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

C. Driscoll, A. Chanalaris, C. Knight, C. Gentry, S. Bevan, T.L. Vincent, 1 Kennedy Inst. of Rheumatology, Oxford, United Kingdom; 1 Kings Coll. London, London, United Kingdom; 3 Kennedy Inst. of Rheumatology, London, United Kingdom

Purpose: Pain is the foremost clinical symptom of osteoarthritis (OA), however the processes that lead to pain in the joint 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 anaesthetics were per se anti-NGF specific where NGF 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 that is released upon cartilage injury, was also examined. Finally, we investigated the regulation of NGF in painful murine OA joints, specif-}

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

R.E. Miller, J.B. Tran, S. Ishihara, J. Larkin, A.-M. Malfait, 1 Rush Univ. Med. Ctr., Chicago, IL, USA; 2 GlaxoSmithKline, Upper Merion, PA, USA

Purpose: 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 (i.p. 10 mg/kg). Untreated mice served as a control group. For the next 12 weeks, mice were monitored bi-weekly for mechanical al-}

Abstracts / Osteoarthritis and Cartilage 22 (2014) S7–S56 335
CHARACTERISATION OF PAIN-RELATED BEHAVIOURS IN ASSOCIATION WITH JOINT PATHOLOGY IN AN 8-WEEK ANTIGEN-INDUCED ARTHRITIS MODEL


Purpose: Inflammation and immune modulation play a role in processing of nociceptive input in the dorsal root ganglia (DRG), contributing to the development of chronic pain. Macrophage infiltration into DRG, first demonstrated in neuropathic pain models, has recently been implicated in pain and sensitization in animal models of inflammatory arthritis and osteoarthritis. The relationship between DRG macrophage infiltration, pain, and progression of joint pathology has not been studied. We investigated this relationship using a monoarticular antigen-induced arthritis (AIA) model in mice.

Methods: AIA was induced by intra-articular (IA) injection of mBSA into the right knee joint of 12-week old male C57BL/6 mice immunized intradermally 3 weeks and 1 week previously with mBSA in CFA. Immunized control (IC) mice received IA saline in place of mBSA. An operator blinded to treatment assessed mechanical allodynia (von Frey) and thermal hyperalgesia (hotplate) in the hindpaw, knee hyperalgesia (Pressure application measurement), hindlimb weight distribution (forceplate) and spontaneous behaviour (LABORAS) at 0, 1, 2, 4, 6 and 8 weeks after IA injection. At 1, 4 and 8 weeks mice (AIA and IC) were sacrificed and DRG and knee joints harvested. L3-L5 DRG neurons were cultured for 4 days and supernatant MCP-1 quantified by ELISA (n = 5); L2-5 DRG were immune-stained for F4/80 (n = 2); knees were histologically scored for synovitis, cartilage proteoglycan (PG) loss and erosion, subchondral bone (SCB) vascular invasion and sclerosis (n = 6).

Results: Joints in IC mice showed no histological change at any time. In AIA joints synovitis, SCB vascular invasion and cartilage PG loss peaked at W1. At W4, cartilage PG loss persisted and erosion started to develop, SCB vascular invasion decreased as SCB sclerosis started to develop, and synovitis persisted but was reduced. At W8, synovitis had significantly decreased while cartilage erosion and SCB sclerosis progressed. AIA mice developed ipsilateral secondary mechanical allodynia (W1 to W8), knee hyperalgesia (W2 to W6), and thermal hyperalgesia (by W6). AIA mice had a significant reduction in ipsilateral hindlimb weight bearing (W1), and a decrease in distance travelled and rearing frequency (W1) that resolved by W4. Interestingly, 40% of IC mice also developed ipsilateral mechanical allodynia at W1, and all IC mice had mechanical allodynia at W4, persisting until W8; these mice displayed no other pain-related behaviours. At W1 and W4, both AIA and IC mice had increased F4/80 expression in L2-5 DRG, although greater in AIA compared to IC at W1. Four weeks post AIA, cultured DRG cells produced increased MCP-1 protein compared to age matched naïve mice.

Conclusions: In summary, AIA mice developed secondary mechanical and thermal sensitization. In addition, these mice developed pain-related behaviors such as changes in weight-bearing and locomotion changes in association with progressive joint pathology over 8 weeks. This was associated with macrophage infiltration in the ipsilateral DRG L2-5 and production of MCP-1 by DRG cells. IC mice also developed secondary mechanical allodynia, in the absence of joint pathology or any other pain-related behaviours. This was accompanied by F4/80 staining in the DRG at W1 and W4. These findings suggest that intra-dermal immunization alone is sufficient to trigger mechanical allodynia and concomitant cellular changes in the DRG, in the absence of joint pathology. However, joint pathology occurring as a result of intra-

Figure 1. Temporal changes in (a) mechanical allodynia, (b) hindlimb weight distribution (R/L), (c) synovitis, and (d) articular cartilage erosion (tibia), in unilateral antigen-induced arthritis (AIA) or immunized control (IC) mice; as measured at W1, W2, W4 and W8. Values expressed are mean ± S.E.