hand SF as measured by BrdU proliferation assay ($p < 0.05$, $n = 3$). Apoptosis of hand SF increased at 48 hour of HOTTIP silencing ($p < 0.05$, $n = 3$).

Conclusions: The lncRNA HOTTIP, which is specifically expressed in hand joints via epigenetic mechanisms, is a master regulator of mitotic cell cycle genes and proliferation in hand SF. Distal-specific expression of HOTTIP might imprint hand SF with enhanced proliferative potential, thereby shaping the location-specific joint pathology, e.g. prominent synovial hyperplasia and increased severity of hand arthritis in RA.

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SAT0067

ROLE OF NOX2-DERIVED REACTIVE OXYGEN SPECIES IN S100A8/A9-DRIVEN INFLAMMATORY OSTEOARTHRITIS

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Background: Synovitis in inflammatory osteoarthritis (OA) is driven by locally released DAMPs like S100A8/A9 proteins that have been shown to enhance joint destruction. S100A8/A9 induce ROS (reactive oxygen species) release by phagocytes in OA synovium via the NADPH-oxidase 2 (NOX2)-complex. Assembly of this complex is dependent on the neutrophils cytosolic factor (Ncf1). In this complex, the NOX2 protein is responsible for ROS production.

Objectives: In the present study we investigated whether NOX2-derived ROS are involved in joint pathology during collagenase-induced OA (CiOA).

Methods: CiOA was induced in knee joints of wild type (WT) and Ncf1-deficient (Ncf1^{-/-}) mice. Synovial gene expression of NOX2-subunits was measured with qRT-PCR. Joint pathology was assessed using histology and antibodies against aggrecan neo-epitope VDIPEN. Levels of inflammatory proteins were measured with Luminex or ELISA. Phagocytes present in synovium, blood, bone marrow and spleen were analysed with flow cytometry. Extracellular ROS production by bone marrow-derived phagocytes was measured using an Amplex Red ROS detection assay.

Results: CiOA induction in knee joints of WT mice caused significantly increased synovial gene expression of NOX2 subunits. On day 7 of CiOA, synovial thickening, synovial S100A8/A9 levels and synovial percentages of inflammatory macrophages, PMNs, and monocytes were comparable between WT and Ncf1^{-/-} mice. Cartilage damage and MMP activity, as measured by VDIPEN staining, were comparable, as well as levels of inflammatory mediators in serum and phagocyte percentages in blood, bone marrow and spleen. On day 42 of CiOA, synovitis, cartilage damage, and osteophyte formation in Ncf1^{-/-} mice were unaltered when compared to WT mice. ROS production by Ncf1^{-/-} PMNs was completely absent but Ncf1^{-/-} macrophages, the more predominant phagocyte involved in development of pathology during CiOA, produced ROS in similar amounts as WT macrophages. Ncf1 deficiency thus seems to exclusively affect PMNs, this surprising finding might explain the lack of differences observed between CiOA development in WT and Ncf1^{-/-} mice. ROS production by WT and Ncf1^{-/-} macrophages was strongly upregulated by S100A8 and almost completely inhibited by the pan-NOX inhibitor diphenyliodonium chloride (DPI). In order to determine whether NOX1 complexes caused the compensation responsible for Ncf1 independent ROS production, we co-stimulated Ncf1^{-/-} macrophages with NOX1-specific inhibitor ML171. However, no ML171-induced inhibition of ROS production was observed.

Conclusions: Absence of PMN-derived ROS does not alter synovitis and joint pathology in S100A8/A9-driven experimental inflammatory OA. The mechanism that enables Ncf1-independent ROS production by macrophages should be further investigated.

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SAT0068

BILIRUBIN PROMOTES DOWN-REGULATION OF RUNX2 AND UP-REGULATION OF RANKL GENE EXPRESSION IN BONE EXPLANTS AND IN OSTEOBLASTIC AND OSTEOCYTIC CELL LINES

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Background: *In vitro* studies have shown that the retained substances of cholestasis have deleterious effects in human osteoblasts and osteocytic cells. Bilirubin (BIL) and lithocholic acid (LCA) induce alterations in the proliferation, differentiation and apoptosis of osteoblastic and osteocytic cells. However, their effects in human bone tissue and in bone cell lines have not been deeply analysed.

