IMMEDIATE EFFECTS OF VARUS BRACING ON KNEE MECHANICS IN PEOPLE WITH PREDOMINANT LATERAL KNEE OSTEOARTHRITIS AND VALGUS MALALIGNMENT, 12 YEARS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Purpose: Lateral knee osteoarthritis (OA) is observed in more than 50% of people with knee OA after anterior cruciate ligament reconstruction (ACLR). Lateral and medial knee OA are associated with lower peak external knee adduction moments than medial OA. Thus, it is important to investigate targeted interventions with the potential to address abnormal knee mechanics associated with lateral knee OA following ACLR. The aim of this study was to investigate the immediate effects of a varus unloader brace on knee kinematics and moments in people with predominant lateral knee OA and valgus malalignment after ACLR.

Methods: Nineteen participants who had undergone a primary ACLR 5–21 years previously (Knee Injury and Osteoarthritis Outcome Score (KOOS) criteria) and radiographic (Kellgren & Lawrence ≥2) lateral knee OA and valgus malalignment were recruited from the community in Melbourne, Australia. Quantitative gait analyses were conducted during walking trials at self-selected speeds, under three test conditions in a randomized order: i) no brace; ii) unadjusted brace (sagittal plane support, no varus adjustment); and iii) adjusted brace (sagittal plane support with varus adjustment). Participants rated their average level of knee pain on visual analogue scales upon completion of each test condition. Post-processing of gait data involved calculation of knee kinematics, ground reaction forces and external joint moments for the reconstructed limb. First and second peak values were identified during stance phase. Data were statistically analyzed using repeated measures analysis of variance (p<0.05).

Results: The cohort consisted of 15 (79%) males (mean±SD age 37±7 yrs, height 1.72±0.06m, body weight 80±10kg; KOOS subscales: pain 80±15, symptoms 74±13, activities of daily living 88±15, sport/recreation 69±26, quality of life 58±23). There were no significant differences in knee pain between the three test conditions (p=0.655). Compared to the no brace condition, the adjusted brace resulted in immediate increases in the first peak knee flexion angle (mean difference, 95% confidence interval: -3.2° to -1.3°) and moment at peak 1 (-1.0 Nm/kg, -1.5 to -0.5) and peak 2 (-0.8 Nm/kg, -1.3 to -0.4), increases in peak 1 and peak 2 knee adduction angles (-2.5° to -1.0 to -1.4, respectively) and moments (-0.7 Nm/kg, -1.0 to -0.5; -0.7 Nm/kg, -1.0 to -0.4, respectively). Increases in peak 1 and peak 2 knee internal rotation angles (2.9° to 3.3°, 2.1 to 4.6, respectively) and reduction in peak 1 internal rotation moment (-0.08 Nm/kg, -0.13 to -0.02) were noted with the adjusted brace.

Conclusion: Knee bracing significantly increased peak sagittal and frontal plane knee kinematics and moments at the knee joint, and reduced peak transverse plane knee kinematics and increased transverse plane moments in people with knee OA after ACLR. The varus adjusted brace produced more pronounced changes in frontal and transverse plane kinematics than the unadjusted brace. In younger individuals with predominant lateral knee OA and valgus malalignment after ACLR, the varus unloader brace may be able to mitigate abnormal knee joint mechanics. The long-term effect of this on progression of lateral compartment degenerative joint disease following ACLR requires further investigation.

Figure 1. Knee joint kinematics (A, B, C) and external net joint moments (D, E, F) during stance phase for the adjusted, unadjusted and no brace conditions.
per cell (um²) (P < 0.01) compared to the control group (6 months old mice).

Conclusion: These results support the hypothesis that autophagy is decreased with aging and that compromised autophagy represents a novel mechanism in the development of OA.

51 CARTILAGE INJURY REGULATES NERVE GROWTH FACTOR (NGF) IN VITRO AND IN VIVO AND DRIVES PAINFUL BEHAVIOUR IN MURINE OA

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Purpose: Pain is the foremost clinical symptom of osteoarthritis (OA), however the processes that lead to pain in the join are poorly understood. We have previously shown that nerve growth factor (NGF) is regulated in the joints of mice at the time they get OA-induced pain and NGF neutralisation is an effective analgesia (McNamee et al. 2010). In pharmaceutical trials of monoclonal anti-NGF antibodies, clinical efficacy in the treatment of OA pain has been demonstrated (Lane et al. 2010) but a small minority of patients developed accelerated disease, raising the possibility that anahtogenetic anti-NGF specifically contributes to disease progression. This might occur by removing the mechanical protection afforded by painful behaviour, or be due to a direct disease modifying effect of the antibody. The purpose of this study was to investigate the regulation of NGF in painful murine OA joints, specifically focusing on where it is regulated and its induction following mechanical injury. The dependence of NGF on FGF2, a cytokine released upon cartilage injury, was also examined. Finally, we modelled the effects of chronic NGF neutralisation or indomethacin (a non-steroidal anti-inflammatory agent) on disease progression in murine OA.

Methods: Surgical joint destabilisation, a validated model of OA, was performed on 10 week old male or female mice and painful behaviour (a combination of Von Frey, cold plate sensitivity, algometer and Linton incapacitance) assessed weekly. RNA was isolated from whole knee joints or micro-dissected tissues (articular cartilage, meniscus and epiphysis). For cartilage injury responses in vitro, RNA was isolated from lip epiphoyses of 5 week old wild type or FG2 knockout mice. Additional injury studies were performed on porcine cartilage that had been pre-incubated with the FGF receptor inhibitor SB402451. Anti NGF, indomethacin or relevant controls were administered to wild type OA mice from the time of pain onset for a further 6 weeks. The analgesic response to anti-NGF was measured. Joints were sectioned and scored.

