of all fucoidans ($p < 0.05$). By scratch wound assay, we observed that TGF- β induced cell mobility to close the scratch, which was inhibited by all fucoidans. Similarly, FU and FM were also able to attenuated cell invasion after TGF stimulation. Additionally, we also detected that fucoidans showed anti-inflammatory effects in FLS as they reduced the NO production and IL-6 expression induced by IL-1.

Conclusion: Our results indicate a protective effect of fucoidans against activated pro-fibrotic pathways in fibroblast-like synoviocytes. However, we detected that these beneficial activities vary between fucoidans from different species and further studies are warranted.

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Bone diseases, including osteoporosis and osteoimmunology: aetiology, pathology and animal models

AB0079 ANGIOPOETIN-LIKE PROTEIN TYPE 3 AS AN INDICATOR OF RHEUMATOID INFLAMMATION AND RESORPTION OF BONE TISSUE IN RHEUMATOID ARTHRITIS

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Objectives: to study the role of type 3 angiotensin-like protein (ANGPTL3) in the development of osteoporotic processes associated with inflammation in rheumatoid arthritis (RA).

Methods: 88 patients with RA were examined (women - 100%, average age - 54.2 ± 12 years old, disease duration - 11.2 ± 8.7 years, positive for rheumatoid factor (RF-IgM) - 72.7%, positive for anti-citrullinated protein antibody (ACPA) - 67%, DAS28 activity: remission - 21.6%, minimal - 11.4%, medium - 59.1%, high - 7.9%), functional class: 0 - 1.1%, I - 25%, II - 65.9%, III - 8%). The study was conducted on a bone X-ray densitometer LUNAR DPX (GE, USA). Most of the patients (96.6%) were residents of cities, and 67 (76.1%) people lived in the metropolis (number of inhabitants more than 1 million people).

The concentration of ANGPTL3 in serum was determined by enzyme immunoassay using a commercial test system "Human Angiotensin-like Protein 3 ELISA" ("Bio Vendor").

Results: Osteoporosis is found in 52 (59%) people. Increased ANGPTL3 values (> 445 ng / ml) were determined in 80.7% of cases. A significant positive correlation was found between the level of ANGPTL3 and the age of patients ($r = 0.23$, $p = 0.032$), the functional class ($r = 0.214$, $p = 0.046$), the presence of osteoporosis ($r = 0.36$, $p = 0.039$), living in the metropolis ($r = 0.214$, $p = 0.046$) and smoking ($r = 0.31$, $p = 0.036$), as well as a negative relationship with the duration of walking per day ($r = -0.314$, $p = 0.003$) and weekly ($r = -0.319$, $p = 0.002$) was determined. The level of ANGPTL3 correlated with the activity of RA calculated by the DAS28-CRP index ($p = 0.037$), but not by the DAS28-ESR index ($p = 0.135$).

It is noteworthy that ANGPTL3 is closely related to changes in bone mineral density (BMD) in the femoral neck (BMD Total: $r = -0.33$, $p = 0.042$; BMD Troch: $r = -0.36$, $p = 0.038$; BMD Wards: $r = -0.44$, $p = 0.009$), but not in the spine (L1-L4) ($p > 0.05$). The lack of connection of ANGPTL3 with ACPA ($p = 0.128$) may indicate different mechanisms of influence on systemic BMD in patients with established RA.

Conclusion: ANGPTL3 can be used as an indicator of pathological processes associated with rheumatoid inflammation and the development of osteoporosis. Living in a metropolis, smoking and low physical exertion has an additional negative effect on resorptive processes in bone tissue in women with active RA.

Disclosure of Interests: None declared

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AB0080 A SYSTEM-LEVEL APPROACH IDENTIFIES A CRITICAL REGULATOR OF CHONDROSARCOMA PROGRESSION

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Background: Chondrosarcomas are cartilaginous tumors that constitute one-third of skeletal system cancers. Chondrosarcomas are capable of transitioning to highly metastatic and treatment-refractory states, resulting in significant patient mortality. However, the molecular events accompanying this behavior remain unknown.

