in Micro-CT data analysis was found between PEMFs group and gene knockouts, although a slight increase could be observed in $TNF\alpha^{-/-}$ mice when compared to the PEMFs group. Negative effects on bone and cartilage was proved by testing key cytokines in anabolism and catabolism. PEMFs treatment and gene knockouts corrected the negative effects by targeting mediators in molecular pathways like Wnt and RANK. The differences in mRNA and protein level changes between PEMFs and gene knockouts were minor.

Study Design

PEMFs exposure system (Version 1.0)

Patent No. CN201058179Y

PEMFs exposure system (Version 2.0)

Conclusions: PEMFs alleviated surgeries induced bone loss and cartilage degeneration by promoting anabolism and inhibiting catabolism possibly in a similar mechanism to $TNF-\alpha$ and $IL-6$ gene knockouts, which imply that $TNF-\alpha$ and $IL-6$ may become new potential targets for PEMFs in treating degenerative bone diseases.

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SAT0070

ROLE OF C/EBPβ IN 1,25D-INDUCED ACTIVATION OF RANKL EXPRESSION

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Background: 1 alpha 25-dihydroxyvitamin D3 (1,25D) is the active form of vitamin D3, which is responsible for osteoblast activation, subsequently bone formation. Although recent studies have shown that 1,25D stimulates RANKL expression in osteoblast differentiation¹, its molecular mechanism of action is not fully understood.

Objectives: The aims of this study were to evaluate cellular response of human bone-derived cells to 1,25D treatment by observing expression during osteoblast differentiation

Methods: In this study, MG63, SaOS2, and primary bone-derived cells (BdCs) were cultured and isolated to further elucidate the effect of 1,25D on osteoblasts. Those were incubated in osteogenic medium (ascorbic acid, beta-glycerol phosphate, and dexamethasone) for 1, 3, and 7 days with or without 20 μM 1,25D. The

osteoblast activity and differentiation status were evaluated by intercellular Alkaline Phosphatase (ALP) activity, ALP staining, Alizarin Red S (ARS) staining, and hydroxyapatite staining. In this situation, C/EBPβ gene manipulation with siRNA or overexpression system were subjected to report assay of human RANKL promoter, quantitative PCR(qPCR), immunoblotting and immunostaining of osteoblastic gene expression (alkaline phosphatase, osteocalcin, vitamin D3 receptor, RANKL, and C/EBPβ etc.)

Results: 1,25D promotes osteoblast differentiation and expression of osteogenic markers in three different cells. Intriguingly, treatment of 1,25D to those cells are accompanied by stabilising C/EBPβ proteins and stimulating RANKL expression. Moreover, Overexpression of C/EBPβ significantly increases RANKL mRNA and protein. In contrast, suppression of C/EBPβ decreases RANKL expression. Thus, C/EBPβ is a key mediator involved in 1,25D induced RANKL expression.

Conclusions: our preliminary data indicated that human bone-derived cells response to vitamin D3 promoted RANKL expression via activation of C/EBPβ, and enhanced osteoblast activity and differentiation. This study provides insight into the molecular mechanism of RANKL expression and osteoblast activation in human bone-derived cells response to 1,25D.

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SAT0071

SUBCHONDRAL OSTEOPENIA BUT NOT CARTILAGE DAMAGE IS PREVALENT IN KNEE JOINTS OF PREMATURELY AGEING MITOCHONDRIAL DNA MUTATOR MICE

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Background: Mitochondrial dysfunction has been demonstrated in ageing and osteoarthritic tissues. However it remains unclear whether dysfunctional mitochondria are directly implied in the pathogenesis of osteoarthritis.

Objectives: We investigated knee joints of prematurely ageing mitochondrial DNA mutator mice (*Polg*^{D275A}) to evaluate a causal relationship between mitochondrial dysfunction and different features of osteoarthritis.

Methods: Bone structural parameters and chondropathy were evaluated in knee joints of mice displaying increased mtDNA mutations rates and accelerated ageing, due to expression of a proofreading-deficient mtDNA polymerase, using micro-computed tomography and histopathological analysis.

Results: Homozygous mutants displayed osteopenia of the epiphyseal trabecular bone and subchondral cortical plate in comparison to wild type controls and heterozygous mutants. Osteopenia was associated with a strong increase of osteoclast numbers (0.88±0.30/mm bone perimeter) compared to heterozygous (0.25±0.03/mm) and wild type mice (0.12±0.04/mm). New bone formation was not observed. Wild type mice displayed only low grade cartilage degeneration (OARSI grade ≤1) due to loss of cartilage proteoglycans. Increased tibio-femoral chondropathy was not apparent in hetero- and homozygous mitochondrial DNA mutator mice.

Conclusions: Mitochondrial dysfunction and premature ageing in mice with somatically acquired mtDNA mutations predisposes to enhanced subchondral bone resorption as potential early step of osteoarthritis, but not to cartilage damage or new bone formation. This phenotype potentially corresponds to an osteoporotic osteoarthritis phenotype in humans.

Disclosure of Interest: None declared

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SAT0072

MIRNA-146A IS A KEY PLAYER IN BONE METABOLISM AND OSTEOPOROSIS

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Background: Micro RNAs (miRNAs) play a crucial role in the regulation of bone metabolism. MiR-146a, an important anti-inflammatory miRNA, was found to negatively impact osteogenesis and bone regeneration *in vitro*, by controlling the differentiation of mesenchymal stem cells. But to date the role of miR-146a in bone

remodelling, its influence on bone stability and development of osteoporosis is not known.

Objectives: The objective of this project is the analysis of the role of miR-146a in bone metabolism.

