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biosynthesis and contains vicinal RGD motif that bind specifically to $\alpha V\beta 3$ and $\alpha V\beta 5$ integrins. Since chondrostatin reaches the highest level during cartilage formation and it inhibits angiogenesis, it is an excellent candidate for the molecular mechanism by which cartilage remains avascular.

A10 TRANSFORMING GROWTH FACTOR-BETA INDUCES PERSISTENT SYNOVIAL FIBROSIS WHILE CONNECTIVE TISSUE GROWTH FACTOR-INDUCED FIBROSIS IS REVERSIBLE. ROLE FOR LYSYL HYDROXYLASE

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Purpose: The main characteristics of osteoarthritis are cartilage damage, osteophyte formation and synovial fibrosis. Synovial fibrosis can contribute to the loss of the function of an OA joint. TGF- β is considered one of the main players in fibrotic diseases. However, CTGF, which can be induced by TGF- β , has been reported to be an important player as well, stated to contribute to maintenance of fibrotic tissue. We investigated the underlying mechanism in that leads to the observed difference in fibrosis persistence between TGF- β - and CTGF.

Methods: We injected C57Bl/6 mice intra-articularly with Ad-TGF- β or Ad-CTGF. After 3, 7 and 21 days knee joint synovial tissue was isolated for RNA isolation or whole knee joints for histology. With Q-RT-PCR relative mRNA levels were determined of matrix molecules, proteases, protease inhibitors, and growth factors. To analyze the enzymes involved in collagen cross link formation, mRNA expression of lysyl hydroxylase (LH) was determined.

CTGF-levels induced by TGF- β were measured by ELISA in 24 hour patella-synovial wash-outs of C57Bl/6 mice intra-articularly injected with Ad-TGF- β (3, 7 and 14 days).

Results: TGF- β and CTGF induced synovial fibrosis in murine knee joints as shown by histology (as observed by an increase in synovial width). However, TGF- β -induced fibrosis was very persistent, whereas CTGF-induced fibrosis resorbed by day 28.

TGF- β induced elevated collagen type I and very high levels of aggrecan expression and hardly any changes in collagen type II and III. CTGF induced no clear changes in collagen type I, II and III. CTGF even decreased aggrecan expression (day 21 only).

CTGF induced no changes in MMP3, -9, -13, ADAMTS-4 or -5, whereas TGF- β increased MMP-3, -13 and ADAMTS4. Thus elevated levels of matrix degrading enzyme expression cannot explain the less persistent CTGF-induced fibrosis.

TIMP1 (associated with matrix accumulation in fibrotic disorders), was highly up regulated by TGF- β (all days) and only slightly up regulated by CTGF (day 7). TGF- β also induced elevated mRNA levels of TGF- β 1 and CTGF.

Only TGF- β induced high levels of LH expression, especially LH2b, which has been implicated in hard-to-degrade collagen linkage and was found up regulated in fibrotic lesions.

As TGF- β can induce CTGF and up regulated CTGF mRNA in our experiments, we measured CTGF levels in 24 hour patella-synovial wash outs and found that TGF- β induced 64 ng CTGF/ml after 3 days and that CTGF levels were still elevated by day 14.

Conclusions: TGF- β induced increased collagen type I and aggrecan mRNA levels in synovial tissue, but also high levels of degrading enzymes. The latter does not explain the persistent nature of TGF- β versus CTGF-induced synovial fibrosis. Lack of collagen type I mRNA induced by CTGF corresponds to findings of other groups. Despite this fact, fibrosis is found. Only TGF- β induced high levels of TIMP1 expression, which was previously found associated with strain dependent fibrosis sensitivity in mice and implicated in accumulation of ECM in fibrotic disorders. TGF- β , not CTGF, induced high levels of LH which are crucial for ECM cross linking. Moreover, LH2b was reported by van der Slot et al. to induce harder-to-degrade crosslinks compared to LH2a. The 2b splicing variant was highly expressed upon stimulation with TGF- β . Since TGF- β clearly up regulated MMP expression a dominant role for TIMP appears unlikely. The strong induction of LH2b by TGF- β compared to CTGF, and consequently harder to degrade cross links, appears to be the most likely cause of the induction of irreversible fibrosis by TGF- β .

