included the mitogen-activated protein kinase (MAPK) p38 and Akt. MTX did not inhibit TNF α -induced nuclear factor kappa B (NF κ B) transcriptional activation, signaling or target gene expression. However, MTX induced pro-inflammatory markers such as vascular cell adhesion molecule (VCAM)-1 in an additive manner with TNF α . Functionally, MTX did not induce apoptosis but caused S-phase cell cycle arrest, which, along with p38 and Akt activation, could be abrogated by supplementation with folic acid.

Findings to date in EC subjected to shear stress are somewhat different. MTX had no or a mild inhibitory effect on kinase signaling in EC under LSS and OSS respectively. MTX did not affect cell proliferation nor baseline or OSS-induced VCAM-1 expression in EC under shear stress.

Conclusion: In static EC, low-dose MTX caused cell cycle arrest through folate depletion, which is a known mechanism of action in other cell types. Of note, this response was not seen in EC pre-conditioned by shear stress and emphasizes the impact of biomechanical forces on endothelial phenotype and response to exogenous stimulation. This is the first report to study the effects of MTX on EC under shear stress, which will be crucial in understanding its molecular actions on the vasculature.

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AB0131

THE CORRELATION OF EXPRESSION OF DIFFERENTIAL DRUG-RESISTANT PROTEINS AND INFLAMMATORY CYTOKINES IN COLLAGEN INDUCED ARTHRITIS MODEL

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Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease. The most characteristic patho-logical changes are chronic synovitis. At present, the combination of traditional disease-difying anti-rheumatic drugs (DMARDs) and biological agents DMARDs has improved the therapeutic effect of RA, but some RA patients still have poor response due to Multidrug resistance (MDR) phenomenon. The main mechanism of MDR is related to the ATP-binding cassette (ABC) transporter superfamily members, which increases drug efflux and reduces intracellular drug concentration. We will study how cytokines regulate the expression of ABC transporters.

Objectives: By comparing the differential expression of ABC transporter family resistance-related proteins P-gp, BCRP, MRP1 and inflammatory cytokines IL-1 β , IL-2, IL-6, IL-10, TNF- α and IL-17 in CIA model mice, to investigate the correlation between Inflammatory cytokines and drug-resistant proteins.

Methods: Fourteen DBA1 mice were successfully induced by collagen and Freund's Adjuvant. According to the scores of synovial pathology, the CIA group was divided into mild, moderate-to-severe groups, another four mice were selected as control. The mRNA expressions of P-gp, BCRP, MRP1 in splenic lymphocyte cells were measured by RT-PCR. The concentrations of IL-1 β , IL-2, IL-6, IL-10, TNF- α , IL-17 in serum were detected by Cytometric Bead Array(CBA). Further analyze the correlation between different inflammatory cytokines and these proteins, then study one of the proteins which is most related with cytokines by immunohistochemical (IHC) in synovium. Two independent samples were analyzed by the Mann-Whitney U test. Non-parametric Kruskal-Wallis H test was performed on multiple independent samples. The correlation between variables was used by Spearman correlation analysis.

Results:

1. Compared with the normal controls, The level of IL-6 and TNF- α in the serum of mild CIA group, moderate-severe CIA group were significantly increased ($Z_1=14.383$, $P_1<0.05$, $Z_2=8.375$, $P_2<0.05$). Compared with the mild CIA group, the level of IL-6 in serum were significantly increased in the moderate-to-severe CIA group ($P<0.05$), but there was no distinct difference in the TNF- α level ($P>0.05$).

2. In the spleen lymphocytes, there was no significant difference in the the mRNA expression level of P-gp and BCRP among the groups, but the mRNA expression level of MRP1 were significantly increased ($P<0.05$). Compared with the mild CIA group, the MRP1 mRNA in the moderate-to-severe CIA group was higher, there was significant difference ($Z=12.634$, $P<0.05$). There was a correlation between mRNA expression of MRP1 and P-gp ($r=0.635$, $P=0.015$).
3. The mRNA expression of MRP1 was positively correlated with IL-6 level ($r=0.711$, $P=0.004$).
4. The expression of MRP1 in normal group, low-level IL-6 group and high-level IL-6 group were respectively as follows: 1.08(0.65,1.30), 1.40(1.13,2.07), 1.90(1.68,2.17).
5. Compared with the controls, the cytoplasm/membrane of the knee and ankle joint synovial tissue in the CIA group was yellowish-brown, which proved that MRP1 expression was positive.

