wear debris and endosomal destabilization, or plasma membrane frustrated phagocytosis, as an additional mechanism for UHMWPE recognition by the immune system.

Conclusions: Our data elucidate the mechanisms by which wear debris of different size, shape and composition can elicit an innate, immune response. Frustrated phagocytosis in response to micro particles, or endosomal destabilization as a result of phagocytosis of nanoparticles, are two of the major pathways through which wear debris activate the NALP3 inflammasome. Activation of Toll-like receptor (TLR) 2 and TLR4 are also pathways by which wear debris induce an inflammatory response. Ultimately, this multifaceted innate immune response will increase osteoclastogenesis and promote bone erosion.

461
HOFFA-SYNOVITIS AND EFFUSION-SYNOVITIS ARE ASSOCIATED WITH KNEES UNDERGOING TOTAL KNEE REPLACEMENT: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: Hoffa-synovitis and effusion-synovitis, which may be assessed on non-contrast enhanced MRI, have been identified as important disease features related to pain and structural progression of knee osteoarthritis (OA). Change in these inflammatory imaging markers is positively associated with pain. As the indication for total knee joint replacement (TKR) is primarily based on clinical parameters, these two inflammatory imaging markers that correlate closely with the clinical disease manifestations are promising structural candidate markers for TKR. This study used a matched case-control design to determine if Hoffa- and effusion-synovitis are associated with TKR cross-sectionally and longitudinally.

Methods: Participants were drawn from the Osteoarthritis Initiative (OAI), a multicenter observational study, including 4796 participants with, or at risk of knee osteoarthritis. We studied knees from 121 OAI participants that underwent TKR before the 48 month visit for the time point prior to TKR, i.e. "T0" (e.g. for a TKR reported at the 48 month (M) visit, T0 = 36M); and 121 control knees that did not undergo TKR that were matched for radiographic disease stage, gender, and age within 5 years and were assessed at the same T0 follow-up visit. MR images were acquired at four OAI clinical centers using dedicated Siemens Trio 3 T scanners. The coronal intermediate weighted (IW) 2D turbo spin-echo (TSE), the sagittal 3D dual echo at steady state (DESS) sequence, coronal and axial multiplanar reformations of the 3D DESS and a sagittal IW fat suppressed TSE sequence were used for semiquantitative assessment. MRIs were read for Hoffa- and effusion-synovitis using the semiquantitative MOAKS system, which scores both features from 0-3 (0 being normal and 3 severe structural change - see Figures 1 and 2).

Conditional logistic regression was applied to assess the association with TKR at T0. In addition, any worsening (increase in at least one grade from baseline to follow-up) in Hoffa- and effusion-synovitis from the time point prior T0 (= T-1) to T0 was analyzed to assess the association with TKR following T0.

Results: Subjects were on average 65.3 years old (SD ± 8.6), predominantly female (58.1%) and overweight (mean BMI 29.6 SD ± 4.9).

In the cross-sectional comparison at T0 (the visit just prior to TKR), knees that underwent TKR were more likely to have any effusion-synovitis at T0 when compared to matched non-TKR knees (OR 2.45 95% confidence interval [CI] 1.22-4.95). No significant associations were found for presence of Hoffa-synovitis (Table 1). In the longitudinal analysis, knees that underwent TKR were more likely to have worsening of Hoffa- (OR= 7.0, [1.59,30.80]) and effusion-synovitis (OR= 2.27, [1.11,4.62]) from T-1 to T0 compared to matched non-TKR knees (Table 1).

Conclusions: Knees undergoing TKR are more likely to have effusion-synovitis compared to non-TKR knees. Worsening of both, Hoffa- and effusion-synovitis was also more likely among TKR knees. Presence and change of these imaging markers may be important prognostic markers with regard to the clinical outcome of knee OA using TKR as the outcome measure.

Table 1. Cross-sectional and longitudinal comparison of Hoffa- and effusion-synovitis in TKR knees vs. matched non-TKR knees

MRI biomarker	N (%)	Odds of MRI biomarker abnormality for TKR compared to non-TKR knees Crude Odds Ratio (95% confidence intervals)
Hoffa-synovitis at T0		
0	42 (17.5)	Reference
1	124 (51.7)	0.87 (0.44,1.73)
2	66 (27.5)	2.25 (0.97, 5.19)
3	8 (3.3)	2.15 (0.44,10.52)
Effusion-synovitis at T0		
0	50 (20.7)	Reference
1	65 (26.9)	1.05 (0.45,2.46)
2	79 (32.6)	2.78 (1.21,6.38)
3	48 (19.8)	8.21 (2.90,23.21)
Worsening of Hoffa- synovitis from T-1 to T0		
No change or improvement	193 (91.9)	Reference
Worsening by at least one grade	17 (8.1)	7.0 (1.59,30.80)
Worsening of effusion synovitis from T-1 to T0		
No change or improvement	169 (80.5)	Reference
Worsening by at least one grade	41 (19.5)	2.27 (1.12,4.62)