Objectives: We aimed to uncover the molecular pathway underlying such tumor progression that confers a higher malignancy to chondrosarcoma.

Methods: We conducted unsupervised gene co-expression network analyses using transcriptomes of patients with chondrosarcoma and extracted a characteristic transcription network underlying chondrosarcoma malignancy. By implementing a system-level upstream analysis of this gene network, we identified the transcriptional factor as a key regulator governing chondrosarcoma progression. We unraveled the functional roles of the identified factor in promoting tumor growth and metastasis of chondrosarcomas in the context of their unique microenvironments.

Results: By conducting system-level upstream analysis, we identified a factor as a transcriptional regulator that governs the malignancy gene module. The identified factor was upregulated in chondrosarcoma biopsies associated with a high histological grade and conferred chondrosarcoma cells invasiveness and tumor-initiating capacity. In an orthotopic xenograft mouse model, the identified factor modulated local outgrowth and pulmonary metastasis of chondrosarcoma. Pharmacological inhibition of the identified factor in conjunction with the chemotherapy agents such as cisplatin or doxorubicin synergistically enhanced chondrosarcoma cell apoptosis and abolished malignant phenotypes of chondrosarcoma in mice.

Conclusion: Our study provides a proof of concept evidence that inhibiting the identified factor suppresses progression of chondrosarcoma and improves the efficacy of chemotherapy in cellular and pre-clinical levels. Taken together, we believe that our findings provide novel molecular insights for the development of new anti-cancer therapies to target chondrosarcomas.

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AB0081 THE ROLE OF LOCAL BISPHOSPHONATES IN THE PRESERVATION OF THE BMD IN THE ZONE OF SURGICAL BONE DEFECT (ANIMAL STUDIES)

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Background: One of the reasons for failures in Arthroplasty is the preservation in the postoperative period in the bone adjacent to the implant of the prevalence of resorption over bone formation. The possibility of inhibition of resorption by bisphosphonates, including their local use in the composition of the biocomposite material, aggravates the situation due to the simultaneous oppression of bone formation. A low level of remodeling in these cases leads to a further loss of bone mass in the intervention zone.

Objectives: To evaluate in the experiment the effect of bisphosphonates in the biocomposite material on the bone mass both in the surgical intervention zone and in the segment as a whole.

Methods: The study was conducted as a comparison with the control. 60 females of white non-linear rats, body weight 130-150g. were divided into 6 groups. In 3 groups, the defect of the tibia was filled with a biocomposite material in the form of a gel (patent No. 2325170) connected to various bisphosphonates Ibandronic acid (Bonviva), zoledronic acid (Aklasta), alendronate sodium (Fosamax) was used in conjunction with a non-demineralized lyophilized bone implant. Groups, the defect was filled with a non-demineralized lyophilized bone implant with biocomposite material without bisphosphonate, in the second control group, non-demineralized lyophilized bone implants without biocomposite material in trolley- defect is not filled.

Assessment of bone mineral density (BMD) in the intervention area and in the segment as a whole was performed using X-ray densitometry (Hologic, Small Animals Program Performing and Analyzing Small Animal Studies). Results Comparison (simple dispersion analysis) of the MIC of all groups using

bisphosphonates on the one hand, with the MIC of all control groups on the other hand, revealed significant differences ($p < 0.002$).

Results: The analysis, using the paired t-test, the average MIC values in the combined group using bisphosphonates and the pooled control group, confirmed that the BMD in the zone of intervention in the bisphosphonate group was significantly higher than in the control: 0.320 ± 0.008 g / cm², respectively, versus 0.285 ± 0.019 g / cm² ($p = 0.002$). If the group was excluded from the analysis, where the defect was not filled, the tendency to differences remained: 0.320 ± 0.008 g / cm² vs. 0.308 ± 0.002 g / cm² ($p = 0.11$).