Conclusion: In the CIA arthritis model, synovial tissue lesion is not only related to inflammatory cytokines, but also related to MRP1 expression in the ABC transport resistance protein family, and it is proved that IL-6 is highly correlated to MRP1.

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AB0132

A NOVEL TARGET FOR TREATMENT OF INFLAMMATORY JOINT DISEASES

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Background: The bile salt-stimulated lipase (BSSL) is a hitherto unrecognized player in inflammation. Animals devoid of BSSL (knockout mice) are protected from developing collagen induced arthritis (CIA) and collagen antibody induced arthritis (CAIA), and antibodies directed towards BSSL has been proven to prevent or mitigate arthritis in mouse and rat arthritis models¹. In humans, BSSL is present in blood² and accumulate at sites of inflammation. Patients with acute pancreatitis have significantly increased plasma BSSL levels compared to healthy controls. Whether BSSL in blood originates from pancreas, inflammatory cells, or both remains to be elucidated.

Objectives: To determine BSSL concentration in blood samples from patients with inflammatory joint disorders and to evaluate possible relationships between circulating BSSL levels and disease-activity variables.

Methods: BSSL concentrations in plasma or serum were determined in patients with rheumatoid arthritis (RA), psoriasis arthritis (PsA), and juvenile idiopathic arthritis (JIA) by a sandwich enzyme-linked immunosorbent assay (ELISA). Correlations between BSSL concentrations and disease activity score, erythrocyte sedimentation rate (ESR), blood levels of C-reactive protein (CRP), S100A8/9, leukocyte- and neutrophil counts, proinflammatory cytokines and chemokines were analyzed using Spearman rank-order correlation.

Results: Significant correlations between BSSL concentration in plasma and disease activity score (DAS28, $r_s=0.31$, $p=0.007$), ESR ($r_s=0.58$, $p<0.000$), CRP ($r_s=0.42$, $p=0.012$), leukocytes ($r_s=0.66$, $p<0.000$), and neutrophils ($r_s=0.71$, $p<0.000$) were found in RA. The BSSL plasma concentration decreased with duration of treatment with the TNF α inhibitor infliximab, in parallel with decreasing DAS28 score.

BSSL concentration was significantly higher in sera from PsA patients with both oligo- and polyarthritis compared with healthy controls. Moreover, BSSL concentration in serum correlated significantly with S100A8/9 and CRP concentrations ($r_s=0.54$, $p<0.001$ and $r_s=0.49$, $p<0.001$, respectively). No correlation between levels of BSSL and cytokines or chemokines were found in RA or PsA plasma or serum, respectively.

In JIA, levels of BSSL in serum correlated significantly with JIA disease activity score (JADAS27) ($r_s=0.26$, $p=0.007$), ESR ($r_s=0.47$, $p<0.000$), and leukocytes ($r_s=0.32$, $p<0.000$).

Conclusion: BSSL concentration in serum and plasma correlated with disease activity in patients with inflammatory joint disorders, i.e. RA, PsA and JIA. These data in humans support the relevance of our previous studies in rodents and

therefore also our hypothesis¹ that BSSL is a novel target for treatment of inflammatory diseases.

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AB0133

HUMAN UMBILICAL CORD-DERIVED MESENCHYMAL STEM CELLS AMELIORATE COLLAGEN-INDUCED ARTHRITIS VIA IMMUNOMODULATORY EFFECT ON T LYMPHOCYTES

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Background: Rheumatoid arthritis (RA) is an autoimmune disease that results in cartilage and bone destruction. Overactivation of T lymphocytes and imbalance of T lymphocyte subsets are closely related to the occurrence and development of RA. These have become important mechanisms of inflammation, immune activation, and bone destruction. RA treatment ideally involves regulation of immune abnormalities and maintenance of immune homeostasis. Mesenchymal stem cells (MSCs) are multipotent adult stem cells with high proliferation, multi-differentiation, and immune regulation. They exert immunoregulatory effects on T lymphocytes to improve RA symptoms, inhibit synovial hyperplasia, and reduce cartilage and bone erosion. However, the specific molecular mechanisms have not been fully elucidated.

