76 BASIC FIBROBLAST GROWTH FACTOR INDUCES OSTEOGENESIS AND SUPPRESSES THE PROGRESSION OF SECONDARY OA IN A RABBIT MODEL OF OSTEONECROSIS OF THE FEMORAL HEAD

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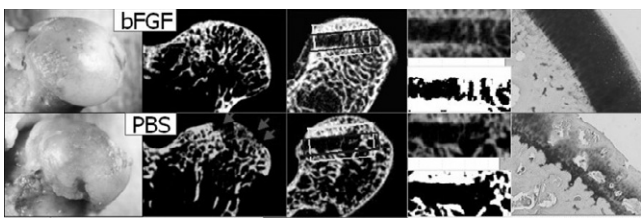
Purpose: Untreated symptomatic osteonecrosis of the femoral head (ONFH) often leads to femoral head collapse and advanced secondary osteoarthritis (OA). The primary goal in the treatment of ONFH is to treat it in early enough stage to preserve the femoral head and avoid total hip arthroplasty. The use of growth factors have been proposed. The purpose of this paper is to evaluate the effects of basic fibroblast growth factor (bFGF) on the repair of ONFH in rabbits.
Methods: To evaluate the in vivo effect of implanted bFGF, we created drill hole (1 mm in diameter and 5 mm in depth) in the femoral head of rabbit ONFH model. Animal model were induced by the treatment combining the administration of high dose corticosteroids (40 mg/kg of methylprednisolone) and capsule resection, accompanied by coagulating of the soft-tissue attachments from femoral surgical neck and acetabulum. 8 weeks after induction of ONFH, we implanted gelatin hydrogel microspheres containing 100 μg bFGF or PBS into the femoral head and articular surface. Thirty-five male Japanese white rabbits underwent ONFH were divided three groups as follows: (1) Control group, in which the rabbits received no further treatment after ONFH; (2) PBS group, in which 8 weeks after ONFH, PBS contained in gelatin hydrogel microspheres were directly injected; (3) bFGF group, in which 8 weeks after ONFH, 100 μg bFGF contained in gelatin hydrogel microspheres were directly injected. The right hip was experimented on in all treated rabbits. Animals in control group were killed at 0, 4, 8, 12, 24 weeks after ONFH (n = 5 each). Animals in the treatment groups were killed at 24 weeks after ONFH (n = 5). Gross morphologic and histologic examinations, and radiographic assessment by micro CT scans were performed.
Results: Injections of bFGF contained in gelatin hydrogel microspheres suppressed the progression of OA in the ONFH rabbit model. Macroscopically, the area of articular surface of the right femoral head involved OA change was significantly less in the bFGF group (14.1±9.0%) compared with the PBS group (42.1±5.4%, $P < 0.01$) or control group (62.5±11.4%, $P < 0.01$). The roundness index of the right femoral head was significantly less in the bFGF group (52.4±4.9%) than that in the PBS group (62.2±4.3%, $P < 0.05$) Radiographic assessment by micro CT scans showed significantly better preservation of the femoral head structure and better osteogenesis in the bFGF group compared with the PBS group or control group. The irregularity of subchondral bone of the femoral head in the bFGF group (17.5±6.6%) was less than that in the PBS group (59.1±13.6%, $P < 0.01$) or control group (54.2±10.7%, $P < 0.01$). Bone formation rate of/around implant area was significantly higher in the bFGF group (71.2±3.3%, 37.9±11.5%) compared with the PBS group (47.8±8.6%, 11.5±4.2%, $P < 0.01$). According to the modified Mankin's histological score, the severity of OA in the bFGF group (3.4±1.6) was significantly less than that in the PBS group (8.8±2.6, $P < 0.01$) or control group (7.8±0.4, $P < 0.05$).
Conclusions: To our knowledge, this is the first study to show that bFGF induces osteogenesis and suppresses the progression of secondary OA in the ONFH animal model. Our findings demonstrated that bFGF into the femoral head and articular surface had therapeutic effects on secondary OA development in the ONFH. Our results suggest the potential feasibility of a new conservative treatment for ONFH.