Mean BMDs of the whole segment with the use of bisphosphonates also proved to be significantly higher than in the control, both with the inclusion in the analysis of the group without replacement of the defect, and with its exception. Thus, when all control groups were included in the analysis, the mean MIC values in the group with bisphosphonates were 0.30 ± 0.01 g / cm² vs. 0.272 ± 0.12 g / cm² ($p < 0.001$). When excluding from the analysis of the group without replacement of the defect, the MIC values were respectively: 0.307 ± 0.01 g / cm² versus 0.285 ± 0.01 g / cm² ($p = 0.01$).

Conclusion: Relative to the control, an increase in BMD in the group using bisphosphonates excludes the possibility of their negative impact on the process of bone formation. The marked positive bone balance confirms the ability of bisphosphonates to maintain the remodeling mechanism at the physiological level.

References: Local application of bisphosphonates, osteoplastic materials, bio-composite material, bone implant reconstruction, bone formation.

Disclosure of Interests: None declared

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Rheumatoid arthritis - aetiology, pathogenesis and animal models

AB0082

INHIBITION OF TGF β SIGNALING USING SB-505124 BLOCKS TH17 DIFFERENTIATION AND RESTORES THE TH17/TREG BALANCE IN VIVO, BUT DOES NOT SUPPRESS EXPERIMENTAL ARTHRITIS

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Background: TGF β is an important growth factor that promotes the differentiation of T helper 17 (Th17) as well as regulatory T-cells (Treg). Due to its dual role, the potential of TGF β as therapeutic target is unclear.

Objectives: In this study we aimed to investigate the effect of inhibition of TGF β signaling with the ALK5 inhibitor SB-505124 on human Th17 differentiation *in vitro*, on cytokine production by human rheumatoid arthritis (RA) synovial explants, and study the effects of local SB-505124 treatment *in vivo* during innate immune and Th17-driven experimental arthritis models.

Methods: Magnetic sorted naïve human T cells were differentiated into Th17 cells with CD3/CD28 activation beads, IL-2, TGF β , IL-1 β , IL-23, α IFN γ and α IL-4 for 6 days. Human RA synovial biopsies were cultured for 24h w/o 5 μ M SB-505124, and supernatant was analyzed by Luminex. T cell-independent SCW arthritis and Th17-driven IL-1/mBSA arthritis were induced in C57Bl/6, and mice were treated with SB-505124 by daily intra-articular injections from day 0-4.

Results: SB-505124 potently reduced human Th17 differentiation *in vitro* by decreasing IL-17 and ROR γ t gene expression and IL-17 protein production. SB-505124 significantly suppressed IL-6 and TNF α protein production by human RA synovial explants. In addition, SB-505124 did not affect acute joint inflammation during SCW-arthritis (T-cell independent model). Interestingly, SB-505124 reduced Th17 levels in draining lymph nodes (dLN) during IL-1/mBSA arthritis while increased levels of Tregs were observed. Surprisingly, despite this skewed Th17/Treg balance, this did not result in suppression of joint inflammation and destruction in this Th17-driven arthritis model, whereas anti-IL-17 antibody treatment showed significant therapeutic effects.

Conclusion: We revealed suppressive effects of SB-505124 on human Th17 differentiation and the Th17/Treg balance in arthritic mice. However, SB-505124 did not suppress joint inflammation and destruction. This indicates that despite the importance of TGF β in Th17 differentiation, targeting TGF β signaling is not enough to suppress experimental arthritis.

Disclosure of Interests: None declared

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AB0083

STUDY OF THE ROLE OF ANGIOPOIETIN-LIKE PROTEIN TYPE 4 IN METABOLIC DISORDERS CAUSED BY INFLAMMATION IN RHEUMATOID ARTHRITIS

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Background:

Objectives: To assess the potential role of angiotensin-like protein type 4 (ANGPTL4) in metabolic disorders caused by inflammation in rheumatoid arthritis (RA).

