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THE ROLE OF TRANSFORMING GROWTH FACTOR ALPHA IN A MOUSE MODEL OF OSTEOARTHRITIS

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Purpose: Osteoarthritis (OA) affects approximately ten percent of all Canadians and is the leading cause of physical disability and impaired quality of life in North America. Despite the prevalence and severity of this degenerative joint disease, its underlying pathological mechanisms are not well understood. Recently, our lab established a surgical rodent model of OA in order to study gene expression changes in degenerating articular cartilage. We found that transforming growth factor alpha (TGF alpha) gene expression was upregulated in our model, and thus identified TGF alpha as a novel growth factor involved in OA. Further in vitro studies showed that TGF alpha treatment suppressed chondrocyte expression of the anabolic factors aggrecan and type II collagen and increased expression of the catabolic factor matrix metalloproteinase 13 (MMP13). The purpose of this study is to examine the requirement for TGF alpha in the progression of osteoarthritis in vivo. We hypothesize that Tgfa null mice will experience delayed OA progression compared to control littermates in a surgical disease model.
Methods: Ten week old Tgfa null mice and their heterozygous littermates underwent meniscotibial transaction (MTX) of the left knee joint in order to create a mild form of degenerative disease. Mice from both groups also received sham surgery (capsulectomy). Seven weeks post-surgery, animals were sacrificed, and their knee joints were isolated and prepared for histology. Tissues were stained with safranin-O/fast green and joint histopathology was scored using the Osteoarthritis Research Society International (OARSI) criteria. Tissues were also immunostained for MMP13 expression.
Results: Preliminary results show that MTX appears to produce a very mild form of degenerative joint disease while sham surgery shows no sign of disease at seven weeks-post surgery. Importantly, Tgfa null mice have lower OARSI scores and express less MMP13 than their heterozygous littermates at this time point.
Conclusions: TGF alpha appears to play an important role in the progression of osteoarthritis in vivo. Future studies will examine the expression of additional anabolic and catabolic factors in Tgfa null joints as well as the potential role of TGF alpha in the cartilage growth plate.

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IMPLEMENTATION OF A SCID ENGRAFTMENT MODEL WITH SYNOVIAL FIBROBLASTS AND CARTILAGE TO CHARACTERIZE OA PATIENTS

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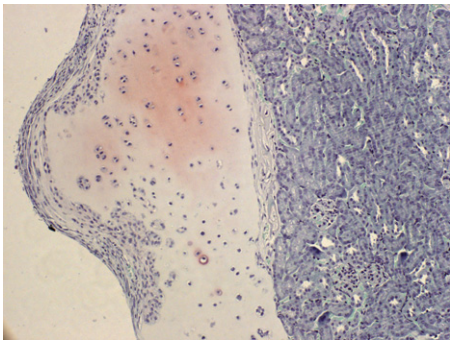
Purpose: Patient heterogeneity is probably one of the reasons for failure of osteoarthritis (OA) clinical trials. We aim at identifying novel biomarkers and disease mechanism by focussing on adipose and synovial tissue from OA patients for improved patient stratification
Methods: For this purpose, we implemented an engraftment model in the SCID mouse for *in vivo* characterization of synovial and adipose tissue from OA patients. The model was set up using synovial fibroblasts from rheumatoid arthritis (RA) patients that are known for their invasive behaviour. A sterile gelfoam sponge was seeded with synovial fibroblasts and co-implanted together with bovine cartilage. Evaluation of cartilage destruction and synoviocyte invasion was performed 60 days after implantation by H&E and safranine-O staining and compared with cartilage implanted with synovial fibroblasts from healthy donors.
Results: Cartilage destruction and invasion of RA synovial fibroblast in the cartilage was observed.



Conclusions: This model will be used to study the effects of adipose and synovial tissue from OA patients on cartilage integrity and invasive behaviour

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A STATISTICAL MODELING APPROACH OF THE RELATIONSHIPS BETWEEN SPECIFIC TISSUE LESIONS AND FUNCTIONAL DISABILITY IN EXPERIMENTAL CANINE OSTEOARTHRITIS

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Purpose: Pain, morphological alterations and functional disability are cardinal features of the osteoarthritic (OA) joint. However, the relationship of joint structural damages to functional limb impairment remains to be clarified. This study aimed at investigating in an experimental canine anterior/cranial cruciate ligament (ACL)-induced instability model, the time-course of the relationship between some variables monitored with podobarometric gait analysis and the joint structural damages using magnetic resonance imaging (MRI).
Methods: OA was surgically induced by transection of the right ACL in five dogs, which were subject to concurrent podobarometric gait analysis and MRI examinations prior to surgery (baseline), as well as 4, 8, and 26 weeks afterwards. The peak vertical force (PVF) and ground contact area (GCA) were measured, and ordinal scales were used to grade the cartilage defects, joint effusion, and osteophytosis found at MRI, as well as the subchondral bone marrow lesions (BML) assessed on T1GRE, T2wFS, and SPGR sequences. Changes in cartilage volume were quantified from computerized reconstruction. A mixed-effect general linear model for repeated measures with first-order autoregressive covariance structures was built for testing global mobility with ln (PVF), and a second one for testing gait changes with GCA. Time, the MRI variables, and selected dual interactions were added sequentially as fixed effects in both models, and GCA was an additional fixed-effect predictor of ln_(PVF). Both models were solved with maximum likelihood estimation at the 0,05 α-level.