77 ASSOCIATION OF OSTEOCHONDRAL ANGIOGENESIS, CARTILAGE LESION AND BEHAVIOURAL PAIN IN A RAT MODEL OF OSTEOARTHRITIS

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Purpose: We have previously demonstrated chondro-protection and reduced weight-bearing asymmetry with a Matrix Metalloproteinase inhibitor (MMPi) in the rat meniscal transection (MNX) model of osteoarthritis (OA). The purpose of the current study was to elucidate the analgesic mechanism of the MMPi by investigating angiogenesis at the osteochondral junction (OCJ) as a surrogate of nerve growth.
Methods: This was a convenience study of an experiment that assessed the effect of an MMPi in the MNX model of OA, the results of which have been reported previously. Briefly, pathology was induced in male Lewis rats, (n = 10/group) (270 g, Harlan, UK) by transecting the medial collateral ligament and making a full thickness cut through the meniscus (day 0). Sham (SHAM) animals underwent the same procedure with omission of the meniscus transection. MNX animals were dosed orally with vehicle (HPMC/tween, 1%DMSO) or an equipotent MMP 2, 8, 9, 13 inhibitor (0.125, 0.5, and 2.5 mg/kg twice per day). Rats were sacrificed 35 days post surgery. Angiogensis was assessed by counting the blood vessels crossing the OCJ of the medial tibial plateaux in at least three central sections per case and an arithmetic mean determined for each animal. Geometric means were then calculated for each group of 10 animals and were analysed by 1 way ANOVA with Bonferroni corrections for multiple comparisons. Correlations between the angiogenesis and weight bearing asymmetry (assessed using an incapacitance meter) and cartilage lesions (assessed by toluidine blue stained coronal step sections across the entire knee joint) were undertaken.
Results: Blood vessels crossing the OCJ were elevated in the in MNX animals (mean 7.1, C.I 8.2−6.1) versus the SHAM treated animals (mean 1.0, CI 1.4−0.6) ($p < 0.001$). The angiogenesis observed in the MNX animals was reduced by treatment with MMPi 2.5 mg/kg (mean 2.1, CI 2.8−1.3; mean difference 5.0, CI 6.2−3.8) and 0.5 mg/kg (mean 4.2, CI 4.6−3.8; mean difference 2.9, CI.4.1−1.6), (both $p < 0.001$). At the highest dose the number of vessels crossing the OCJ was not different ($p > 0.05$) from the SHAM treated controls (mean 1.0, CI 0.6−1.4; mean difference 1.0, CI −0.1−2.3). The correlation between vessels crossing the OCJ and dose of MMPi (Spearman's correlation −0.892, $p < 0.001$), was found to be independent of cartilage lesion score using partial correlations. Amelioration of the asymmetrical weight bearing in the MNX animals by treatment with the MMPi was found to correlate (Spearman's correlation −0.52, $p < 0.001$) with the reduction of vessels crossing the OCJ.
Conclusions: Cartilage is usually thought to be an avascular and aneuronal tissue although in human disease such as OA there is known to be vascular and neuronal activity in the junction between cartilage and bone. Here we show that there is vascular penetration in a rat surgical model of OA and that treatment with an MMPi is associated with reduction in osteochondral angiogenesis and supports the anti-angiogenic effects observed with MMP inhibitors in other pre-clinical models. The correlation between angiogenesis and behavioural pain in the MMPi treated group may be explained by the fact that angiogenesis correlates with new nerve growth in human and rat tissues. These data suggest that agents, which target angiogenic mechanisms, may have utility in the treatment of pain associated with osteoarthritis.

78 UTILITY OF THE STR/ORT MOUSE MODEL OF SPONTANEOUS OA

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Purpose: This study was designed to evaluate the reproducibility of spontaneous knee osteoarthritis (OA) in STR/ort mice and to determine the potential utility of this model to test therapeutics aimed at disease-modification of OA.
Methods: Two trios of STR/ort mice were obtained from the Imperial College, London and the colony rederived for internal studies. Mice were group-housed with up to 5 single-sex mice/cage and allowed free-access to food and water on an IACUC-approved protocol. At 6−8 wks of age, mice were provided custom feed incorporating vehicle or 50 mg/kg/day of a broad-spectrum MMP inhibitor (MPI-369). Three groups of 20−22 mice were evaluated in this study: vehicle treated males and females, and MPI-369 treated males with 20−22 mice/group. Mice were euthanized at 12 months of age and plasma harvested for pharmacokinetic analysis.