LEPTIN INDUCES DETRIMENTAL CHANGES IN HUMAN OA CARTILAGE. EFFECTS ON NITRIC OXIDE, PGE2, IL-6 AND IL-8 PRODUCTION

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Purpose: Obesity is an important risk factor for OA of weight-bearing joints, but also for hand joints pointing to an obesity-related metabolic factor that influences on the susceptibility or pathogenesis of OA. Leptin is a proinflammatory adipokine regulating energy balance and it has lately been related also to arthritis and cartilage metabolism. In the present study, we investigated the effects of leptin on human OA cartilage.

Methods: Cartilage tissue obtained from the leftover pieces of total knee replacement surgery from patients with OA were used in the experiments.

Results: Leptin alone and in combination with IL-1 induced iNOS expression and NO production, COX-2 expression and PGE2 production, and IL-6 and IL-8 secretion in human OA cartilage in a concentration dependent manner. The effects of leptin were mediated through transcription factor NF-κB and MAP kinases JNK and p38 (the latter only in the case of COX-2 and PGE). In addition, JAK-STAT pathway seems to mediate the leptin effect on iNOS and NO. There were significant inter-individual differences in the responsiveness to exogenous leptin, and its relation to BMI, severity of OA, and SOCS-3 expression was assessed.

Conclusions: The findings support the idea of leptin as a detrimental factor in OA cartilage and as a link between obesity and increased risk for osteoarthritis.

CHONDROCYTE HYPERTROPHY IN ANK-/ANK- MICE: IMPLICATIONS FOR OSTEOARTHRITIS

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Purpose: Chondrocyte hypertrophy is a morphologic feature of both the normal calcified cartilage layer of the articular plate and of uncalcified cartilage in pathologic states such as osteoarthritis. The relationships of chondrocyte hypertrophy to chondrocyte matrix domains and to cartilage maturation, although commonly observed, are not well understood. As we have recently demonstrated (Osteoarthritis and Cart, 14(Suppl B 2006); pS147, December 2006), ank+/- mice show an increased population of hypertrophic chondrocytes in the uncalcified cartilage layer. To determine whether chondrocyte hypertrophy is a generalized feature of ank+/- mice and to determine implications on calcified cartilage matrix and subchondral bone, we extended our studies to examine chondrocyte size in calcified and epiphyseal cartilages and their relationships to calcified cartilage and subchondral bone thickness.

Methods: Knee joints in 18 mice, homozygous (ank+/-), and controls (ank++), 3 mice each at each of the following 3 time points: 6 weeks, 12 weeks and 18 weeks were studied. Five μm sections from fixed, decalcified, paraffin-embedded knee joints were stained with hematoxylin and eosin. Chondrocyte size distribution and cartilage matrix domains were determined for uncalcified, calcified and epiphyseal cartilages, as well as subchondral bone thickness. The measurements were performed on a Visiopharm Integrator Image Analysis System, Leica DM 4500 3 microscope and an Olympus D70 camera. With selection of the central 50% of the tibial plateau articular plate and underlying epiphysis, as the region of interest, the chondron areas of chondrons containing nucleated chondrocytes were measured for uncalcified, calcified and epiphyseal cartilage. As well, uncalcified cartilage, calcified cartilage and subchondral bone thicknesses and areas were measured over the study region.

Results: We observed that compared to wild type controls, ank chondrocytes in uncalcified cartilage and epiphyseal cartilage at all ages were enlarged. In contrast, within calcified cartilage, the ank chondrocytes were smaller than controls at 12 and 18 weeks. Calcified cartilage in ank mice was significantly thicker at all ages. Conversely, subchondral bone thickness in ank mice although thicker than controls at 6 weeks, was significantly thinner at 18 weeks of age.

Results: typically at 18 weeks

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<th>Wild Type</th>
<th>ank Mice</th>
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<tr>
<td>Calcified cartilage thickness (μm)</td>
<td>59±12</td>
<td>86±11</td>
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<tr>
<td>Subchondral bone thickness (μm)</td>
<td>423±18</td>
<td>331±12</td>
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Conclusions: ank-/ank- mice have a generalized defect in chondrocytes which leads to chondrocyte hypertrophy of uncalcified and epiphyseal chondrocytes. These changes are associated with increased calcified cartilage thickness, which in turn appears related to decreased bone thickness within the articular plate. The intriguing predicted implication is that uncalcified chondrocyte hypertrophy, which in osteoarthritis is focal, may result in focally thinner underlying subchondral bone. This subchondral bone, in turn, would more readily permit microfractures leading to articular plate remodelling, a characteristic feature of osteoarthritis.