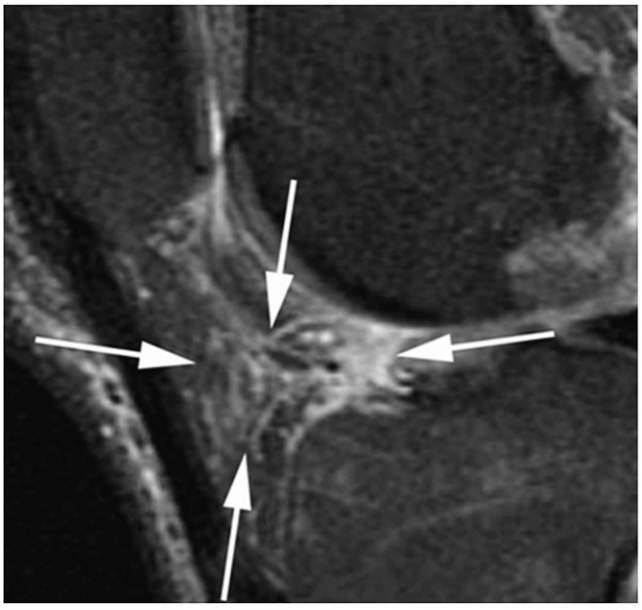

Figure 1.

Example of Hoffa-synovitis (grade 2). Marked hyperintensity in Hoffa's fat pad is depicted on sagittal IW fat suppressed image.

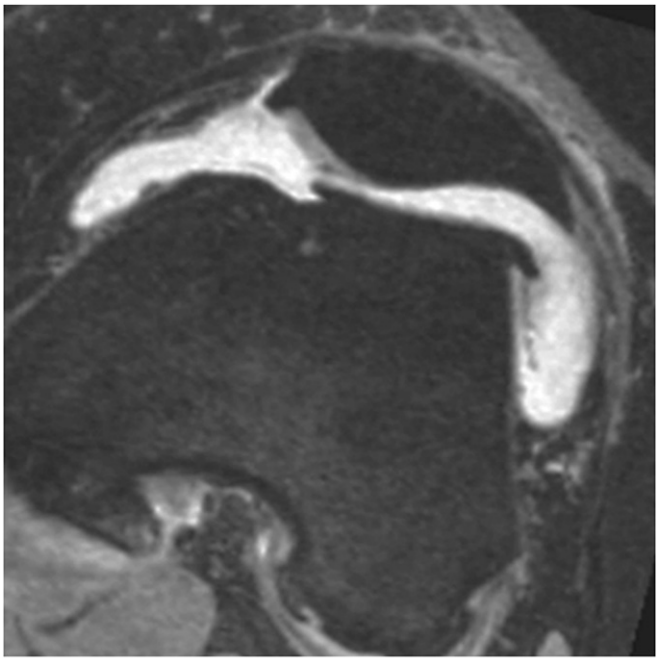

Figure 2.
Example of effusion-synovitis (grade 2). Marked fluid-equivalent hyperintensity is seen on axial DESS image. Hyperintensity reflects joint effusion and synovial thickening.

462
TNFα GENE TARGETING VIA TRIPLE-HELIX FORMATION: COULD AN ANTI-GENE STRATEGY BE AN ALTERNATIVE TO ANTI TNF ANTIBODIES FOR ARTHRITIS?

