. Over an average of 12 months, the mean (SD) weight change was -0.31 (4.24) kg; mean (SD) weight change was -4.37 (3.97) kg, -0.03 (0.72) kg and 3.49 (2.58) kg for the tertile that lost weight, had stable weight and gained weight, respectively. In analyses adjusted for age, sex, race and use of analgesics and/or antiinflammatory drugs at each visit, weight change was significantly correlated with change in both WOMAC function and WOMAC total as well as 20-meter walk speed (see Table 1). Analyses comparing change in outcomes across tertiles revealed trends for associations with WOMAC function and 20-minute walk speed ($P < 0.10$) with greater improvement in those with either stable weight or weight loss compared to those who gained weight (see Table 2).

Table 1. Correlations of Weight Change with Clinical Outcomes

Clinical Outcome	Correlation
WOMAC Pain	0.004
WOMAC Function	0.067 (P = 0.02)
WOMAC Total	0.058 (P = 0.04)
KOOS Symptoms	-0.032
KOOS Pain	-0.021
KOOS Function	-0.033
KOOS Quality of Life	-0.020
20-meter walk speed	-0.065 (P < 0.03)

Change in Clinical Outcomes (mean [SD]) by Tertile of Weight Change

Clinical Outcome	Weight loss (N=398)	Weight stable (N=396)	Weight gain (N=395)
WOMAC Pain	-0.61 (3.34)	-0.70 (3.03)	-0.59 (3.10)
WOMAC Function	-2.33 (10.90)	-2.26 (9.46)	-0.88 (9.39)
WOMAC Total	-3.28 (14.65)	-3.39 (12.64)	-1.70 (12.78)
KOOS Symptoms	2.61 (14.14)	4.19 (13.92)	2.53 (13.36)
KOOS Pain	4.39 (16.52)	4.83 (15.26)	3.79 (15.37)
KOOS Function	4.54 (18.52)	4.88 (21.34)	3.73 (22.19)
KOOS Quality of Life	5.09 (16.89)	3.67 (17.00)	4.34 (17.21)
20-meter walk speed	0.01 (0.15)	0.01 (0.14)	-0.01 (0,15)

Conclusions: These data support an association between weight loss and improvement in function measured by both self-report and performance but not improvement in pain and other symptoms. Limitations of this analysis include a low level of symptoms and physical dysfunction at baseline and a small amount of weight change over 12 months. Further analyses of 24-month follow-up data will be completed when these data become available.