Objectives: To investigate the effects of BIL, LCA and ursodeoxycholic acid (UDCA) in gene expression of human trabecular bone explants as well as in osteoblastic (SAOS2) and osteocytic cells (MLO-Y4/MLO-A5).

Methods: Bone tissue harvested from trabecular bone fragments, SAOS2 and MLO-Y4/MLO-A5 cells were cultured and treated with BIL (50 μ M), LCA (10 μ M) and UDCA (10/100 μ M) for 24 hour. Gene expression of osteocalcin (*BGLAP*), *Cbfa1* (*RUNX2*)/*Osterix* (*OSX*) and *RANKL* (*TNFRSF11B*)/osteoprotegerin (*TNFRSF11B*) were quantified by real time PCR.

Results: BIL diminishes *RUNX2* gene expression in bone tissue (-37%), SAOS2 (-75%), MLO-Y4 (-56%) and MLO-A5 (-77%), and increases *RANKL* expression in 60%, 27%, 72% and 60%, respectively ($p \leq 0.02$). In bone tissue and in osteoblastic and osteocytic cells, LCA increases gene expression of *BGLAP* (NS) and *RANKL* ($p \leq 0.03$). UDCA 100 μ M increases *RUNX2* and *OSX* expression in bone tissue (78% and 82%), MLO-Y4 (72% and 80%) and SAOS2 (75% and 70%) ($p \leq 0.03$). In addition, UDCA 100 μ M significantly increases expression of *BGLAP*, *OPG* and *RANKL* in bone tissue and in osteocytic lines. UDCA 10/100 μ M counteracts the decrease in *RUNX2* induced by BIL in bone tissue, SAOS2, MLO-A5 and MLO-Y4 cells.

Conclusions: The retained substances of cholestasis, particularly bilirubin, cause noxious effects on transcription factors of osteoblast differentiation and on osteoclastic activators in bone tissue and in osteoblastic and osteocytic cells. Ursodeoxycholic acid reverses the harmful effects of bilirubin. These results provide new insights into the low bone formation and at some stages, high resorption, associated with chronic cholestasis.

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SAT0069

ABNORMAL BONE AND CARTILAGE METABOLISM COULD BE ANTAGONISED BY PULSED ELECTROMAGNETIC FIELDS (PEMFs) AND TNF-A AND IL-6 GENE KNOCKOUTS IN A SIMILAR MECHANISM

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Background: Pulsed electromagnetic fields (PEMFs), as a safe and non-invasive method, could positively affect bone and cartilage metabolism. However, the effect and underlying mechanisms of PEMFs on osteoporosis and osteoarthritis remain poorly understood.

Objectives: The present study is designed to investigate the effect of PEMFs on osteoporotic bone and degenerative cartilage together with its potential molecular mechanisms in mice with different gene background.

Methods: Twenty 12 week male and Female wild-type (WT), *TNF α* knockout (*TNF α ^{-/-}*) or *IL6* knockout (*IL6^{-/-}*) mice, respectively, were sham-operated (SHAM) or subjected to destabilisation of the medial meniscus (DMM) and ovariectomy (OVX) surgeries. After surgeries, WT mice were equally assigned to the non-treatment and PEMFs groups. Mice in PEMFs group were subjected to daily 1 hour PEMFs exposure with 8 Hz, 3.8 mT (peak value). Then all mice were euthanized after 4 weeks. Bone mass and subchondral microarchitecture were determined using micro-CT. Bone and cartilage metabolism was assessed by histological analysis, serum analyses, qRT-PCR and Western-Blot.

Results: The surgical models of osteoporosis and osteoarthritis were proved successful evidenced by the analysis of micro-CT data and histological analysis. The bone loss and damaged cartilage were largely repaired by *TNF α* and *IL6* gene knockout and partially inhibited by PEMFs exposure. Interestingly, no difference