Conclusions: The knee cartilage of the Hartley guinea pig undergoes an increase in the expression of genes associated with hypertrophy by 12 months of age coincident with the development of severe osteoarthritic changes. Compared to the OA-prone Hartley strain, Strain 13 guinea pig knee cartilage showed much lower expression of genes associated with the hypertrophic cartilage phenotype. These findings are compatible with the lesser severity of OA in this model. Interestingly, Hartley and Strain 13 guinea pigs showed similar and high ADAMTS-5 mRNA expression, suggesting that the ADAMTS-5 may be relevant in OA development in the guinea pig model, but may not account for the differential susceptibility of the two strains to OA.

FRIZZLED RELATED PROTEIN (FRZB) IS INVOLVED IN DIFFERENT ASPECTS OF JOINT BIOLOGY AND PATHOLOGY


Purpose: The Frizzled related protein (FRZB) gene has been associated with susceptibility to osteoarthritis in different cohorts. FRZB is a secreted antagonist of the WNT signaling pathway originally identified in a chondrogenic extract of articular cartilage. We have generated Frzb−/− mice and demonstrated that this loss of function model shows increased cartilage damage in different induced mouse models of osteoarthritis. Deletion of Frzb is associated with increased Wnt signaling and increased matrix metalloproteinase activity and expression. In addition, the thickness and adaptive bone formation upon loading are increased in Frzb−/− mice as compared to wild-type. Here, we further evaluated the spontaneous development of knee and hip osteoarthritis in a cohort of normal aging mice as well as a cohort of mice exposed to voluntary running activity. In addition we studied the effect of Frzb deletion on enthesophyte/oстеophyte formation in the spontaneous model of arthritis in DBA/1 mice.

Methods: Aging Frzb−/− and wild-type mice were evaluated by X-rays at week 26 and 52. In another cohort, Frzb−/− and wild-type mice were grouped and a running wheel was introduced into the cage at the age of 7 weeks. At week 8, all mice were caged separately with a running wheel available. Mice were allowed free exercise for 6 to 12 months and distances run were recorded daily. At the end of the experiment, mice were sacrificed and joints were processed for histological evaluation. Cartilage damage, synovitis and osteophyte formation were scored. Muscle fiber composition of the soleus and extensor digitorum longus were studied by immunofluorescence. Frzb−/− mice were backcrossed onto the DBA/1 background for over 7 generations. Male DBA/1 mice from different litters were caged together at the age of 10 weeks (>5 males per cages) and observed for clinical signs of arthritis. Alternatively wildtype DBA/1 males were treated with intramuscular injections of plasmid containing Frzb under control of a CMV promoter every three weeks (week 11, 14, 17 and 20). At the end of these experiments (week 30 and 25 respectively), mice were sacrificed and histological severity of disease was evaluated.

Results: No statistical differences in spontaneous incidence or severity of osteoarthritis were seen between Frzb−/− mice and wild-type mice. At the age of 6 months, both female and male wild-type mice showed significantly greater voluntary running activity than the Frzb−/− mice (p < 0.05). At one year, the difference was still significant for male mice, but not for females. Running exercise did not significantly affect severity of osteoarthritis. Differences in distances run were not explained by abnormalities in muscle composition.

In the spontaneous model of joint remodeling, average clinical disease severity score and average clinical severity score per affect animal were higher in wildtype as compared to Frzb−/− mice. Average histomorphological severity score was also higher in wildtype as compared to Frzb−/− mice. In contrast, overexpression of Frzb by intramuscular plasmid injection did not affect clinical incidence, severity and histomorphological disease severity scores.

Conclusions: Absence of Frzb in mice does not lead to increased incidence or severity of osteoarthritis. However, reduced voluntary physical activity in running wheels suggests that absence of Frzb affects locomotoric function. The underlying mechanisms are not yet fully understood. Deletion of Frzb also reduces enchondral bone formation in a mouse model of ankylosis. These combined data further establish a role of FRZB and WNT signaling in postnatal musculoskeletal biology and disease. Functional polymorphisms in FRZB in humans may also affect osteophyte formation and disease progression.