Results: NGF was regulated in whole murine joints at the time the mice developed pain. When micro-dissected tissues were examined separately, NGF was specifically regulated in the articular cartilage and not in the bone or meniscus. NGF was strongly regulated (>-200 fold) upon in vitro cartilage injury. In vitro injury-induced NGF was dependent upon FG2, as the induction was suppressed when FG2 knockout cartilage was explanted, and when porcine cartilage was pre-incubated with the FGF receptor inhibitor prior to injury. Despite the dependence of NGF on FG2 in vitro, FG2 knockout mice still developed anti-NGF sensitive pain following joint destabilisation and pain in these mice occurred earlier than in wild type mice in keeping with their more severe cartilage injury scores (Chia et al 2009). Neutralising NGF for 6 weeks in mice with painful OA produced sustained analgesia but did not alter the severity of cartilage degradation over this time. Similarly, chronic dosing with indomethacin had no apparent disease modifying effects.

Conclusions: NGF is a validated pain target in murine OA and is regulated largely within the articular cartilage in vivo and upon cartilage injury in vitro. Cartilage injury-induced NGF in vitro was strongly FG2 dependent, but this did not seem to be the case in vivo. Indeed, FG2 knockout mice developed earlier pain, apparently correlating with accelerated disease seen in this strain. We were unable to demonstrate any differences in disease progression between mice chronically dosed with anaglesics and those with pain over this period of study.

52 THERAPEUTIC EFFICACY OF ANTI-ADAMTS5 ANTIBODY IN THE DMM MODEL

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Purpose: Adatoms-5 null mice are protected from cartilage degeneration and accompanying mechanical alldyonia in experimental osteoarthritis induced by destabilization of the medial meniscus (DMM). A highly selective and potent monoclonal antibody (Ab) that neutralizes ADAMTS-5 was able to mimic these findings when administered pharmacally through 8 weeks post DMM surgery. The goal of the current study was to test whether this Ab can provide similar beneficial effects when administered in a therapeutic setting, i.e., after onset of joint pathological changes and mechanical alldyonia. The therapeutic effects of anti-ADAMTS-5 on progression of joint damage, mechanical alldyonia in the hindpaw, and concomitant molecular changes in the nociceptive pathway were analyzed.

Methods: DMM surgery was performed in the right knees of 10-week old male C57Bl/6 mice. Four weeks later, mice were administered weekly injections of anti-ADAMTS-5 or IgG isotype control Ab (p.o. 10 mg/kg). Untreated mice were administered with control group. For the next 12 weeks, mice were monitored bi-weekly for mechanical alldyonia in the ipsilateral hind paw using von Frey fibers and the up-down staircase technique. Sixteen weeks post DMM, mice were taken down (n=11-12), and knees were collected for histopathology according to OARSI recommendations. Total joint score is a sum of cartilage degeneration, osteophyte formation on both the lateral and medial sides of the joint, with a maximum possible score for cartilage degeneration = 60, and osteophyte formation = 6 (max total joint score = 66). Additionally, subchondral bone sclerosis in the medial compartment was assessed, using a bone score with a maximum score of 5. In addition, a set of n=4 mice/treatment group were taken down 8 weeks after surgery. Ipsilateral knee innervating dorsal root ganglia (DRG) L3-L5 were harvested, and sensory neurons were isolated and cultured for 4 days. Cell culture supernatants were analyzed for the pro-algesic chemokines, MCP-1 and fraktalkine, via ELISA.

Results: Histopathology of the knee joint 16 weeks post surgery revealed that untreated mice developed moderate levels of cartilage degeneration and osteophyte formation (total joint score = 19.3±3.3) and subchondral bone sclerosis (bone score = 2.5±0.7). When anti-ADAMTS5 was administered beginning at 4 weeks post DMM, mice were protected against cartilage degeneration and osteophyte formation (total joint score = 9.5±2.0) (p=0.02), but not against subchondral bone changes (bone score = 2.6±0.3) (p=0.92) by 16 weeks post surgery. IgG isotype control Ab afforded some protection against change in the total joint score, but this was not statistically significant compared to untreated DMM mice (total joint score = 13.1±3.0) (p=0.2). Four weeks after DMM surgery, mice presented with robust mechanical alldyonia in the ipsilateral hind paw, an indicator of sensiti- zation in the pain pathway. In untreated mice and in mice receiving IgG isotype control Ab, the alldyonia was maintained through 16 weeks post surgery (p<0.0001). In mice treated with anti-ADAMTS-5, the alldyonia resolved and this protection lasted through 12 weeks post surgery. By 16 weeks post surgery, mechanical alldyonia had returned (p<0.05) (Fig 1). Eight weeks after surgery, innervating DRG neurons from untreated DMM mice produced elevated levels of MCP-1 and fraktalkine protein compared to naive and sham mice. When DRG neurons were cultured from mice treated with anti-ADAMTS5 between weeks 4 and 8 post DMM, the levels of MCP-1 and fraktalkine were significantly downregulated compared to untreated mice (p<0.01). This downregulation reflects decreased activation of sensory neurons and correlates with decreased mechanical alldyonia after treatment with anti-ADAMTS-5.

Conclusions: This study demonstrates therapeutic efficacy of a potent and selective anti-ADAMTS-5 Ab in the DMM model, when adminis- tered in early stages of disease. Therapeutic effect on cartilage degeneration, mechanical alldyonia as an indicator of pain and concomitant molecular changes in sensory neurons further supports the idea that structural joint damage and development of pain are linked. These studies will help elucidate whether slowing progression of joint dam- age can prevent or slow the development of pain. Ongoing experiments are evaluating therapeutic effect of ADAMTS-5 blockade in late stage experimental osteoarthritis.