Conclusions: The results of this study suggest that HDMPs might be a common feature in ageing and degenerating weight bearing joints. The existence of these structures provides novel insights into the mechanism of joint destruction, highlighting the central role of micro-anatomical changes on the subchondral plate. HDMPs provide a novel imaging biomarker of joint destruction for diagnosis of joint disease and to monitor disease progression.

503 CHANGES IN EPIPHYSAL BONE, SUBCHONDRAL BONE PLATE AND EPiphyseal TRABECULAR BONE IN SURGICALLY AND CHEMICALLY INDUCED RAT MODELS OF OSTEOARTHRITIS

Purpose: Several experimental animal models have been developed for human osteoarthritis (OA) and used to study the preclinical efficacy of disease and symptom modifying OA drug candidates. The preclinical efficacy has been determined by various microscopic scoring systems and joint pain assessments. The histopathology initiative of Osteoarthritis Research Society International (OARSI) has presented recommendations for OA assessment in order to standardize preclinical efficacy studies. Recommendations for rat samples include the histological analysis of cartilage degeneration and extracellular matrix (ECM) loss, osteophytes, calcified cartilage and subchondral bone, synovium, joint capsule, and growth plate. As subchondral bone has been identified to play an important role in the development and progression of OA, treatment effects on bone tissue have been studied even in more detailed. In this study, we performed a systemic characterization of epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone together with the assessment of knee joint discomfort and pain and degenerative changes in articular cartilage and synovium in four rat OA models.

Methods: The study was conducted using male Lewis rats (body weight range 330-380 g). Unilateral OA was induced in their knee joints by applying the following models: 1) intra-articular injection of monoiodacetate (MIA) at the dose of 1 mg, 2) medial meniscal tear (MMT) combined with medial collateral ligament transection (MCLT), 3) anterior cruciate ligament transection (ACLX) combined with partial medial meniscectomy (pMMx), 4) ACITL. Body weight and OA symptoms were followed in each model during the study. Knee joint discomfort and pain were used as the symptoms of OA. Knee joint discomfort was analyzed as static weight bearing using Incapacitance Tester and knee joint pain as static mechanical allodynia using von Frey monofilaments. Knee joints were harvested at two different time points in each model as follows: in the MIA model at 2 and 4 weeks, in the MMT + MCLT model at 3 and 6 weeks, in the ACLX - pMMX model at 4 and 8 weeks, and in the ACLT model at 5 and 10 weeks. The structure of epiphyseal bone, subchondral bone plate and trabecular bone were analyzed in coronal sections of medial tibial plateau followed by the histological OA assessment as recommended by the OARSI histopathology initiative. This experimental protocol was approved by National Animal Experiment Board, Regional State Administrative Agency for Southern Finland, Hameenlinna, Finland.

Results: Knee joint discomfort was observed in operated hind limbs as decreased static weight bearing during the first week of the study. Knee joint pain was identified in operated and MIA-injected hind limbs as decreased paw withdrawal threshold during the first week and at the end of in-life phase of each model. In the rat MIA model, this knee joint pain was associated with mild synovial inflammation at 2 weeks, cartilage degeneration and ECM loss in superficial layer at 2 weeks and exacerbating down to intermediate layer at 4 weeks, and with the reduction in the amount of epiphyseal and subchondral bone. In the rat MMT + MCLT model, the knee joint pain was observed together with synovial inflammation, cartilage degeneration and the loss of ECM from superficial layer down to tidemark at 3 and 6 weeks, large osteophytes, and with the increased amount of epiphyseal and subchondral bone. In the rat ACLX + pMMX model, the pain of knee joint was identified in association with synovial inflammation, cartilage degeneration and ECM loss from superficial layer down to tidemark at 4 and 8 weeks, and with large osteophytes. In the rat ACLT model, the knee joint pain was associated with mild synovial inflammation, cartilage degeneration and the loss of ECM from superficial layer at 5 weeks and exacerbating down to deep layer at 10 weeks, osteophytes, and with the reduction in the amount of subchondral bone.

Conclusions: This study characterized changes in the structure of epiphyseal bone, subchondral bone plate and epiphyseal trabecular bone together with degenerative changes in articular cartilage and synovium, and knee joint discomfort and pain in four rat OA models. The amount of bone decreased in the rat OA models exhibiting from mild to moderate degenerative changes in articular cartilage, whereas the amount of bone remained unchanged or increased in the rat OA models exhibiting from moderate to severe degenerative cartilage changes. These results can be used to design studies for testing the preclinical treatment effects of OA drug candidates on articular cartilage, synovium, epiphyseal bone, and knee joint discomfort and pain.

504 COMMON GENES BETWEEN HUMAN AND RODENT OSTEOARTHRITIS CARTILAGE STUDIES SHOW LITTLE OVERLAP WITH AN INFLAMMATORY GENE-SET
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Purpose: We were interested to compare published gene sets of microarray studies on cartilage samples from rodent models of surgically induced, chemically induced and spontaneous osteoarthritis (OA). We also compare the datasets to published gene sets from human osteoarthritic cartilage, in order to determine genes that are dysregulated in osteoarthritic regardless of species and models used. Furthermore we were interested to identify which of those genes might be related with inflammation.

Methods: We used gene sets that adhered to the following criteria: 1) Was from pure cartilage or from samples enriched for cartilage 2) The species of origin was mouse, rat or human 3) We only preferred studies that have been deposited in a public database 4) We compared the datasets to a gene-set that was bioinformatically constructed to consider genes that are involved on the onset, resolution and response to inflammation. The study was gene centric, rather than probe centric and the genes mapping to the probes for each microarray was used for annotation purposes. For comparison of the different species, all genes were converted to the mouse ENTREZ gene ids. The common data sets were examined for gene ontology term enrichment and KEGG pathway enrichment.

Results: A high degree of overlap between the surgically and chemically induced OA models in rodents was observed. KEGG pathway analysis reveals that TGF beta pathway is the only pathway that is not over-represented in the chemically induced array. In total we identify 75 genes that are common in more than 50% of the arrays. In this group of 75 genes only 7 appear to be present in the inflammatory gene-set (p>0.05). However, if single arrays are examined the probability mass function of the overlap with the inflammatory gene-set is always less than 0.05 and for some arrays as low as 6.2 x 10^-14. At the 4 weeks time point the probability mass function increased. 10 genes are present in more than 8 out of the 11 OA datasets studied with no inflammatory counterpart.

Conclusions: The cartilage response that leads to OA appears to follow a common transcriptional trajectory regardless of the insult that has caused it. Although inflammatory molecules produced by the cartilage are part of the OA response, a significant part of the transcriptional cartilage response appears to be independent to inflammation.

505 MCP-1-CCR2 LIGAND-RECEPTOR AXIS IN HUMAN CHONDROCYTE DEGRADATION AND DISEASE PROGRESS IN OSTEOARTHRITIS
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Purpose: To investigate the role of (OA).

Methods: Expression of the C-C chemokines monocyte chemoattractant protein 1 (MCP-1), and its receptor CCR-2, was assessed in 16 OA patients and 6 normal controls, by reverse transcriptase-polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA) on MCP-1 stimulated chondrocytes, and the apoptosis of the chondrocytes was detected by flow cytometry. While, the Expression of the markers, collagen I, V, IX, XI and Matrix metalloproteinases (MMP), of chondrocyte degeneration was assessed by ELISA. Finally, as to estimate the essentiality of MCP-1-CCR2 ligand-receptor axis in induce and maintain the pathologic features of OA, the CCR-2 antagonist (RS102895) was used to block the animal model of OA in rats induced by