Methods: The study included 88 patients with significant RA, 64 patients with other rheumatic diseases (RD) (36 patients with osteoarthritis (OA); 28 patients with psoriatic arthritis (PsA); 17 patients with ankylosing spondylitis (AS)) and 32 healthy individuals. Estimation of ANGPTL4 was carried out by enzyme immunoassay using the commercial test system "RayBio Human ANGPTL4 ELISA Kit" (RayBiotech, USA) in blood serum. Levels of ESR, CRP, RF, antibodies to cyclic citrullinated peptide (anti-CCP) and modified vimentin (anti-MCV) in the ELISA test were determined for all patients with RA.

Results: The level of ANGPTL4 in the blood serum of patients with RA was significantly higher than in healthy people ($p < 0.001$) and patients with other RD ($p = 0.012$ compared with OA; $p = 0.046$ with PsA; $p = 0.008$ with AS). ANGPTL4 indices in patients with RA correlated with the age of onset of RA ($r = -0.658$, $p < 0.001$), disease activity according to DAS-28 ($r = 0.449$, $p = 0.001$), level of education ($r = 0.235$, $p = 0.029$), dose of glucocorticoid hormones ($r = 0.321$, $p = 0.009$) and methotrexate ($r = -0.496$, $p = 0.05$), the presence of osteopenia ($r = 0.44$), signs of kidney damage - proteinuria ($r = 0.309$, $p = 0.037$) and hypoalbuminemia ($r = 0.386$, $p = 0.022$), as well as with CRP levels ($r = 0.488$, $p = 0.003$), ESR ($r = 0.458$, $p = 0.002$), serum vitamin D ($r = -0.417$) and urinary calcium when recalculated to creatinine ($r = 0.797$, $p = 0.032$).

Patients with RA showed a high frequency of insulin resistance (according to the HOMA-IR index) [1.27 [0.84–1.62] in patients with RA; 0.76 [0.44–1.02] in healthy individuals; $p < 0.001$) and the presence of coronary heart disease, as well as a positive correlation between disease activity (according to DAS-28) and insulin resistance (according to the HOMA-IR index) ($p = 0.033$).

Higher values of C-reactive protein ($p = 0.04$) and serum ANGPTL4 levels ($p = 0.042$, compared with patients with RA without type 2 diabetes; $p = 0.026$, compared with healthy individuals) were determined in the group of patients with RA with the presence of type 2 diabetes. ANGPTL4 acts as an inhibitor of lipoprotein lipase. His contribution to the development of dyslipidemia in RA can be demonstrated by the results we obtained when comparing groups of patients with / without signs of metabolic syndrome (MS). A positive correlation between ANGPTL4 and triglyceride levels ($r = 0.42$, $p = 0.018$) was found. An increase in the level of ANGPTL4 in blood serum of patients with RA with MS ($p = 0.027$ compared with RA without MS) can predict the development of cardiac pathology in this group of patients.

Conclusion: ANGPTL4 is directly involved in the regulation of glucose homeostasis, lipid metabolism, and insulin sensitivity. Cardiovascular diseases associated with atherosclerosis, insulin resistance and metabolic syndrome are known as the most common extraarticular manifestations of RA; the study of the role of ANGPTL4 in metabolic disorders caused by inflammation can show a new direction in the development of laboratory and therapeutic technologies in RA.

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AB0084

TNF RECEPTORS PROFILE CHANGES ON CYTOTOXIC T CELLS SUBSETS IN RHEUMATOID ARTHRITIS ARE ASSOCIATED WITH EFFECTIVE TREATMENT

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Background: Previous studies of co-expression profile of receptors to tumor necrosis factor alpha (TNF) in rheumatoid arthritis (RA) have revealed a number of indicators associated with diseases activity with 93% sensitivity and 90% specificity. However, the ratio of receptors to cytokines remains poorly understood. However, the question of therapy effect and its effectiveness in various alteration of cytokine receptors balance remains under investigated.

Objectives: To evaluate the dynamics of co-expression and quantitative expression of type 1 and 2 receptors for TNF in the subpopulations of CD3+CD8+ cells associated with changes in disease severity before and after effective basic therapy.