ORAL CALCITONIN REDUCES CARTILAGE EROSION IN AN OA RAT MODEL WITH BOTH TRAUMATIC INJURY AND INCREASED SUBCHONDRAL BONE TURNOVER

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Purpose: Osteoarthritis (OA) is a disease that affects the entire articular joint, with both changes to the bone and cartilage compartments. Increased bone turnover, as caused by oestrogen deficiency, has been speculated to augment the severity of cartilage erosion and to accelerate the pathogenesis of OA. An optimal intervention strategy for OA may therefore ideally target both bone and cartilage malmetabolism. Calcitonin has been shown to affect both osteoclasts and chondrocytes. We investigated whether a novel oral formulation of salmon calcitonin could reduce cartilage erosion and attenuate osteophyte formation, observed secondary to induction of OA by combined partial medial meniscectomy and ovariectomy of rats.

Methods: Four groups of 6 months old rats were subjected to sham, ovariectomy (OVX) or a combined ovariectomy and partial medial meniscectomy (OVX+MNX) and administered twice daily with oral salmon calcitonin (CT) (150 mg/kg 5-CNAC + 2 mg/kg calcitonin) or vehicle control (V) (150 mg/kg 5-CNAC) in the following way: (1) Sham+V; (2) OVX+V; (3) OVX+MNX+V; (4) OVX+MNX+CT. Serum samples were collected at baseline and 3, 6 and 8 weeks after surgery, and weights were recorded at regular intervals. Animals were sacrificed 8 weeks after surgery, and the tibia was processed for histology. C-terminal telopeptide of type II collagen (CTX-II) was measured in the serum. Histological sections were stained with Fast Green/Safranin O. The tibial plateau was equally distributed using automatic delineations in ImagePro. Areas of osteophytes situated in the lateral compartment were scored separately.

Results: OVX surgery increased serum CTX-II levels by 260%, 240% and 53% in week 3, 6 and 8 after surgery, respectively. Meniscectomy did not further increase the systemic CTX-II levels. Treatment with oral calcitonin significantly (p < 0.05) reduced CTX-II concentrations to below sham levels. Ovariectomy alone resulted in a moderate cartilage loss of 5.8% in the central tibial compartment compared to sham animals, whereas OVX+MNX+V caused a heavy 33.3% (p < 0.05) cartilage loss. Treatment with oral calcitonin reduced that cartilage loss by 52% (p = 0.06). The area of laterally occurring osteophytes increased 15-fold (p < 0.01) from OVX+V to OVX+MNX+V animals. The effects of oral calcitonin reduced the area of osteophytes by 55% when comparing the group OVX+MNX+V to OVX+MNX+CT.

Conclusions: Currently there are no treatments available for OA. These data are the first to demonstrate that an oral formulation of calcitonin protects against cartilage erosion and osteophyte formation in an in vivo OA model with both traumatic injury and increased subchondral bone turnover. The chondroprotective effects of salmon calcitonin may be a combination of direct effect on chondrocytes in addition to the well-established effect on bone resorption. Further clinical studies are needed to validate the herein documented effects on cartilage erosion.

DELETION OF ESTROGEN RECEPTORS INDUCES OSTEOPHYTES BUT DOES NOT PROMOTE EARLY CARTILAGE DAMAGE IN MICE

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Purpose: Since the prevalence of osteoarthritis OA is much higher in postmenopausal than in premenopausal women, and cartilage damage is increased after ovariectomy in several animal models, it is believed that estrogen depletion plays a role in the onset or progression of OA. To investigate the effects via the estrogen receptors (ER) α and β. It is known that deletion of ERs leads to changes in the metaphyseal bone. We hypothesize that deletion of one or both estrogen receptors in female mice will promote osteoarthritic changes in the cartilage and subchondral bone.

Our aim was to study cartilage and subchondral bone changes in knee joints of female ERα−/−, ERβ−/−, and double ERα−/−ERβ−/− mice. Methods: Tibias of 6-month-old female ERα−/−, ERβ−/−, and ERα−/−ERβ−/− mice and their wildtype (wt, C57Bl/6 background) littermates (n=6 per group) were analyzed with microCT and histology.

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