A11 EFFICACY OF A SINGLE ULTRASOUND GUIDED INJECTION IN HIP OSTEOARTHRITIS

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Purpose: There is increasing evidence for intra-articular hyaluronic acid and especially corticosteroids in the treatment of osteoarthritis (OA) from studies using fluoroscopy guidance or triple ultrasound guided injections. Having previously demonstrated the accuracy of ultrasound guided injection and how competency can be achieved we aimed to demonstrate the duration of objective improvement in pain, function and global health assessment in patients with moderate/severe hip OA with a single intra-articular injection.

Methods: 77 patients with hip OA were recruited to a prospective, randomised controlled trial and randomised to one of four groups: standard care (non-injection group), normal saline (3mls), non-animal stabilized hyaluronic acid (durolane, 3mls/60mg) and methylprednisolone acetate (depomedrone, 3mls/120mg). All patients met the ACR criteria for hip OA. Those in the injection groups received a single ultrasound guided injection. All baseline data were obtained with both patients and investigators blinded to the group allocation, and injection patients remained blinded throughout the study. The primary outcome measure was 'worst pain' using a numerical rating scale (NRS 0-10), and other outcome measures included the aggregate pain and function scales of the WOMAC. These evaluations were performed at baseline and weeks 1, 4, 8 and 16.

Results: Mean age was 69 (SD 8) years. Mean BMI was 28.5 (SD 5.2) $\text{kg}\cdot\text{m}^{-2}$. The 4 groups were matched with respect to age, BMI, and scores of the outcome measures (ANOVA). At week 1 and week 4 there was a significant improvement in NRS pain, as well as WOMAC pain and function for the steroid arm with the differences being statistically significant compared to all the other groups; the effect sizes were striking: 1.5 for NRS pain, 1.9 for WOMAC pain and 1.3 for WOMAC function at week 1. There were 22 responders as defined by the OMERACT-OARSI responder criteria in an intention to treat analysis at week 1: 14 in the steroid group (74%), 4 in saline group (21%), 2 in durolane group (11%) and 2 in non-injection group (10%); Chi-squared test for comparison between the groups, $p < 0.001$. At 8 weeks the differences were still significant between the steroid group and the saline group (NRS pain: t test, $p = 0.018$).

Conclusions: This is the first single ultrasound guided injection study in hip OA comparing a moderately high dose of corticosteroid, hyaluronic acid, a control injection and standard care. Our data demonstrate the efficacy of intra-articular corticosteroid, with a statistically significant and clinically important improvement in pain and function sustained for at least 8 weeks post injection, suggesting this is an important and practical treatment option for those with moderate/severe hip OA.

A12 DOSE DEPENDENT CHONDROPROTECTIVE EFFECTS OF ALLOGENIC STRO-3+ MESENCHYMAL PRECURSOR STEM CELLS FOLLOWING DIRECT INTRA-ARTICULAR INJECTION INTO JOINTS OF AN OVINE MODEL OF EARLY OSTEOARTHRITIS

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Purpose: Purpose: Our previous studies had shown that bilateral total meniscectomy (BTM) in merino sheep resulted in pathological changes in articular cartilage (AC), subchondral bone and synovial tissues that were progressive and simulated the development of early human osteoarthritis (OA). We previously used this animal model to evaluate potential disease-modifying OA drugs. Mesenchymal stem cells (MSC) + bio-scaffolds have been widely investigated for their ability to enhance repair of chondral/osteochondral defects, but their chondroprotective effects when injected directly into OA joints has received limited attention. The objective of this study was to address this deficiency using immunoselected Stro-3+ mesenchymal precursor stem cells (MPC) in the BTM model.

Methods: BTM was undertaken in 36 adult Merino wethers. Two weeks post BTM, joints were randomly injected with either 2mL high MW Hyaluronan (HA) or 2mL allogenic Stro-3+ MPC suspended in HA. Four doses of MPC were studied: Group A = 10 million (mil) MPC [n=6]; Group B = 25 mil MPC [n=6]; Group C = 100 mil MPC [n=18] and Group D = 150 mil MPC [n=6]. Groups A, B and D were sacrificed