Objectives: This study investigated the effect of human umbilical cord mesenchymal stem cells (hUCMSCs) on collagen-induced arthritis (CIA) in rats in comparison with that of methotrexate (MTX), a classical drug for RA. It evaluated T lymphocyte proliferation, apoptosis, differentiation, and associated inflammatory factors, further explored the regulatory mechanism of T lymphocyte differentiation at the gene transcription level. This study elucidated that hUCMSCs play an immunoregulatory role in T lymphocytes of CIA rats through multiple pathways and explored the possible mechanism of hUCMSCs in RA treatment via the immunomodulated T lymphocyte pathway.

Methods: The effects of hUCMSCs on arthritis, radiological and synovial pathological changes in CIA rats were assessed. Flow cytometry was conducted to detect T lymphocyte proliferation, apoptosis, the ratio of Th17 and Treg cells in the spleen, and IL-17 and TGF- β levels in the sera from CIA rats. Further, Foxp3 and ROR- γ T expression in the spleen were assessed by immunohistochemistry, Foxp3 mRNA and ROR- γ T mRNA expression were assessed by reverse transcription-polymerase chain reaction (RT-PCR).

Results: hUCMSCs inhibited proliferation and promoted apoptosis of T lymphocytes, up-regulated Foxp3 mRNA and protein expression, increased the proportion of Treg cells, down-regulated ROR- γ T mRNA and protein expression, and decreased the proportion of Th17 cells in the spleens of CIA rats. Correction of the Foxp3/ROR- γ T imbalance to regulate the Treg/Th17 ratio, promoted anti-inflammatory factor TGF- β expression and inhibited pro-inflammatory factor IL-17 expression, thereby improving arthritis in CIA rats, delaying radiological progression, and inhibiting synovial hyperplasia. This effect was similar to that of MTX.

Conclusion: hUCMSCs exert immunoregulatory effects on T lymphocytes in CIA rats through many pathways and are expected to become a new immunoregulatory therapy for RA.

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AB0134

ANALYSIS OF INTESTINAL MICROBIOME PROFILE OF PATIENTS WITH ESTABLISHED RHEUMATOID ARTHRITIS AND HEALTHY CONTROLS

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Objectives: Describe the intestinal microbiome profile in RA patients and analyze the mechanisms through which intervenes in the pathogenesis RA.

Methods: **Design:** Controlled, observational, cross-sectional study of established RA cohort. **Patients:** Forty consecutive RA patients (ACR/EULAR 2010 criteria) >16 years, selected from a prospective inception cohort (2007-2011) and 40 sex-age matched healthy controls. **Protocol:** Cases and controls were evaluated by a rheumatologist. Clinical data of disease activity were collected during the follow-up and analytical values were determined. Fecal samples were frozen within 24 hours of collection. **Main outcome:** Fecal samples exam. Microbial DNA was extracted from fecal samples using QIAamp DNA stool Mini kit. The concentration and quality of DNA was determined by Nanodrop. **Secondary Other variables:** Demographic, clinical-analytical and therapies (DMARDs). **Statistical analysis:** Analysis of microbiota profile: UniFracPCoA (Principal Coordinate Analysis) was performed with the abundance data of operational taxonomic units (OTU) by means of the variance-covariance matrix implemented in Quantitative Insights Into Microbial Ecology (QIIME). The relative abundance of each OTU (taxa) was compared using a Wilcoxon test. The variations of abundance and diversity were compared by ANOSIM pathway. The calculation of α and β -diversity was carried out using QIIME.

Results: Most of subjects were women (75%) (table). In RA patients, the average DAS28 was 3.6. β -diversity data showed that patients tend to differ from healthy subjects according to their microbiota ($p = 0.07$). Patients with RA exhibited decreased gut microbiome diversity compared with controls, although was not statistically significant. Regarding in species richness, the analysis suggested an increase of the *Collinsella aerofaciens* species and *enterococcus* genera in patients compared with controls. Likewise, an increase of arginine deaminase activity was observed, which belonged, in approximately 90%, to the RA genes of the genus *Collinsella*. The multivariate analysis identified ACPA positive (β [95% CI], 0.33 [27.4-390]), smoking (0.3 [8.8-256.4]) and age (-0.3 [27.4-390.0]) as factors associated with *Collinsella*. Also, we observed a decrease in other bacterial lineages. On the other hand, RA patients showed an altered metabolic capacity for the transport of zinc and copper.

Conclusion: These observations suggest a dysbiosis in RA patients, resulting from the abundance of certain bacterial (i.e. *Collinsella*) and decrease of other bacterial lineages. These alterations could influence in a significant way in the perpetuation of the autoimmunity of the disease.