Methods: Systemic bone, tibiae and femur, of wt and miR-146a deficient animals was assessed histologically and via μ CT analysis, over a period of 3 to 18 months of age. Serum cytokine levels were analysed by Elisa. mRNA expression levels in bone were analysed by qPCR. To induce osteoporosis, ovariectomy (OVX) induced bone loss was performed.

Results: When we analysed bone volume of long bones histologically as well as with μ CT analysis we detected significantly increased trabecular bone mass in miR-146a deficient compared to wt animals, starting at an age of 6 months. However, cortical thickness of systemic bones from miR-146a knock out animals was significantly reduced compared to control mice. Analysis of serum in aged miR-146a deficient animals displayed elevated activity of bone resorbing osteoclasts as amounts of CTX I in miR-146a^{-/-} mice were significantly increased compared to wt animals. Q-PCR analysis of important osteoclast as well as osteoblast marker genes in bones *ex vivo* displayed elevated expression of signature molecules of both cell types in aged miR-146a deficient mice, suggesting a regulatory role of miR-146a in both osteoclasts as well as osteoblasts. When we induced osteoporosis using the OVX disease model, histological analysis of long bones showed significant trabecular bone loss in ovariectomized wt mice. In contrast, we detected no trabecular bone loss in ovariectomized miR-146a knock out animals, suggesting that loss of miR-146a deficiency protects bone loss induced by oestrogen deficiency.

Conclusions: MiR-146a seems to control bone turnover and miR-146a deficient mice accrue bone over time. Moreover this miRNA has a negative influence on bone loss occurring during oestrogen loss induced osteoporosis. Therefore miR-146a could be possibly used as a therapeutic target in the treatment of osteoporosis.

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SATURDAY, 16 JUNE 2018

Rheumatoid arthritis – prognosis, predictors and outcome

SAT0073

ACPA AND RF AS PREDICTORS OF SUSTAINED CLINICAL REMISSION IN RHEUMATOID ARTHRITIS PATIENTS: RESULTS FROM THE ONTARIO BEST PRACTICES RESEARCH INITIATIVE (OBRI)

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Background: Positive anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) are included among the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA). Previous studies have shown that autoantibodies are positive predictors of response in RA patients treated with some biologics whereas other studies suggest worse prognosis if positive for ACPA and RF.

Objectives: The purpose of this study was to evaluate the interaction of RF and ACPA in predicting sustained clinical response in a large observational registry of RA patients followed in routine practice.

Methods: RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) registry, with active disease (≥ 1 swollen joint), available autoantibody information, and at least 1 follow-up assessment were included in the analysis. Sustained clinical remission was defined as CDAI ≤ 2.8 in at least 2 sequential visits separated by at least 3 and maximum of 12 months. Time to sustained remission was assessed by plotting cumulative incidence curves and multivariate cox regression.

Results: A total of 970 (30%) out of 3251 patients in the registry were included, of whom 262 (27%) were anti-CCP^{neg}/RF^{neg}, 60 (6.2%) anti-CCP^{pos}/RF^{neg}, 117 (12.1%) anti-CCP^{neg}/RF^{pos}, and 531 (54.7%) anti-CCP^{pos}/RF^{pos}. At baseline, significant differences were observed between groups in age ($p=0.02$), CDAI ($p=0.03$), tender joint count ($p=0.02$), and HAQ-DI ($p=0.002$), with anti-CCP^{pos}/RF^{pos} and anti-CCP^{pos}/RF^{neg} patients being youngest and having the lowest disease activity and disability. No differences were observed in terms of biologic use (20.2% of patients).

Sustained remission was 10% more likely if anti-CCP^{pos}, and was achieved by 43.5% of anti-CCP^{pos}/RF^{pos} patients, 43.3% of anti-CCP^{pos}/RF^{neg} patients, 31.6%

of anti-CCP^{neg}/RF^{pos} patients and 32.4% of anti-CCP^{neg}/RF^{neg} patients ($p=0.01$). Significant differences were observed in the time to achieving sustained clinical response from enrolment in the OBRI based on anti-CCP status ($p<0.001$), RF status ($p=0.06$), and both ($p=0.004$) (figure 1). ACPA^{pos}/RF^{pos} (median: 3.7 years; 95% CI: 3.0–4.3) and ACPA^{pos}/RF^{neg} (median: 3.4 years; 95% CI: 2.4–NE) patients achieved sustained remission earlier than ACPA^{neg}/RF^{neg} patients (median: 5.1 years; 95% CI: 3.7–6.2), respectively (figure 1).

Multivariate cox regression adjusting for baseline CDAI score, age and sex also showed differences between groups; statistically significance in anti-CCP^{pos}/RF^{pos} vs. anti-CCP^{neg}/RF^{neg} patients (HR [95% CI]: 1.30 [1.01–1.67]; $p=0.04$).

Abstract SAT0073 – Figure 1. Cumulative incidence of first sustained remission by ACPA/RF status

Conclusions: These results suggest that anti-CCP but not RF positivity may be associated with a higher chance of remission, possibly due to an improved treatment response.

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SAT0074

IDENTIFICATION OF A PROTEIN PANEL USEFUL FOR THE PREDICTION OF RESPONSE TO METHOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: The treatment of rheumatoid arthritis (RA) aims to control a patient's signs and symptoms, prevent joint damage, and maintain his/her quality of life. Among the best known disease-modifying antirheumatic drugs, Methotrexate (MTX) is one of the most effective and widely used medications. It is used as a general first-choice drug, although some patients will not respond to this treatment and it is not free from side effects.

Objectives: To identify circulating proteins that could be useful as predictors of the patient's response to MTX.