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Purpose: We investigated if an anti-TNF-α triplex-forming oligonucleotide (TFO), employed as anti-gene strategy, could be an alternative to antisense technology in silencing TNF-α activation during articular inflammation. In this study, we analyzed in vitro and in vivo anti-inflammatory potentialities of an anti-TNF-α TFO, as judged from effects on two rat arthritis models.
Methods: The inhibitory activity of this TFO on articular cells stimulated by IL-1ß (synoviocytes and chondrocytes) was assessed and compared to that of small interfering RNA (siRNA) in vitro, at mRNA expression levels by real-time RT-PCR, as well as at proteins level (TNF-α & NO release). In vivo, the biological effects of a preventive intraarticular injection of such an oligonucleotide were first investigated in an acute arthritis model, by the follow-up of clinical (body weight, pain, joint swelling), biochemical (anabolism loss, cytokines levels) and histological (synovium, cartilage,and bone) parameters. We then confirmed the efficiency of a preventive ia injection of anti-TNF-α TFO in an immunological experimental chronic arthritis model, according to similar parameters (clinical, biochemical and histological assessments).
Results: In vitro, we have demonstrated that a TFO designed to target TNF-α promoter was able to inhibit mRNA expression (86%) and to prevent TNF-α release into supernatants (62%) as well as NO release (80%). The inhibition rate, at mRNA level, was similar to the one observed with TNF-α specific siRNA, the main advantage of TFO being the concentration used (1nM vs 75 nM for siRNA). A difference was observed at proteins level, with approximatively a 20% more efficient inhibition with TFO, compared to siRNA.
The use of the anti-TNF-α TFO as a preventive and local treatment in both acute and chronic arthritis models significantly reduced disease development. In the acute inflammatory model, the TFO provided a stronger inhibition than the siRNA, with a long lasting biological effect, confirmed by histological assessement. In the immunological RA model, we have demonstrated that a preventive ia injection of the TFO lead to a significant correction of body weight distribution (incapacitancy test), confirmed by the histological grading of the knees. Indeed, fibrosis and infiltration were significantly decreased compraed to arthritic rats. Analysis of synovial fluid has demonstrated a significant decrease of inflammatory mediators like cytokines (TNF-a, IL-1ß, IL-2, IL-5) and chemokines (MCP1, MIP-1a) in animals preventively treated with TFO compared to naives. Furthermore, the TFO efficiently blocked synovitis and cartilage and bone destruction in the joints.
Conclusions: We showed the effectiveness of siRNA and TFO in modulating both in vitro and in vivo inflammatory processes. Interestingly, silencing was increased with TFO, enabling improved protection of articular components. We extended our findings by demonstrating for the first time that in rats developing arthritis, a preventive injection of anti-TNF-αTFO led to local and systemic TNF-α inhibition associated with improvement of ancillary clinical signs of arthritis. The results presented here provide the first evidence that gene targeting by anti-TNF-α TFO modulates arthritis in vivo, thus providing proof-of-concept that it could be used as therapeutic tool for TNF-α-dependent inflammatory disorders.

463
SUSTAINED REGULATION OF INFLAMMATION IN CHONDROCYTES BY BIOMECHANICAL SIGNALS VIA THE JAK3-STAT3 PATHWAY

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Purpose: Exercise is essential for maintaining cartilage health and therapeutic for degenerating cartilage during the progression of early osteoarthritis (OA) as shown in our animal models. At the molecular level, we have also shown that physiological magnitudes of mechanical forces are anti-inflammatory and suppress the transcriptional activities of nuclear transcription factor kappaB (NF-κB) by intercepting NF-κB signaling cascades. In this study, we examined the role of IL-11 via JAK3-STAT3-SOCS3 signaling cascade in inducing sustained anti-inflammatory state by physiological magnitudes of dynamic compressive strain (DCS). These findings further correlate with the attenuation of pro-inflammatory genes during the progression of OA by exercise in an animal model.
Methods: OSU Institutional Animal and Care Committee preapproved all protocols. Rat chondrocytes (5 x 10^5 cells/scaffold) were inoculated on 3D 6x3 mm cylindrical scaffolds fabricated by electrospinning of poly(ε-caprolactone), 6 days prior to experimentation. Subsequently, the constructs were subjected to various conditions: 1) untreated control, 2) IL-1β (1 ng/ml), 3) DCS alone (10% cyclic strain at 1 Hz), or 4) IL-1β and DCS for various durations. The effects of DCS on the overall gene expression were analyzed by Affymetrix Rat GeneChip 1.0 ST microarrays and the results confirmed by real time PCR using custom designed primers for IL-11 and SOCS3. Activation of the JAK-STAT pathway was examined via phosphorylation of JAK1, -2, -3, and phosphorylation of STAT3, -5, and IL-11 protein expression by Western blot analysis (WBA). To investigate the relationship between IL-11 and JAK-STAT activation, IL-11 was knocked down by siRNA. All experiments were performed at least in triplicate and statistical significance calculated by ANOVA with Tukey's post-hoc. Results: Microarray gene expression analysis on the ACs subjected to IL-1β (1 ng/ml) alone or 10% DCS in the presence of IL-1β revealed that 1163 genes out of approximately 27000 genes (detectable by GeneChip) were significantly regulated more than ±2 fold as compared to untreated controls. Specifically, most of the genes that were upregulated by IL-1β and drastically downregulated by DCS, were related to inflammation including *Ccl20*, *Nos2a*, *Cxcl2*, *Ccl7*, *Cx3cl1*, *Tnf*, *Cxcl6*, *Lcn2*, *Il23a*, and *Tnfaip2*, known to be under the control of the NF-κB pathway. On the other hand, IL-11 and its transcriptional regulators (*Fosb*, *Fos*, *Jun*, *Jund*, and *Atf3*) were significantly upregulated by DCS in the presence of IL-1β. The WBA revealed that JAK3 and STAT3 are activated by DCS regardless of the presence of IL-1β. The interference of DCS-induced IL-11 synthesis by IL-11 siRNA resulted in the inhibition of STAT3 activation, likely indicating that DCS induces the JAK3-STAT3 phosphorylation via IL-11 induction. The activation of STAT3, in